

## Central Nervous System-Related

**Web URL:** <http://www3.interscience.wiley.com>

### 1. Synthesis and neurotrophic activity of silyl propargyl alcohols and sulfides

Ramona, A., Liga, Z., Edgars, A., Kira, R., Pavel, A., Marina, V., Olga, P., Maija, D., Ilona, D., Irina, S., Juris, P. and Edmunds, L.

Latvian Institute of Organic Synthesis, Riga, Latvia

*Applied Organometallic Chemistry* 2004, **18**(4), 181-186; *C.A.* **141**(2): 17429z

**Abstract:** The current invention deals with the preparation of synthetic analogues of silyl propargyl alcohols and sulfides. These compounds possess low toxicity and exhibited the LD<sub>50</sub> (anticonvulsant) in the range of 700-1300 mg kg<sup>-1</sup>.

**Activity and bioassay:** These compounds showed anticonvulsant activity. The highest anticonvulsant activity was exhibited by the two 3-(benzoazolylthio)-1-propynyl(trimethyl)silane. These compounds also showed memory improving activity in the passive avoidance response test. 250% of the control level was observed for di-1-(methyl-3-hydroxybutyn-1-yl)methyl(3-idoprosyl)silane. (3-trimethylsilyl-2-propynyl) thioenzyme or diphenylsilane remarkably reduced the phenamine induced hyperactivity.

**Origin:** Natural product

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**Web URL:** <http://sciencedirect.com/science/journals>

### 2. Eugenol exhibits antidepressant-like activity in mice and induces expression of metallothionein-III in the hippocampus

Yoshifumi, I., Nanae, I., Naoko, A., Naoko, A., Atsushi, I., Kenji, W. and Ming, K. W.

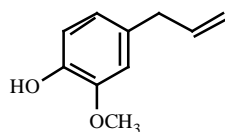
Department of Oriental Medicine, Keio University School of Medicine, Shinjuku, Tokyo, Japan 160-8582

*Brain Research* 2004, **101**(2), 243-246; *C.A.* **141**(2): 17459j

**Abstract:** Eugenol exhibited antidepressant-like activity and induced brain derived neurotrophic factor (BDNF).

**Activity and bioassay:** Antidepressant-like activity of eugenol was determined by a forced swim test and a tail suspension test in mice. It induced BDNF with the induction of metallothionein-III (MT III), whereas imipramine induced BDNF without inducing MT III.

**Origin:** Natural product



Eugenol

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### 3. Preparation of peptide-related substituted ureas and carbamates for the treatment of Alzheimer's disease

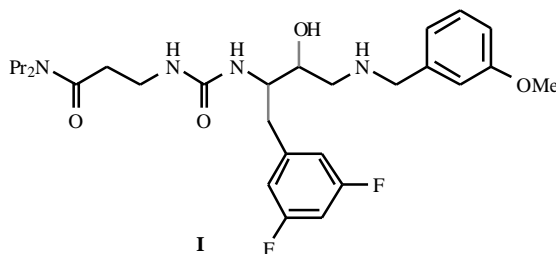
Elan Pharmaceutical, Inc.; Pharmacia & Upjohn Company; Pully, Shon R.; Tucker John A. USA

**PCT Int. Appl. WO 2004, 50, 609** (Cl. C07C271/20), 17 Jun 2004, US Appl. PV429, 769, 27 Nov. 2002: 213 pp; *C.A.* **141**(2): 23911s

**Abstract:** Synthesis of peptide-related substituted ureas and carbamates of general formula **I**  $R^N$ -T-X-NR<sup>20</sup>CHR<sup>1</sup>CH(OH)CR<sup>2</sup>R<sup>3</sup>NR<sup>20</sup>R<sup>C</sup> [X is CO, CS, SO, SO<sub>2</sub> or C:N-Z, where Z is R<sup>20</sup> or OR<sup>20</sup>, T is absent NR<sup>20</sup> or O; R<sup>20</sup> is H, CN, alk(en)yl, haloalkyl or cycloalkyl; R<sup>1</sup> is (CH<sub>2</sub>)<sub>1-2</sub>S(O)<sub>0-2</sub>-alkyl, (un)substituted alk(en)(yn)yl, (hetero)aryl, heterocyclyl, etc.; R<sup>C</sup>, R<sup>N</sup> are (un)substituted alkyl, (hetero)aryl, heterocyclyl, etc.; R<sup>2</sup>, R<sup>3</sup> are H or (un)substituted alkyl (with provisos)] was carried out, and the pharmaceutical significance in the treatment of Alzheimer's disease and related diseases was assessed.

