METHODS AND COMPOSITIONS FOR STIMULATING NEURITE GROWTH

TECHNICAL FIELD OF THE INVENTION

The present invention relates to methods and pharmaceutical compositions for stimulating the growth of neurites in nerve cells. The compositions comprise a neurotrophic amount of a compound which binds to the FK-506 binding protein (FKBP) and a neurotrophic factor, such as nerve growth factor NGF. The methods comprise treating nerve cells with the above-described compositions or compositions comprising the FKBP binding compound without a neurotrophic factor. The methods of this invention can be used to promote repair of neuronal damage caused by disease or physical trauma.

BACKGROUND OF THE INVENTION

Immunophilins are a family of soluble proteins that mediate the actions of immunosuppressant drugs such as cyclosporin A, FK506 and rapamycin. Of particular interest is the 12 kDa immunophilin, FK-506 binding protein (FKBP12). FKBP12 binds FK-506 and rapamycin, leading to an inhibition of T-cell activation and proliferation. Interestingly, the mechanism of action of FK-506 and rapamycin are different. For review, see, S. H. Solomon et al., Nature Med., 1, pp. 32-37 (1995).

FK-506 binds to FKBP12 and the resulting complex binds to and inhibits calcineurin, a cytoplasmic phosphatase. The phosphatase activity of calcineurin is necessary for dephosphorylation and subsequent translocation into the nucleus of the transcription factor NF-AT. NF-AT causes interleukin-2 gene activation which in turn mediates T-cell proliferation.

The rapamycin-FKBP12 complex, on the other

hand, associates with a protein of unknown function, termed RAFT1/FRAP. This tripartite complex is known to inhibit various kinases in the cell (i.e., p70S6, p34cdc2, cdk2) which are necessary for cell cycle progression in T-cells. Rapamycin is also known to be a potent antagonist of FK-506, presumably by acting as a competitive inhibitor for the FKBP12 binding.

More recently, it has been discovered that FKBP plays other important roles in the body. It has been found that FKBP12 forms a complex with the intracellular calcium ion channels -- the ryanodine receptor (RyR) and the inositol 1,4,5-triphosphate receptor (IP_3R) [T. Jayaraman et al., J. Biol. Chem., 267, pp. 9474-77 (1992); A. M. Cameron et al., Proc. Natl. Acad. Sci. USA, 92, pp. 1784-44 (1995)], helping to stabilize calcium release. The ryanodine receptor has been found in skeletal muscle, cardiac muscle, brain and other excitable tissues. IP_3R mediates intracellular calcium release elicited by hormones and neurotransmitters that act at the cell surface to activate phospholipase C and generate inositol 1,4,5-triphophase (IP_3). Most IP_3R is found associated with the endoplasmic reticulum, but some may occur on the cell surface and mediate calcium flux into the cell.

For both the RyR and the IP_3R, it has been demonstrated that FK506 and rapamycin are capable of dissociating FKBP12 from the receptor. In each case, the "stripping" off of FKBP12 leads to increased leakiness of the calcium channel and lower intracellular calcium concentrations.

Another role of FKBP12 is the regulation of neurite outgrowth in nerve cells. W. E. Lyons et al. [Proc. Natl. Acad. Sci. USA, 91, pp. 3191-95 (1994)] demonstrated that FK506 acts synergistically with nerve growth factor (NGF) in stimulating neurite outgrowth in a

rat pheochromocytoma cell line. Interestingly, rapamycin did not inhibit the effects of FK-506 on neurite outgrowth, but rather was neurotrophic itself, displaying an additive effect with FK-506. In sensory ganglia, FK-506 demonstrated similar neurotrophic effects, but those effects were blocked by rapamycin. These results led the authors to speculate that FK-506 was exerting its neurotrophic effect through its complexing with FKBP12 and calcineurin and inhibition of the latter's phosphatase activity. Alternatively, the authors proposed FK-506 was acting via a "stripping" mechanism, such as that involved in the removal of FKBP12 from RyR and IP_3R.

In view of the wide variety of disorders that may be treated by stimulating neurite outgrowth and the relatively few FKBP12-binding compounds that are known to possess this property, there remains a great need for additional neurotrophic, FKBP12-binding compounds.

SUMMARY OF THE INVENTION

Applicant has solved the problem referred to above by discovering that two genera of novel FKBP12-binding compounds he had previously co-invented also possess neurotrophic activity. Applicant had previously described a series of acylated amino acid derivatives which bind to FKBP12 in PCT patent publications WO 92/19593 and WO 94/07858. Another series of FKBP12 ligands are described in applicant's United States Patents 5,192,773 and 5,330,993 and PCT patent publication WO 92/00278. Each series of compounds stimulate neurite outgrowth in the presence of exogenous or endogenous NGF.

