

Patent Annotations:

GALANTHAMINE DERIVATIVES AND ANALOGS

1. **Total synthesis of galanthamine, analogues and derivatives thereof**, *Thal, C., Guillou, C., Beunard, J.-L., Gras, E., Potier, P., WO02102803A1 (2002)*.

Commentary:

This invention gives an account of the synthesis of galanthamine, their derivatives and analogs. Galanthamine compounds are used for treating neurological disorders such as Alzheimer's disease and are prepared by oxidizing α -ethylene ketone into corresponding spirodienones.

2. **Novel derivatives and analogues of galanthamine**, *Jordis, U., Frölich, J., Treu, M., Hirnschall, M., Czoller, L., Kalz, B., Welzig, S., WO0174820A1 (2001)*.

Commentary:

This invention relates to the preparation of novel derivatives and analogs of galanthamine. These novel acetyl and butyryl choline esterase derivatives and analogs are used for treating Alzheimer's disease, Parkinson's disease and epilepsy.

GABA ANALOGS

1. **Orally administered dosage forms of GABA analog prodrugs having reduced toxicity**, *Cundy, K.C., Gallop, M.A., US6833140B2 (2004)*.

Commentary:

Sustained release of oral dosage of GABA analog covalently linked with the promoiety from the prodrug is claimed in this invention for the treatment of epilepsy.

2. **Prodrugs of GABA analogs, compositions and uses thereof**, *Gallop, M.A., Cundy, K.C., Zhou, C.X., Yao, F., Xiang, J.N., US6818787 (2004)*.

Commentary:

The invention relates to the preparation and different therapeutic compositions of prodrugs of GABA analogs. These prodrugs attached with the promoiety are used for the prevention of epilepsy.

3. **Mono- and disubstituted 3-propyl gamma-aminobutyric acids**, *Belliotti, T.R., Bryans, J.S., Ekhato, I.V., Osuma, A.T., Schelkun, R.M., Schwarz, J.B., Thorpe, A.J., Wise, L.D., Wustrow, D. J., Yuen, P.-W., US6642398B2 (2003)*; **Gamma aminobutyric acid analogs**, *Belliotti, T.R., Wustrow, D.J., US6627771B1 (2003)*.

Commentary:

Preparation and the usage of novel mono- and disubstituted 3-propyl gamma aminobutyric acids acting as GABA agonists are described. The compounds serve as therapeutic agents in the treatment of neurodegenerative

disorders, depression, anxiety, panic, pain, neuropathological disorders, arthritis, sleep disorders, IBS, gastric damage, epilepsy, faintness attacks, hypokinesia and cranial disorders. The process for the synthesis of intermediates is also discussed.

4. **3-Heteroarylalkyl substituted GABA analogs**, *Yuen, P.W., US6833385B2 (2004)*.

Commentary:

Epilepsy, faintness attacks, neurodegenerative disorders, Parkinson's disease, depression, anxiety, panic, pain, neuropathological disorders, gastrointestinal disorders such as irritable bowel syndrome (IBS), and inflammation, especially arthritis are treated with pharmaceutical compositions comprising 3-heteroarylalkyl substituted gamma-aminobutyric acid derivatives. Methods for the synthesis of the intermediates and novel 3-heteroarylalkyl substituted GABA analogs are discussed in the present invention.

BIOMOLECULAR BASIS OF DEPRESSION

1. **Use of tianeptine in the production of medicaments to treat neurodegenerative pathologies**, *Deslandes, A., Spedding, M., US6599896 (2003)*.

Commentary:

The present invention describes the preparation and usage of tianeptine, tianeptine enantiomers and its salts in the treatment of neurodegenerative disorders i.e. cerebral ischemia, cerebral traumatism, cerebral aging trauma, Alzheimer's disease, multiple sclerosis, plate sclerosis and amyotrophic lateral sclerosis, demyelating pathologies, encephalopathies, chronic fatigue syndrome, myalgic encephalomyelitis post-viral fatigue syndrome, the state of fatigue following a bacterial or viral infection, and the dementia syndrome of AIDS.

ASTROCYTIC GABA_A/BENZODIAZEPINE-LIKE RECEPTOR

1. **Imidazopyrimidines and triazolo-pyrimidines : benzodiazepine receptor ligands**, *Xi, L., Han, B., Xu, Y., Maynard, G., Chenard, B., Shaw, K., Gao, Y., WO05012306A2 (2005)*.

Commentary:

The invention presents application and preparation of imidazopyrimidines and triazolopyrimidines: benzodiazepine receptor ligands for the prevention of anxiety, depression, sleep disorder, attention deficit disorder, Alzheimer's dementia and short-term memory loss disorders in humans, livestock and domesticated companion animals. These imidazopyrimidines and triazolopyrimidines can be used alone or in combination with one or more central nervous system agents or without combination. The identification of GABA receptors is also discussed.