**Activity:** These compounds showed -secretase enzyme inhibition activity.

**Origin:** Synthetic



#### 4. Propargyl-trifluoromethoxy-amino-benzothiazole derivatives with neuroprotective activity, and their preparation, pharmaceutical compositions, and use

Jeffrey, S., Liat, H., Eliezer, F., Yaacov, H. and David, L.

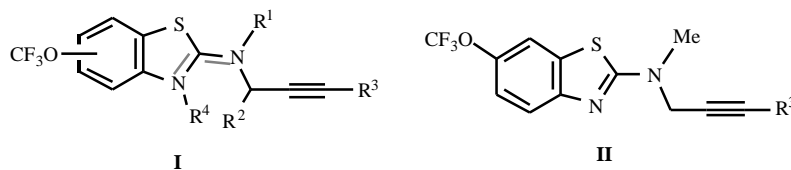
Yeva Pharmaceutical Industries, Ltd.; Teva Pharmaceutical USA, Inc.; Israel

PTC Int. Appl. WO 2004, 47, 756 (Cl. A61K), 10 Jun 2004, US Appl. 301, 540, 24 Nov. 2002; 78 pp; C.A. 141(3): 38603s

**Abstract:** Synthesis of propargyl-trifluoromethoxy-amino-benzothiazole derivatives with **I** [wherein R<sup>1</sup> is present or absent. and when present = H, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkynyl, (CH<sub>2</sub>)<sub>y</sub>S(CH<sub>2</sub>)<sub>x</sub>CH<sub>3</sub>, C<sub>1-6</sub> aminoalkyl C<sub>1-6</sub> hydroxyalkyl, or C<sub>1-6</sub> alkynyl, (CH<sub>2</sub>)<sub>n</sub> CO (C<sub>6</sub>H<sub>2</sub>) R<sup>2</sup>; R<sup>2</sup> = H or C<sub>1-4</sub> alkyl; R<sup>3</sup> = H or C<sub>1-4</sub> alkynyl, R<sup>4</sup> is present or absent, and when present = H, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkynyl, (CH<sub>2</sub>)<sub>y</sub>S(CH<sub>2</sub>)<sub>x</sub> CH<sub>3</sub>, C<sub>1-6</sub> aminoalkyl C<sub>1-6</sub> hydroxyalkyl, or (CH<sub>2</sub>)<sub>a</sub> CO(C<sub>6</sub>H<sub>4</sub>)(CH<sub>2</sub>)R<sup>2</sup>; n = 1-6 wherein x = 0-5, such that (x+y) < 6; at least one of R<sup>1</sup> or R<sup>4</sup> is present; dashed line = bond between one of two N atoms and the intervening C atom; and the compound is charged when both R<sup>1</sup>, R<sup>4</sup> and R<sup>4</sup> are present; including any specific enantiomer, or any pharmaceutically acceptable salt] together with their biological activities are described.

**Activity and bioassay:** Therapeutic effects of dose of any of these compounds to cure neurological disorders (Parkinson's disease, Alzheimer's disease, amyotrophic lateral sclerosis, stroke, neuromuscular disorders, schizophrenia, cerebral infarction, head trauma, glaucoma facialis and Huntington's disease), or multiple sclerosis are also monitored. **I** inhibited the proliferation of microbes. **II** was fully effective for the treatment of mice against mortality in an experimental allergic encephalomyelitis (EAE) model of multiple sclerosis at the dose of 10 mg/Kg, when given twice a day; **III** exhibited neuroprotective activity against MMP toxicity both *in vitro* (PC-12 cell) and *in vivo* (mice).