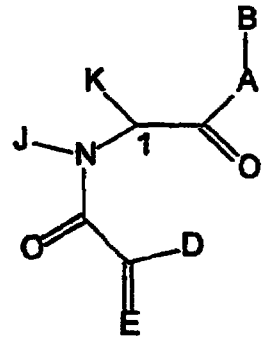
The compositions provided comprise a compound from one of the two genera described above and a neuronal

growth factor. The methods described herein employ those previously described compounds and compositions comprising them to effectuate neurite outgrowth are useful to treat nerve damage caused by various diseases and physical traumas.

DETAILED DESCRIPTION OF THE INVENTION

According to one embodiment, the present invention provides pharmaceutical compositions which comprise:

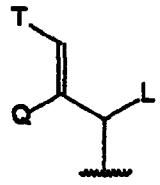
a) a compound with affinity for FKBP12 having the formula (I):



(I)

and pharmaceutically acceptable derivatives thereof, wherein A in O, NH, or N-(C1-C4 alkyl);

wherein B is hydrogen, CHL-Ar, (C1-C6)-straight or branched alkyl, (C2-C6)-straight or branched alkenyl, (C5-C7)-cycloalkyl, (C5-C7)-cycloalkenyl or Ar substituted (C1-C6)-alkyl or (C2-C6)-alkenyl, or



wherein L and Q are independently hydrogen, (C1-C6)-straight or branched alkyl or (C2-C6)-straight or branched alkenyl;

wherein T is Ar or substituted cyclohexyl with substituents at positions 3 and 4 which are independently selected from the group consisting of hydrogen, hydroxyl, O-(C1-C4)-alkyl or O-(C2-C4)-alkenyl and carbonyl;

wherein Ar is selected from the group consisting of 1-naphthyl, 2-naphthyl, 2-furyl, 3-furyl, 2-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl and phenyl having one to three substituents which are independently selected from the group consisting of hydrogen, halo, hydroxyl, nitro, CF_3, (C1-C6)-straight or branched alkyl or (C2-C6)-straight or branched alkenyl, O-(C1-C4)-straight or branched alkyl or O-((C2-C4)-straight or branched alkenyl), O-benzyl, O-phenyl, amino and phenyl;

wherein D is U; E is either oxygen or CH-U, provided that if D is hydrogen, then E is CH-U or if E is oxygen then D is not hydrogen;

wherein each U is independently selected from hydrogen, O-(C1-C4)-straight or branched alkyl or O-((C2-C4)-straight or branched alkenyl), (C1-C6)-straight or branched alkyl or (C2-C6)-straight or branched alkenyl, (C5-C7)-cycloalkyl or (C5-C7)-cycloalkenyl substituted with (C1-C4)-straight or branched alkyl or (C2-C4)-straight or branched alkenyl, 2-indolyl, 3-indolyl, [(C1-C4)-alkyl or (C2-C4)-alkenyl]-Ar or Ar;

wherein J is hydrogen or C1 or C2 alkyl; K is (C1-C4)-straight or branched alkyl, benzyl or cyclohexylmethyl; or wherein J and K may be taken together to form a 5-7 membered heterocyclic ring which may contain an O, S, SO or SO_2 substituent therein;

wherein the stereochemistry at carbon position 1 is R or S;

b) a neurotrophic factor; and

c) a pharmaceutically suitable carrier.

More preferably, in the compound with affinity for FKBP12 in these pharmaceutical compositions:
A is oxygen; J is hydrogen or C1 or C2 alkyl; K is (C1-C4)-straight or branched alkyl, benzyl or cyclohexylmethyl; or J and K are taken together to form pyrrolidyl or piperidyl; and the stereochemistry at carbon position 1 is S.

In the above preferred compounds wherein J and K are taken together to form pyrrolidyl or piperidyl and E is CH-U, U is preferably dimethylaminophenyl, methoxyphenyl, dimethoxyphenyl, trimethoxyphenyl, nitrophenyl, furyl, indolyl, pyridyl, or methylenedioxyphenyl.

In the above preferred compounds wherein J and K are taken together to form pyrrolidyl or piperidyl and E is oxygen:
B is preferably benzyl, naphthyl, tert-butyl, hydrogen, E-3-phenyl-2-methyl-prop-2-enyl, E-3-(4-hydroxyphenyl) 2-methyl-prop-2-enyl, E-3-[trans(4-hydroxycyclohexyl)]-2-methyl-prop-2-enyl, cyclohexylethyl, cyclohexylpropyl, cyclohexylbutyl, cyclopentylopropyl, E-3-(4-methoxyphenyl)-2-methyl-prop-2-enyl, E-3-(3,4-dimethoxyphenyl)-2-methyl-prop-2-enyl or E-3-[cis(4-hydroxycyclohexyl)]-2-methyl-prop-2-enyl; and D is preferably phenyl, methoxyphenyl, cyclohexyl, ethyl, methoxy, nitrobenzyl, thiophenyl, indolyl, furyl,

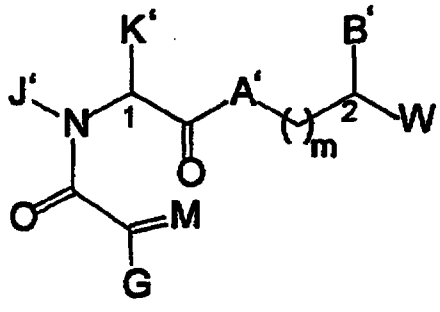
pyridyl, pyridyl-N-oxide, nitrophenyl, fluorophenyl, trimethoxyphenyl or dimethoxyphenyl.