GLYCINE TRANSPORTER INHIBITORS

1. **Glyt1 transporter inhibitors and uses thereof in treatment of neurological and neuropsychiatric disorders**, *Coulton, S., Hadley, M.S., Herdon, H.J., Jin, J., Joiner, G.J., Porter, R.A., Rahman, S.S., WO03055478 (2003)*.

Commentary:

The present invention outlines the process of preparation of sulfonamide compounds useful for the cure of disorders caused by actions of glycine transporter 1, such as depression or Alzheimer's disease.

2. **Derivatives of N-[phenyl(piperidin-2-yl)methyl] benzamide, the preparation method thereof and application of same in therapeutics**, *Dargazanli, G., Estenne, B.G., Magat, P., Marabout B., Medaisko, F., Roger, P., Sevrin, M., Veronique, C., WO03089411 (2003)*.

Commentary:

The invention involves different compositions of glyt1 and/or glyt2 glycine transporter inhibitors comprising N-(piperidinyl-benzyl)-trifluoromethyl-benzamides. These compounds with different substituents are used for the cure of schizophrenia, depression, muscle spasms, pain or epilepsy.

3. **Piperidine-benzenesulfonamide derivatives**, *Albertati-Giani, D., WO2004072034 (2004)*.

Commentary:

The invention describes the piperidine-benzene-sulfonamide derivatives containing different substituents. These new compounds act as glycine uptake inhibitors for the treatment of psychoses, pain, dysfunction in memory and learning, schizophrenia, dementia, attention deficit disorders and Alzheimer's disease.

DEPRESSION AND ANXIETY DISORDERS

1. **Metabotropic glutamate receptor-5 modulators**, *Munoz, B., Stearns, B., Vernier, J.-M., Wang, B., Bonnefous, C., Zhao, X., Arruda, J., Campbell, B.T., Cube, R.V., WO03048137 (2003)*.

Commentary:

The invention provides fused heterobicyclo substituted phenyl compounds with a fused bicyclo moiety. The fused bicyclo moiety is obtained from a five-membered heterocycle fused to a six-membered carbocycle, to a six-membered aryl, or to a six-membered heteroaryl and a pharmaceutically acceptable carrier. The mGluR5 modulators are beneficial for the treatment of psychiatric and mood disorders i.e. schizophrenia, anxiety, depression, and panic, pain and other diseases.

2. **Imidazol-4-yl-ethynyl-pyridine derivatives**, *Buettelmann, B., Ceccarelli, S.M., Jaeschke, G., Kolczewski, S., Porter, R.H.P., Vieira, E., WO2004080998 (2004)*.

Commentary:

The invention is directed to the usage of 4-(1-(hetero)aryl-imidazol-4-ylethynyl)-2-alkyl-pyridine derivatives for

the cure of disorders partially or fully mediated by metabotropic glutamate receptor 5 in acute, traumatic and chronic degenerative processes of the nervous system, i.e. Alzheimer's disease, senile dementia, Parkinson's disease, Huntington's chorea, amyotrophic lateral sclerosis and multiple sclerosis, psychiatric diseases such as schizophrenia and anxiety, depression, pain and drug dependency.

3. **Modulators of melanocortin receptor**, *Vos, T.J., Patane, M., Solomon, M.E., Blackburn, C., Danca, M.D., WO2004050610A2 and WO2004050610A3 (2004)*.

Commentary:

The invention relates to the preparation of amine compounds acting as melanin receptor antagonists used for the treatment of MC4-R associated disorders i.e. weight loss disorders including cachexia resulting from cancer and other chronic illnesses. e.g. catabolic wasting, anorexia, pain and neuronal disorder.

4. **Substituted spirobenzazepines**, *Patel, M., Rybczynski, P.J., Xiang, M.A., WO2005037795A3 (2005) and WO2005037795A2 (2005)*.

Commentary:

In this invention substituted spirobenzazepine compounds, vasopressin receptor antagonists, are claimed to be useful for the treatment of hypertension, congestive heart failure, cardiac insufficiency, hyponatremia, inner ear disorders and coronary vasospasm, cardiac ischemia, liver cirrhosis, hyponatremia, renal vasospasm, renal failure, diabetic nephropathy, cerebral edema, cerebral ischemia, stroke, thrombosis, or water retention.

5. **Phenyl pyrrolidine ether tachykinin receptor antagonists**, *Devita, R.J., Mills, S.G., Young, J.R., Lin, P., WO2005032464A3 and WO2005032464A2 (2005)*.