**Origin:** Synthetic



#### 5. Preparation of benzoxazinones as ligands for 5-HT1 receptors and their use in the treatment of CNS disorders, in particular serotonin-related disorders

Barbara, B., Manuela, B., Andrea, B., Mark, B. S., Enrice, G., Colin, L., Shalina, S., Luigi, S., Antonic, V. and Valeria, Z.

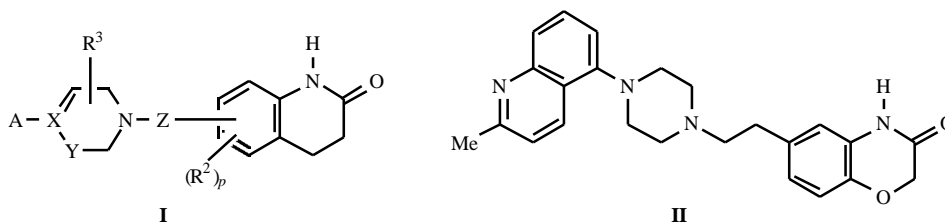
Glaxo Group Limited, UK

**PCT Int. Appl. WO 2004, 46, 124** (Cl. C07D265/36), 3 Jun 2004, GB Appl. 2002/27, 240, 21 Nov. 2002; 121 pp; C.A. 141(2): 23540v

**Abstract:** These compounds with formula **I** [wherein A = (un)substituted bicyclic 6,5 or 6,6 hetero/aromatic; R<sup>1</sup> = H halo/cyclo/cycloalkyl/aryl/alkyl, alkenyl, alkynyl; p = 0-2; R<sup>2</sup> = independently halo, halo/alkyl, CN alkanoyl, OH and derives.; R<sup>3</sup> = (R<sup>4</sup>)<sub>r</sub>; R<sup>4</sup> = halo/hydroxy/alkoxy/cyclo/alkyl, halo, halo/aryl/alkoxy, oxo, CN, NO<sub>2</sub>, alkylthio, alkoxy carbonyl, alkylsulfonyl, arylsulfonyl, alkylsulfonyl, alkylsulfonyl, arylsulfonyl, alkyl sulfonamido, aroyl, acyl, aryl, etc.; X = CH, N C; q = 0-2, with the proviso that when q = 0, X is not N; Z = attached to the 6-or 8-position of the benzoxazinone group, and is 3- to 7-membered cycloalkylene, cycloalkenylene, cycloalkenylene, or (CH<sub>2</sub>)<sub>n</sub>-Y-(CH<sub>2</sub>)<sub>m</sub>; m,n = independently 0-2; Y = single bond, 3- to 7-membered cycloalkenylene, CH:CH, C:O, C:(CH<sub>2</sub>), ,O, etc.; provided that when A = naphthyl,5,6,7,8 -tetrahydronaphthyl or 2,3-dihydroindene, Z is not-(CH<sub>2</sub>CH(OH))-,-(CH<sub>2</sub>CH<sub>2</sub>CH(OH))-,-(CH<sub>2</sub>C(:O)-); and their salts] were synthesized and screened for their biological activities as ligands for 5-HT1 receptor and/or inhibitors of serotonin reuptake.

**Activity and bioassays:** Some of these compounds of series **I** exhibited strong binding affinity for 5-HT1A, 5-HT1B, and 5-HT1D with pK<sub>i</sub> values in the range 8.0-10.0 in as radioligand assay; some showed potency at the uptake site of PIC<sub>50</sub> > 7.0, few are 5-HT1 antagonists, while others appeared to be inverse agonists, agonists or partial agonists using the [<sup>35</sup>S] GTP S functional assay (no data).

**Origin:** Synthetic



## 6. Preparation of phenylalkyl guanidines and isothiurea as nitric oxide synthase inhibitor

Yungen, X., Jingxin, Z., Weiye, H. and Dongha, Z.