The most preferred compounds of formula (I) useful in the compositions and methods of this invention are those of formulae Ia, Ib, Ic and Id, listed in Tables 1a through 1d, respectively, set forth in Example 1, below.

The synthesis of compounds of formula (I) with affinity for FKBP12 in these compositions is described in United States Patents 5,192,773 and 5,330,993 and PCT patent publication WO 92/00278, the disclosures of which are herein incorporated by reference.

According to an alternate embodiment, the present invention provides pharmaceutical compositions which comprise:

a) a compound with affinity for FKBP12 having the formula (II):



(II)

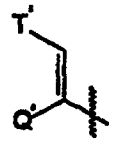
and pharmaceutically acceptable derivatives thereof,

wherein A' is CH_2, oxygen, NH or N-(C1-C4 alkyl);

wherein B' and W are independently:

(i) hydrogen, Ar', (C1-C10)-straight or branched alkyl, (C2-C10)-straight or branched alkenyl or alkynyl, (C5-C7)-cycloalkyl substituted (C1-C6)-straight or branched alkyl, (C2-C6)-straight or branched alkenyl or alkynyl, (C5-C7)-cycloalkenyl substituted

(C1-C6)-straight or branched alkyl, (C2-C6)-straight or branched alkenyl or alkynyl, or Ar' substituted (C1-C6)-straight or branched alkyl, (C2-C6)-straight or branched alkenyl or alkynyl wherein, in each case, any one of the CH_2 groups of said alkyl, alkenyl or alkynyl chains may be optionally replaced by a heteroatom selected from the group consisting of O, S, SO, SO_2, N, and NR, wherein R is selected from the group consisting of hydrogen, (C1-C4)-straight or branched alkyl, (C2-C4)-straight or branched alkenyl or alkynyl, and (C1-C4) bridging alkyl wherein a bridge is formed between the nitrogen and a carbon atom of said heteroatom-containing chain to form a ring, and wherein said ring is optionally fused to an Ar' group; or



(ii)

wherein Q' is hydrogen, (C1-C6)-straight or branched alkyl or (C2-C6)-straight or branched alkenyl or alkynyl;

wherein T' is Ar' or substituted 5-7 membered cycloalkyl with substituents at positions 3 and 4 which are independently selected from the group consisting of oxo, hydrogen, hydroxyl, O-(C1-C4)-alkyl, and O-(C2-C4)-alkenyl;

wherein Ar' is a carbocyclic aromatic group selected from the group consisting of phenyl, 1-naphthyl, 2-naphthyl, indenyl, azulenyl, fluorenyl, and anthracenyl; or a heterocyclic aromatic group selected from the group consisting of 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrrolyl, oxazolyl, thiazolyl,

imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, 1,2,3-oxadiazolyl, 1,2,3-triazolyl, 1,3,4-thiadiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,3,5-triazinyl, 1,3,5-trithianyl, indolizinyl, indolyl, isoindolyl, 3H-indolyl, indolinyl, benzo[b]furanyl, benzo[b]thiophenyl, 1H-indazolyl, benzimidazolyl, benzthiazolyl, purinyl, 4H-quinolizinyl, quinolinyl, isoquinolinyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, 1,8-naphthyridinyl, pteridinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, and phenoxazinyl;

wherein Ar' may contain one to three substituents which are independently selected from the group consisting of hydrogen, halogen, hydroxyl, hydroxymethyl, nitro, trifluoromethyl, trifluoromethoxy, (C1-C6)-straight or branched alkyl, (C2-C6)-straight or branched alkenyl, O-[(C1-C4)-straight or branched alkyl], O-[(C2-C4)-straight or branched alkenyl], O-benzyl, O-phenyl, 1,2-methylenedioxy, amino, carboxyl, N-[(C1-C5)-straight or branched alkyl or (C2-C5)-straight or branched alkenyl)carboxamides, N,N-di-[(C1-C5)-straight or branched alkyl or (C2-C5)-straight or branched alkenyl)]carboxamides, N-morpholinocarboxamide, N-benzylcarboxamide, N-thiomorpholinocarboxamide, N-picolinoylcarboxamide, O-X, CH_2-$(CH_2)_q$-X, O-$(CH_2)_q$-X, $(CH_2)_q$-O-X, and CH=CH-X;

wherein X is 4-methoxyphenyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrazyl, quinolyl, 3,5-dimethylisoxazoyl,

isoxazoyl, 2-methylthiazoyl, thiazoyl, 2-thienyl, 3-thienyl, or pyrimidyl; and

q is 0-2;

wherein G is U';