Commentary:

Phenyl pyrrolidine ether compounds and their formulations are claimed to be useful as neurokinin-1 (NK-1) receptor antagonists and tachykinin inhibitors including substance P for prevention of diseases such as emesis, depression and anxiety.

6. **NK1 antagonist**, *Wager, T.T., Welch, W.M. Jr. O'Neill, B.T., WO2004110996A1 (2004)*.

Commentary:

Neurokinin 1 antagonists comprising piperidinyl and pyrrolidinyl amide compounds reveal neurokinin inhibitory properties and are used for the cure of hemorrhoids, nausea, vomiting, pain and Alzheimer's disease. The antagonist to tachykinins include substance P and other neurokinins (NK) for the treatment of neurokinin-mediated conditions.

7. **Spiro-substituted tetrahydroquinazolines as corticotropin releasing factor (CFR) antagonists**, *Clark, R.D., WO2005013997 (2005)*.

Commentary:

The present invention encompasses the treatment of stress-related illnesses, mood disorders, eating disorders and

neurodegenerative diseases by spiro-substituted tetrahydroquinazoline derivatives. The process for the preparation of spiro-substituted tetrahydroquinazoline compounds and the compositions is also described.

- Dihydrobenzodiazepin-2-one derivatives for the treatment of neurological disorders**, Adam, G., Goetschi, E., Wichmann, J., Woltering, T.J., WO03066623 (2003).

Commentary:

The invention discloses preparation of dihydrobenzo (b) (1,4) diazepin-2-one derivatives and their use in the treatment of acute and chronic neurological disorders i.e. psychosis, schizophrenia, opiate addiction, nicotine addiction, anxiety and Alzheimer's disease.

- Novel benzothiazine derivatives, their preparation and use**, Goulijev, A.H., Larsen, M., Verming, T., Mathiesen, C., Johansen, T.H., Nielsen, K.S., Hartz, B., Scheel-Kruger, J., WO03031422A1 (2003).

Commentary:

Formulations of benzothiazine derivatives beneficial as modulators of the AMPA sensitive glutamate receptors for the cure of Alzheimer's disease, senile dementia, schizophrenia, stroke and depression are discussed.

VOLTAGE-GATED SODIUM CHANNEL BLOCKERS

- Aryl substituted pyrimidines**, Hogenkamp, D.J., Nguyen, P., Shao, B., US6867210 (2005).

Commentary:

The invention describes formulation of aryl substituted pyridines, pyrimidines, pyrazines or triazines compounds for usage in the prevention or treatment of neuronal damage following global and focal ischemia, neurodegenerative conditions i.e. amyotrophic lateral sclerosis (ALS), either acute or chronic pain, as antitinnitus agents, as anti-convulsants, as antimanic depressants, as local anesthetics and as antiarrhythmics and prevention of diabetic neuropathy.

- Sodium channel modulators**, Choi, S.K., Fatheree, P.R., Green, D.C., Marquess, D., US6646012 (2003).

Commentary:

Therapeutic composition and method of administration of sodium channel modulating compounds comprising aminophenol derivatives are discussed. Their role in the treatment of disorders related to sodium channel activity e.g. neuropathic pain in human is also discussed.

- Carbocyclic and heterocyclic substituted semicarbazones and thiosemicarbazones and the use thereof**, Wang, Y., Cai, S.X., Lan, N. C., Keana, J.F.W., Ilyin, V.I., Weber, E., US6613803 (2003).

Commentary:

The present invention provides formulation of carbocyclic and heterocyclic substituted semicarbazones and thiosemicarbazones to cure diseases responsible for blocking

sodium channels i.e. arrhythmia and neuronal damage following global and focal ischemia. These compounds are also used in the prevention of neurodegenerative conditions such as amyotrophic lateral sclerosis (ALS), for the treatment and prevention of otoneurotoxicity and eye diseases involving glutamate toxicity and for the treatment, prevention or amelioration of pain, as anticonvulsants, and as antimanic depressants, as local anesthetics and for the treatment or prevention of diabetic neuropathy and urinary incontinence.

REPAIR OF THE DAMAGED SPINAL CORD

- Method for inducing partial recovery of lost voluntary motor function after spinal cord injury in a mammal**, Tuszynski, M.H., Grill, R., Gage, F.H., US6167888 (2001).

Commentary:

This invention describes a method for slight recovery of the lost motor function as a result of spinal cord injury involving lesion of the cerebrospinal projections (CST) of the cord in mammals, with the help of recombinant vector for expressing CST neurotrophin by administering neurotrophin-3 to the site.

- Neurite growth regulatory factors**, Schwab, M.E., Caroni, P.W., Paganetti, P.A., US6103232 (2000).