China Pharmaceutical University, Peop. Rep. China

**Faming Zhuanli Shenqing Gongkai Shuomng Shu CN 1, 388, 118** (Cl. C07C335/32), 1 Jan. 2003 Appl, 2002, 113, 181, 18jun 2002; 10pp; C.A. 141(1): 6924f

**Abstract:** Syntheses of compounds with formula R<sup>1</sup> (CH<sub>2</sub>)<sub>n</sub> NHCR<sup>3</sup>: NR<sup>2</sup> (R<sup>1</sup>=Ph substituted Ph; R<sup>2</sup> = H or alkyl; R<sup>3</sup> = alkylthio NH<sub>2</sub>, alkylamino; 1-5) and their biological activities were carried out.

**Activity:** These compounds exhibited inhibition of enzyme nitric oxide synthase inhibition of enzyme nitric oxide and prevented septic shock enteritis, rheumatoid arthritis, cerebral ischemic injury, or Alzheimer's disease.

**Origin:** Synthetic

## 7. Preparation of N-oxides of heteroarylmethyl phenyl amines as phosphodiesterase 4 inhibitors

Richard, S. A., Doorly, G. E., Allen, H. T. and Ashok, T.

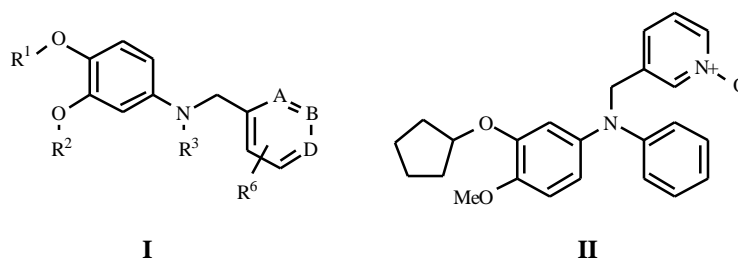
Memory Pharmaceutical Corporation, USA

**PCT Int. Appl. WO 2004, 46, 113** (Cl. C07D213/00), 3 Jun 2004, US Appl. PV427, 221, 19 Nov. 2002; 93 pp; C.A. 141(2): 23427p

**Abstract:** Syntheses of nitrogen oxides of compound **I** [one of A, B, D = NO and the others are CR<sup>6</sup>: R<sup>1-2</sup> = alkyl; R<sup>3</sup> = H cycloalkyl, etc.; R<sup>6</sup> = H halo, alkyl, alkoxy, CN, OH], compound **II** and derivatives were carried out in the current investigations.

**Activity:** These compounds inhibited PDE4 activity and are used to treat depression, Alzheimer's disease etc.

**Origin:** Synthetic



## 8. Preparation of phenylcarboxamide derivatives as $\beta$ -secretase inhibitors for the treatment of Alzheimer's disease

Craig, C. A., Shown, S. J. and Joseph, V. P.