M is either oxygen or CH-U';

provided that if G is hydrogen, then M is CH-U' or if M is oxygen, then G is U';

wherein U' is hydrogen, O-[(C1-C4)-straight or branched alkyl] or O-[(C2-C4)-straight or branched alkenyl], (C1-C6)-straight or branched alkyl or (C2-C6)-straight or branched alkenyl, (C5-C7)-cycloalkyl or (C5-C7)-cycloalkenyl substituted with (C1-C4)-straight or branched alkyl or (C2-C4)-straight or branched alkenyl, [(C1-C4)-alkyl or (C2-C4)-alkenyl]-Y or Y;

wherein Y is selected from the group consisting of phenyl, 1-naphthyl, 2-naphthyl, indenyl, azulenyl, fluorenyl, anthracenyl, 2-pyrrolinyl, 3-pyrrolinyl, pyrolidinyl, 1,3-dioxolyl, 2-imidazolinyl, imidazolidinyl, 2H-pyranyl, 4H-pyranyl, piperidyl, 1,4-dioxanyl, morpholinyl, 1,4-dithianyl, thiomorpholinyl, piperazinyl, quinuclidinyl, and heterocyclic aromatic groups as defined for Ar' above;

wherein Y may contain one to three substituents which are independently selected from the group consisting of hydrogen, halogen, hydroxyl, hydroxymethyl, nitro, trifluoromethyl, trifluoromethoxy, (C1-C6)-straight or branched alkyl, (C2-C6)-straight or branched alkenyl, O-[(C1-C4)-straight or branched alkyl], O-[(C2-C4)-straight or branched alkenyl], O-benzyl, O-phenyl, 1,2-methylenedioxy, amino, and carboxyl;

wherein J' is hydrogen, (C1-C2) alkyl or benzyl;

K is (C1-C4)-straight or branched alkyl, benzyl or cyclohexylmethyl, or wherein J' and K may be taken together to form a 5-7 membered heterocyclic ring which may contain a heteroatom selected from the group consisting of O, S, SO and SO_2; and

wherein m is 0-3;

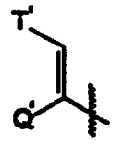
b) a neurotrophic factor; and

c) a pharmaceutically suitable carrier. The compounds of formula (II) exclude any compounds of formula (I).

More preferably, in the compound with affinity for FKBP12 in these pharmaceutical compositions:

B' and W are independently:

(i) hydrogen, Ar', (C1-C10)-straight or branched alkyl, (C2-C10)-straight or branched alkenyl or alkynyl, (C5-C7)-cycloalkyl substituted (C1-C6)-straight or branched alkyl, (C2-C6)-straight or branched alkenyl or alkynyl, (C5-C7)-cycloalkenyl substituted (C1-C6)-straight or branched alkyl, (C2-C6)-straight or branched alkenyl or alkynyl, or Ar' substituted (C1-C6)-straight or branched alkyl, (C2-C6)-straight or branched alkenyl or alkynyl wherein, in each case, any one of the CH_2 groups of said alkyl, alkenyl or alkynyl chains may be optionally replaced by a heteroatom selected from the group consisting of O, S, SO, SO_2; or



(ii) ;

Ar' may contain one to three substituents which are independently selected from the group consisting of hydrogen, halogen, hydroxyl, hydroxymethyl, nitro, trifluoromethyl, trifluoromethoxy, (C1-C6)-straight or

branched alkyl, (C2-C6)-straight or branched alkenyl, O-[(C1-C4)-straight or branched alkyl], O-[(C2-C4)-straight or branched alkenyl], O-benzyl, O-phenyl, 1,2-methylenedioxy, amino and carboxyl; and

Y is selected from the group consisting of phenyl, 1-naphthyl, 2-naphthyl, indenyl, azulenyl, fluorenyl, anthracenyl and heterocyclic aromatic groups as defined for Ar' above.

According to other preferred embodiments, in the compound with affinity for FKBP12 having the formula (II):

at least one of B' or W is independently selected from the group consisting of (C2-C10)-straight or branched alkynyl; (C5-C7)-cycloalkyl substituted (C2-C6)-straight or branched alkynyl; (C5-C7)-cycloalkenyl substituted (C2-C6)-straight or branched alkynyl; and Ar' substituted (C2-C6)-straight or branched alkynyl.

Alternatively, at least one of B' or W is independently represented by the formula $-(CH_2)_r-(Z)-(CH_2)_s-Ar'$, wherein:

Z is independently selected from the group consisting of CH_2, O, S, SO, SO_2, N, and NR;

r is 0-4;

s is 0-1; and

Ar' and R are as defined above in formula II.