Commentary:

The invention provides an account of enhancing neurite growth of nerve fibers in spinal cord lesions by inhibiting neural growth inhibitory factors. The antibodies are used for the identification and also as a therapeutic agent for malignant tumors, nerve damage from trauma, infarction and degenerated central nervous system diseases.

- Nucleotide and protein sequences of Nogo genes and methods based thereon**, Schwab, M.E., Chen, M.S., EP1124846A2 (2001) and EP1124846A4 (2002).

Commentary:

Nogo proteins and nucleic acids are useful for treating neoplastic disorders of the central nervous system and inducing regeneration of neurons.

- Nogo receptor-mediated blockade of axonal growth**, Strittmatter, S.M., US20020012965A1 (2002), US20020077295A1 (2002), EP1248803A2 (2002), EP1451337A2 (2004) and US20050048520A1 (2005); **Nogo receptor homologs**, Strittmatter, S.M., Cate, R.L., Sah, D.W.Y., US20030124704A1 (2003).

Commentary:

The present invention encompasses the composition and usage of genes that encode and modulate the expression of NgR protein homologs, peptides and antibodies for the prevention of axonal growth. Central nervous system disorder, cerebral and cranial trauma injury, spinal cord injury, stroke, and demyelinating diseases are treated with Nogo receptor homolog polypeptide, NgR2 or NgR3 and NgR proteins.

5. **Compositions and methods using myelin-associated glycoprotein (MAG) and inhibitors thereof**, *Filbin, M.T.*, US6399577 (2002).

Commentary:

The invention relates to the compositions containing inhibitor of myelin-associated glycoprotein (MAG), screening methods and assays for monitoring / diagnosis and methods for regulating and enhancing neural growth or regeneration in the nervous system. These compositions are helpful for reversing inhibition of neural regeneration in the central and peripheral nervous system. Treatment of injuries or damage to nervous tissue or neurons is also discussed.

6. **Reducing myelin-mediated inhibition of axon regeneration**, *He, Z., Wang, K.C., Koprivica, V., Kim, J.A.*, US20030113325A1 (2003) and US20030113326A1 (2003).

Commentary:

The invention claims that oligodendrocyte-myelin glycoprotein (OMgp)-specific binding agents are used to reduce OMgp-mediated axon growth inhibition. A combination of Nogo receptor (NgR) and OMgp is used for the identification of agents that are involved in the inhibition of OMgp-specific binding agents or OMgp inhibitors.

7. **Treatment of central nervous system damage**, *McMahon, S.B., Bradbury, E.J., Fawcett J.*, EP1480674A1 (2004); Schwann cell bridge implants and phosphodiesterase inhibitors to stimulate CNS nerve regeneration, *Bunge, M.B., Pearse, D.D.*, US20030220280A1 (2003).

Commentary:

Cyclic nucleotide phosphodiesterase inhibitor and its formulations are administered for the treatment of injuries related to the animal's central nervous system. Intracellular levels of cyclic nucleotide cyclase are increased by the administration of cyclic nucleotide cyclases in combination with phosphodiesterase inhibitors, and cell implant restores their function after this CNS injury.

8. **Olfactory ensheathing cells isolated from the lamina propria**, *Feron, F., Mackay-Sim, A.*, CA2389121AA (2001), AU0111181A5 (2001), EP1235902A1 (2002), US20020127716A1 (2002), AU0770354B2 (2004) and AU4201972AA (2004).

Commentary:

The present invention is related to the isolation of ensheathing cells from olfactory mucosa. Ensheathing cells which facilitate nerve regeneration by separating lamina propria.

9. **Reversibly immortalised olfactory ensheathing glia and their use to promote neuronal regeneration**, *Moreno-Flores, M. T., Martín-Bermejo, M. J., Ávila, J., Wandosell, J.F., Díaz-Nido, J., Lim, F., Pastrana, I.E.*, WO05012513A1 (2005); Olfactory ensheathing cells (OECs) in an extra-cellular matrix for use in axon regeneration, *Raisman, G., Li Y.*, WO04015102A1 (2004) and AU3249092AA (2004).

Commentary:

The present invention describes the formulations comprising reversibly- or reverse-immortalized olfactory ensheathing glia (OEG) cells, which are in an extracellular matrix (ECM) and their usage in boosting neuronal regeneration and prevention of neural damage in the adult mammalian central nervous system.

10. **Olfactory ensheathing glia produced by introducing telomerase**, *Rubio-Rodríguez, M. P., Ramón-Cueto, M. A., Blasco-Marhuenda, M. A.*, WO02088337A1 (2002), WO02088337B1 (2003) and WO02088337C2 (2004).

Commentary:

Central nervous system lesions in mammals, including primates, are treated with olfactory ensheathing glia produced using telomerase or cells derived from telomerase, either in combination or alone.