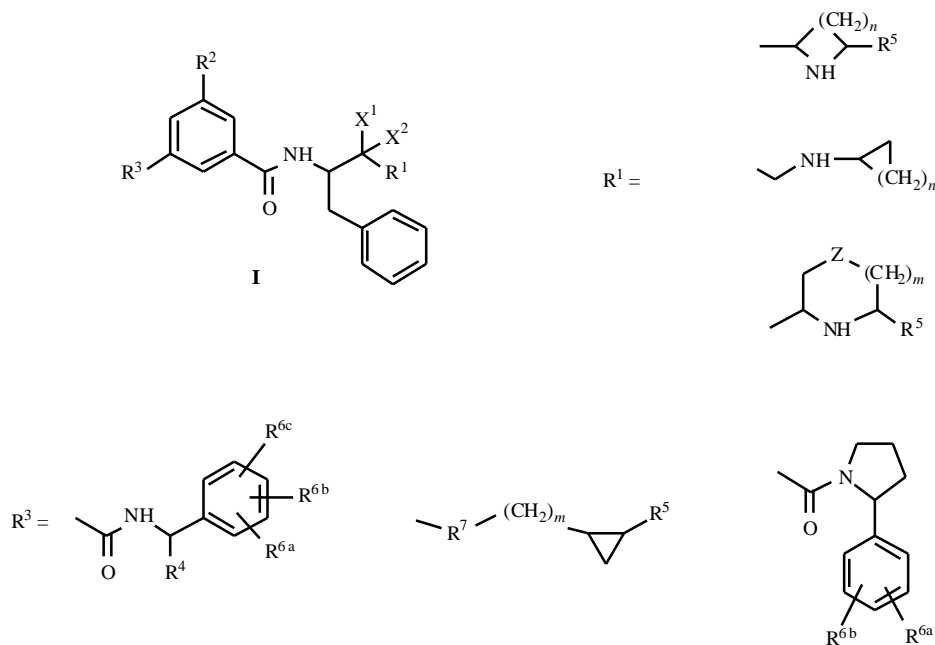
Merck & Co; Ine; USA

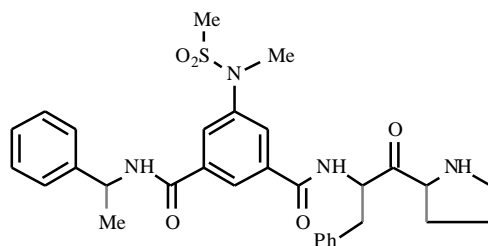
**PCT Int. Appl. WO 2004, 43, 916** (Cl. C07D207/00), 20 May 2004, US Appl. Pv 425,550, 12 Nov. 2002; 65pp. C.A. 141(1): 6920b

**Abstract:** Disclosed in the patent is syntheses of **I** [ $R^2 = R^4-S(O)_m-NR^5-R^4-S(O)_m-R^4NHCO-R^4CONH-R^4RH-R^4R^5N-CN$  halo etc.;  $R^4, R^5 = H, C_1-C_6$  alkyl, Ph or benzyl;  $R^{6a}, R^{6b}, R^{6c} = H, \text{halo}, -OR^5, -SR^5$  or  $C_1-C_6$  alkyl;  $X^1 = X; X^2 = OH$ , or  $X^1, X^2 = \text{oxo}; z$  prepd. as  $CO, CH-OH, CH-F$  or ethylene ketal;  $n = 1-4; m = 0-2$ ] and **II** possessing  $\beta$ -secretase inhibitors.

**Activity and bioassay:**  $IC_{50}$  ranging from 1 nM to 1  $\mu M$  was displayed for the inhibition of  $\beta$ -secretase enzyme by these compounds.

**Origin:** Synthetic





II

Web URL:

## 9. Structures of 1,4-benzodioxane derivatives from the seeds of *Phytolacca americana* and their neuritogenic activity in primary cultured rat cortical neurons

Hironobu, T., Kazue, Y., Masumi, U., Kousuke, N. and Yoshiya, F.

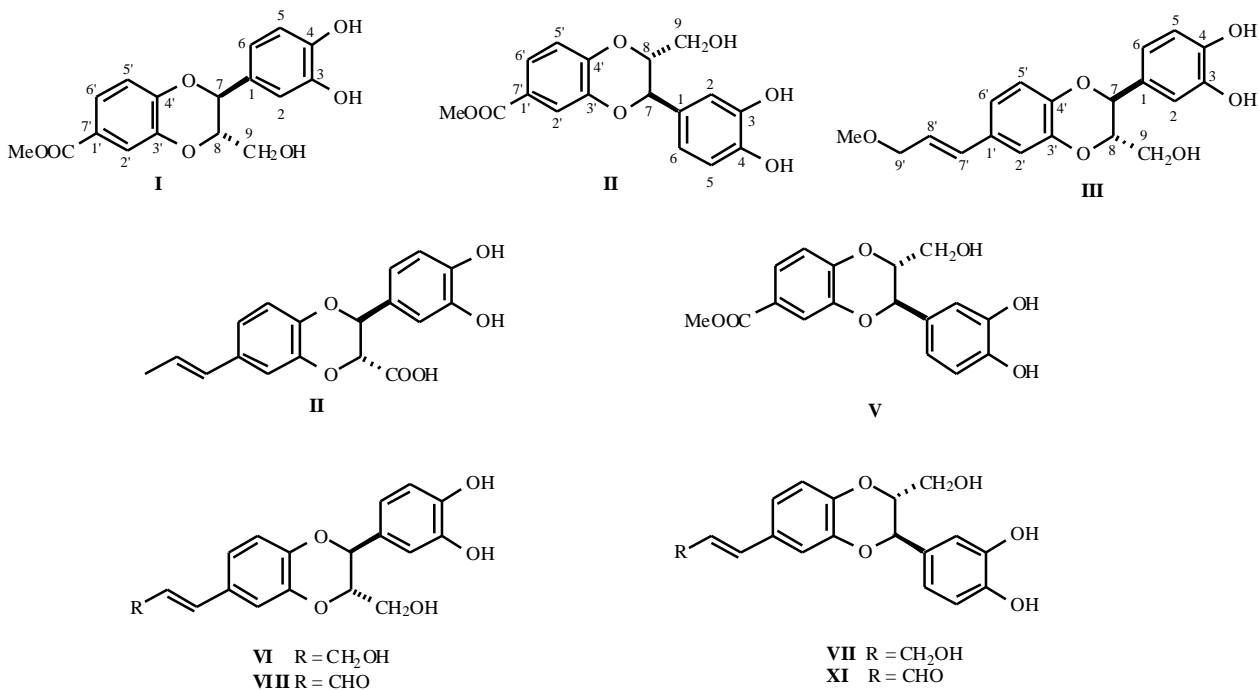
Institute of Pharmacognosy, Faculty of Pharmaceutical Sciences, Tokushima Bunri University, Tokushima, Japan 770-8514