In yet another alternative embodiment of formula II, at least one of B' or W is independently selected from the group consisting of Ar', Ar'-substituted (C1-C6)-straight or branched alkyl, and Ar'-substituted (C2-C6)-straight or branched alkenyl or alkynyl;

wherein Ar' is substituted with one to three substituents which are independently selected from the group consisting of N-(straight or branched (C1-C5)-alkyl or (C2-C5)-alkenyl) carboxamides, N,N-di-(straight or

branched (C1-C5)-alkyl or (C2-C5)-alkenyl)carboxamides, N-morpholinocarboxamide, N-benzylcarboxamide, N-thiomorpholinocarboxamide, N-picolinoylcarboxamide, O-X, CH_2-$(CH_2)_q$-X, O-$(CH_2)_q$-X, $(CH_2)_q$-O-X, and CH=CH-X; and Ar', X and q are as defined above.

Most preferably, the compounds of formula (II) used in the pharmaceutical compositions are selected from those of formula (II') listed in Table 2, set forth in Example 1.

The synthesis of compounds of formula II is described in detail in applicant's PCT patent publications WO 92/19593 and WO 94/07858, the disclosures of which are herein incorporated by reference.

As used herein, the FKBP12 binding compounds used in the pharmaceutical compositions and methods of this invention, are defined to include pharmaceutically acceptable derivatives thereof. A "pharmaceutically acceptable derivative" denotes any pharmaceutically acceptable salt, ester, or salt of such ester, of a compound of this invention or any other compound which, upon administration to a patient, is capable of providing (directly or indirectly) a compound of this invention, or a metabolite or residue thereof, characterized by the ability to promote or augment neurite outgrowth.

If pharmaceutically acceptable salts of the FKBP12 binding compounds are used, those salts are preferably derived from inorganic or organic acids and bases. Included among such acid salts are the following: acetate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate,

methanesulfonate, 2-naphthalenesulfonate, nicotinate, oxalate, pamoate, pectinate, persulfate, 3-phenyl-propionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, tosylate and undecanoate. Base salts include ammonium salts, alkali metal salts, such as sodium and potassium salts, alkaline earth metal salts, such as calcium and magnesium salts, salts with organic bases, such as dicyclohexylamine salts, N-methyl-D-glucamine, and salts with amino acids such as arginine, lysine, and so forth. Also, the basic nitrogen-containing groups can be quaternized with such agents as lower alkyl halides, such as methyl, ethyl, propyl, and butyl chloride, bromides and iodides; dialkyl sulfates, such as dimethyl, diethyl, dibutyl and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides, such as benzyl and phenethyl bromides and others. Water or oil-soluble or dispersible products are thereby obtained.

The FKBP12 binding compounds utilized in the compositions and methods of this invention may also be modified by appending appropriate functionalities to enhance selective biological properties. Such modifications are known in the art and include those which increase biological penetration into a given biological system (e.g., blood, lymphatic system, central nervous system), increase oral availability, increase solubility to allow administration by injection, alter metabolism and alter rate of excretion.

The neurotrophic activity of the FKBP12 binding compounds of this invention is directly related to their affinity for FKBP12 and their ability to inhibit FKBP12 rotomase activity. In order to quantitate these properties, several assays known in the art may be employed. For example, competitive LH20 binding assays

using labelled FK-506 as a reporting ligand have been described by M. W. Harding et al., Nature, 341, pp. 758-60 (1989) and by J. J. Siekierka et al., Nature, 341, pp. 755-57 (1989).

Preferably, the assay measures inhibition of FKBP12 rotomase activity. Such an assay has also been described by M. W. Harding et al., supra and by J. J. Siekierka et al., supra. In this assay the isomerization of an artificial substrate -- N-succinyl-Ala-Ala-Pro-Phe-p-nitroanilide -- is followed spectrophotometrically. The assay includes the cis form of the substrate, FKBP12, the inhibitor and chymotrypsin. Chymotrypsin is able to cleave p-nitroanilide from the trans form of the substrate, but not the cis form. Release of p-nitroanilide is measured.

The second component in each of the pharmaceutical compositions described above is a neurotrophic factor. The term "neurotrophic factor", as used herein, refers to compounds which are capable of stimulating growth or proliferation of nervous tissue. As used in this application, the term "neurotrophic factor" excludes the FKBP12 binding compounds described herein, as well as FK-506 and rapamycin.

Numerous neurotrophic factors have been identified in the art and any of those factors may be utilized in the compositions of this invention. These neurotrophic factors include, but are not limited to, nerve growth factor (NGF), insulin growth factor (IGF-1) and its active truncated derivatives such as gIGF-1, acidic and basic fibroblast growth factor (aFGF and bFGF, respectively), platelet-derived growth factors (PDGF), brain-derived neurotrophic factor (BDNF), ciliary neurotrophic factors (CNTF), glial cell line-derived neurotrophic factor (GDNF), neurotrophin-3 (NT-3)and neurotrophin 4/5 (NT-4/5). The most preferred

neurotrophic factor in the compositions of this invention is NGF.

The third component of the pharmaceutically acceptable compositions of this invention is a pharmaceutically acceptable carrier. Pharmaceutically acceptable carriers that may be used in these pharmaceutical compositions include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat.

The compositions of the present invention may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir. The term "parenteral" as used herein includes subcutaneous, intravenous, intramuscular, intra-articular, intra-synovial, intrasternal, intrathecal, intrahepatic, intralesional and intracranial injection or infusion techniques. Preferably, the compositions are administered orally, intraperitoneally or intravenously.

Sterile injectable forms of the compositions of this invention may be aqueous or oleaginous suspension. These suspensions may be formulated according to techniques known in the art using suitable dispersing or wetting agents and suspending agents. The sterile

injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or di-glycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant, such as Ph. Helv or similar alcohol.

The pharmaceutical compositions of this invention may be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, aqueous suspensions or solutions. In the case of tablets for oral use, carriers which are commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried corn starch. When aqueous suspensions are required for oral use, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening, flavoring or coloring agents may also be added.

Alternatively, the pharmaceutical compositions of this invention may be administered in the form of suppositories for rectal administration. These can be prepared by mixing the agent with a suitable non-irritating excipient which is solid at room temperature

but liquid at rectal temperature and therefore will melt in the rectum to release the drug. Such materials include cocoa butter, beeswax and polyethylene glycols.

The pharmaceutical compositions of this invention may also be administered topically, especially when the target of treatment includes areas or organs readily accessible by topical application, including diseases of the eye, the skin, or the lower intestinal tract. Suitable topical formulations are readily prepared for each of these areas or organs.

Topical application for the lower intestinal tract can be effected in a rectal suppository formulation (see above) or in a suitable enema formulation. Topically-transdermal patches may also be used.

For topical applications, the pharmaceutical compositions may be formulated in a suitable ointment containing the active component suspended or dissolved in one or more carriers. Carriers for topical administration of the compounds of this invention include, but are not limited to, mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene, polyoxypropylene compound, emulsifying wax and water. Alternatively, the pharmaceutical compositions can be formulated in a suitable lotion or cream containing the active components suspended or dissolved in one or more pharmaceutically acceptable carriers. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water.

For ophthalmic use, the pharmaceutical compositions may be formulated as micronized suspensions in isotonic, pH adjusted sterile saline, or, preferably, as solutions in isotonic, pH adjusted sterile saline, either with our without a preservative such as

benzylalkonium chloride. Alternatively, for ophthalmic uses, the pharmaceutical compositions may be formulated in an ointment such as petrolatum.

The pharmaceutical compositions of this invention may also be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other conventional solubilizing or dispersing agents.

The amount of both FKPB12 binding compound and the neurotrophic factor that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated, the particular mode of administration. The two active ingredients of the pharmaceutical compositions of this invention act synergistically to stimulate neurite outgrowth. Therefore, the amount of neurotrophic factor in such compositions will be less than that required in a monotherapy utilizing only that factor. Preferably, the compositions should be formulated so that a dosage of between 0.01 - 100 mg/kg body weight/day of the FKBP12 binding protein can be administered and a dosage of between 0.01 - 100 µg/kg body weight/day of the neurotrophic can be administered to a patient receiving these compositions.

It should also be understood that a specific dosage and treatment regimen for any particular patient will depend upon a variety of factors, including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, rate of excretion, drug combination, and the judgment of the treating physician and the severity

of the particular disease being treated. The amount of active ingredients will also depend upon the particular FKBP12 binding compound and neurotrophic factor in the composition.

According to another embodiment, this invention provides methods for stimulating neurite outgrowth. Such methods comprise the step of treating nerve cells with any of the FKBP12 binding compounds described above. Preferably, this method is used to stimulate neurite outgrowth in a patient and the FKBP12 binding compound is formulated into a composition additionally comprising a pharmaceutically acceptable carrier. The amount of FKBP12 binding compound utilized in these methods is between about 0.01 and 100 mg/kg body weight/day.

According to an alternate embodiment, the method of stimulating neurite outgrowth comprises the additional step of treating nerve cells with a neurotrophic factor, such as those contained in the pharmaceutical compositions of this invention. This embodiment includes administering the FKBP12 binding compound and the neurotrophic agent in a single dosage form or in separate, multiple dosage forms. If separate dosage forms are utilized, they may be administered concurrently, consecutively or within less than about 5 hours of one another.

Preferably, the methods of this invention is used to stimulate neurite outgrowth in a patient.

The methods and compositions of this invention may be used to treat nerve damage caused by a wide variety of diseases or physical traumas. These include, but are not limited to, Alzheimer's disease, Parkinson's disease, ALS, stroke and ischemia associated with stroke, neural paropathy, other neural degenerative diseases, motor neuron diseases, sciatic crush, spinal cord injuries and facial nerve crush.