*Chemical Pharmaceutical Bulletin* 2003, **51**(12), 1377-1381; *C.A.* **141**(1): 4105r

**Abstract:** Phytochemical studies on the methanolic extract of *Phytolacca americana* seeds resulted in the isolation and characterization of three new natural products incorporating 1,4-benzodioxane ring moiety, namely americanoic acid A Me ester (**I**), isoamericanoic acid A Me ester (**II**) and 9-*O*-methylamericanoic acid A (**III**). These new, along with previously reported americanin and isoamericanin-type dicarboxylic acids **IV** and **V**, were subjected to neuritogenic activity in primary cultured rat cortical neurons.

**Activity and bioassay:** Compounds **I-V** were tested for neurotrophic activity in primary culture rat neurons. **I** showed potent neurite outgrowth activity at 0.01  $\mu$ M. Compounds **IV** and **V** induced significant neuritogenesis by increasing the number of neurite branches at concentrations from 0.1  $\mu$ M to 10  $\mu$ M. Compound **IV** induced stronger activity of neuritogenesis than **V**. IC<sub>50</sub> values < 70 nM were observed by all compounds **I-IX**, when examined for antioxidant activity (DPPH and O<sub>2</sub><sup>-</sup>).

**Origin:** Natural product



**Web URL:** <http://www.worldcatlibraries.org>

**10. The neuroprotective effect of 2-(3-pyridyl)-1-azabicyclo[3.2.2]nonane (TC- 1698), a novel  $\alpha_7$  ligand, is prevented through angiotensin II activation of a tyrosine phosphatase**

Mario, M. B., Roger, P. L., Balwinder, B. S., Sean, S. and Merouane, B.

Department of Pharmacology and Toxicology, Vascular Biology Center, Medical College of Georgia, Augusta, GA, USA

*Journal of Pharmacology and Experimental Therapeutics* 2004, **309**(a), 16-27; *C.A.* **141**(2): 17427x

**Abstract:** Compound 2-(3-pyridyl)-1-azabicyclo[3.2.2]nonane designated as TC-1698 is a novel  $\alpha_7$ -selective agonist.

**Activity and bioassay:** It exerted neuroprotective effects by activation of the tyrosine-phosphorylated enzyme Janus kinase 2 phosphatidyl-inositol-3-kinase (JAK2/PI-3K) (PI-3-K) cascade. [JAK2 = tyrosine-phosphorylated enzyme Janus kinase; PI-3-K = 2 phosphatidyl-inositol-3-kinase], which can be neutralized through activation of the angiotensin II (Ang II)  $AT_2$  receptor. JAK2 is claimed to influence nicotinic  $\alpha_7$  receptor-induced activation of the JAK2-PI-3k cascade in PC12 cells, and in this way contributed to  $\alpha_7$  nicotinic acetylcholine receptor (nAChE).

**Origin:** Synthetic