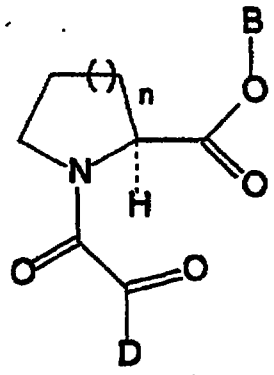
In order that the invention described herein may be more fully understood, the following examples are set forth. It should be understood that these examples are for illustrative purposes only and are not to be construed as limiting this invention in any manner.

EXAMPLE 1

FKBP12 Binding Assay

The inhibition of FKBP rotomase activity by the preferred FKBP12 binding compounds present in the compositions of this invention was assayed. In this assay various quantities of FKBP12 binding compound (0.1 nM - 10 μM) were added to cis-N-succinyl-Ala-Ala-Pro-Phe-p-nitroanilide in the presence of FKBP12 and chymotrypsin. FKBP12 converts the cis form of the substrate to the trans form. This allows chymotrypsin to cleave p-nitroanilide from the substrate. Release of p-nitroanilide was measured spectrophotometrically. This assay allowed me to measure the change in the first order rate constant of the rotomase activity as a function of FKBP12 binding compound concentration and yielded an estimate of apparent K_i. The most preferred FKBP12 binding compounds utilized in the compositions and methods of this invention and their calculated K_i are tabulated below.

TABLE 1a



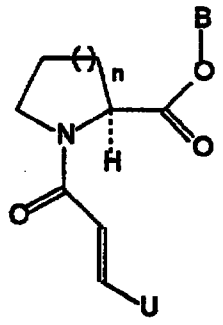
(formula Ia)

B	D	n	K_i (μM)
Benzyl	Phenyl	1	25
Benzyl	Phenyl	2	1.5
Allyl	Phenyl	2	8
1-Naphthyl	Phenyl	2	0.9
2- Naphthyl	Phenyl	2	7
Benzyl	2-Methylpropyl	2	0.9
Benzyl	2-Methoxyphenyl	2	17
Benzyl	3-Methoxyphenyl	2	0.3
Benzyl	4-Methoxyphenyl	2	5
Benzyl	3,5-Dimethoxyphenyl	2	2
Benzyl	2,6-Dimethoxyphenyl	2	50
Benzyl	3,4,5-Trimethoxyphenyl	2	0.1
Benzyl	4-Fluorophenyl	2	4
Benzyl	3-Nitrophenyl	2	160
Benzyl	4-Nitrophenyl	2	160
Benzyl	2-Pyridyl	2	130
Benzyl	2-pyridyl N-oxide	2	>500
tert-Butyl	2-Furyl	1	200
Benzyl	2-Furyl	2	3
Benzyl	3-Indoyl	2	25
Benzyl	2-Thiophenyl	2	0.8
E-3-Phenyl-2-methyl-prop-2-enyl	Phenyl	2	1.5
E-3-(4-Hydroxyphenyl)-2-methyl-prop-2-enyl	Phenyl	2	6
E-3-[cis-(4-Hydroxycyclohexyl)]-2-methyl-prop-2-enyl	Phenyl	2	0.6
E-3-[trans-(4-Hydroxycyclohexyl)]-2-methyl-prop-2-enyl	Phenyl	2	0.5
Benzyl	2-Nitrobenzyl	2	26
Hydrogen	Methoxy	2	ND
tert-Butyl	Methoxy	1	600
Allyl	Methoxy	2	190

B	D	n	K_i (μM)
Benzyl	Methoxy	2	80
2-Cyclohexylethyl	Methoxy	2	45
3-Cyclohexylpropyl	Methoxy	2	20
4-Cyclohexylbutyl	Methoxy	2	6
3-Cyclopentylpropyl	Methoxy	2	35
E-3-(4-Methoxyphenyl)-2-methyl-prop-2-enyl	Methoxy	2	40
E-3-(3,4-Dimethoxyphenyl)-2-methyl-prop-2-enyl	Methoxy	2	10
E-3-(4-Hydroxyphenyl)-2-methyl-prop-2-enyl	Methoxy	2	60
E-3-[cis-(4-Hydroxycyclohexyl)]-2-methyl-prop-2-enyl	Methoxy	2	70
Benzyl	Cyclohexyl	2	1.3
Benzyl	Ethyl	1	400
Benzyl	3-Methoxyphenyl	1	5
Benzyl	2-Pyridyl	1	300
Benzyl	3,4-Difluorophenyl	2	3
Benzyl	(E)-2-(4-Methoxyphenyl)-ethenyl	2	1
Benzyl	1-Hydroxy-1-cyclohexyl	2	1
Benzyl	2-Naphthyl	2	1.5
Benzyl	1-Naphthyl	2	1
(S)-alpha-Methylbenzyl	Phenyl	2	0.5
Benzyl	2-Hydroxy-2-tetrahydropyramyl	2	12
(R)-alpha-Methylbenzyl	Phenyl	2	1.5
Benzyl	3-Trifluoromethylphenyl	2	1.5
Benzyl	3-Benzyloxyphenyl	2	0.5
Benzyl	(E)-2-tert-Butylethenyl	2	9
Benzyl	2-Trifluoromethylphenyl	2	5
4-Cyclohexylbutyl	Phenyl	2	0.4
4-Cyclohexylbutyl	3,4,5-Trimethoxyphenyl	2	0.04
4-Phenylbenzyl	Phenyl	2	5
4-Phenylbenzyl	3,4,5-Trimethoxyphenyl	2	2
Benzyl	3-Ethoxyphenyl	2	0.56
3-Phenoxybenzyl	3,4,5-Trimethoxyphenyl	2	0.018
3-Phenoxybenzyl	Phenyl	2	0.09
4-Phenylbutyl	3,4,5-Trimethoxyphenyl	2	0.019
4-Phenylbutyl	Phenyl	2	0.35
Benzyl	3-(3-Propenyloxy)phenyl	2	1
Benzyl	3-(2-Propoxy)phenyl	2	0.5
Benzyl	1-Methylpropyl	2	1
2-Phenylethyl	Phenyl	2	1.1
6-Phenylhexyl	Phenyl	2	0.5
5-Phenylpentyl	3,4,5-Trimethoxyphenyl	2	0.07
6-Phenylhexyl	3,4,5-Trimethoxyphenyl	2	0.1
6-Cyclohexylhexyl	3,4,5-Trimethoxyphenyl	2	0.05
4-Phenoxybenzyl	3,4,5-Trimethoxyphenyl	2	0.8
5-Cyclohexylpentyl	3,4,5-Trimethoxyphenyl	2	0.09

B	D	n	K_i (μM)
Benzyl	3-(1-Butoxy)phenyl	2	0.36
4- Phenylbutyl	3-(2-Propoxy)phenyl	2	0.1
4-(4-Iodophenyl)butyl	3,4,5-Trimethoxyphenyl	2	0.016
4-Iodobenzyl	3,4,5-Trimethoxyphenyl	2	1.4
2-(2-Naphthyl)ethyl	3,4,5-Trimethoxyphenyl	2	0.22
2-(1-Naphthyl)ethyl	3,4,5-Trimethoxyphenyl	2	0.5
4-Phenylbutyl	4-Iodophenyl	2	0.8
4-Phenylbutyl	3-Iodophenyl	2	0.13
3-Phenylpropyl	3,4,5-Trimethoxyphenyl	2	0.11
3-(3-Indolyl)propyl	3,4,5-Trimethoxyphenyl	2	0.017
4-(4-Methoxyphenyl)butyl	3,4,5-Trimethoxyphenyl	2	0.013
4-Phenylbut-2-enyl	3,4,5-Trimethoxyphenyl	2	0.8
4-Phenylbut-3-enyl	3,4,5-Trimethoxyphenyl	2	0.5
4-(4-Allocaminophenyl)propyl	3,4,5-Trimethoxyphenyl	2	0.011
4-Phenylpropyl	1-Cyclohexenyl	2	0.78
4-(4-Methoxyphenyl)but-3-enyl	3,4,5-Trimethoxyphenyl	2	0.011
4-Phenylpropyl	1-Fluoro-1-cyclohexyl	2	0.54
4-Phenylpropyl	3-Butoxyphenyl	2	1.4
3-[3-(N-Formylindolyl)]propyl	3,4,5-Trimethoxyphenyl	2	0.015
4-(3-Indolyl)butyl	3,4,5-Trimethoxyphenyl	2	0.016
4-Phenylbutyl	Benzyl	2	0.35
4-Phenylbutyl	3-Biphenyl	2	0.04
4-Phenylbutyl	4-tert-Butylphenyl	2	0.6
4-Phenylbutyl	Cyclohexyl	2	0.08
4-Phenylbutyl	Cyclohexylmethyl	2	0.12
4-Phenylbutyl	3,4-Methylenedioxyphenyl	2	0.25
4-Phenylbutyl	4-Tetrahydropyranyl	2	0.44
4-Phenylbutyl	3-Cyclohexyl-4-methoxy- phenyl	2	14
4-Phenylbutyl	4-(4-Methoxybenzyloxy-methyl)-2-furyl	2	0.7
4-Phenylbutyl	tert-Butyl	2	0.18
4-Phenylbutyl	Ethyl	2	1.6
3-(N-Benzimidazolyl)propyl	3,4,5-Trimethoxyphenyl	2	0.11
3-(N-Purinyl)propyl	3,4,5-Trimethoxyphenyl	2	0.13
(S,S)-2-Methyl-3-hydroxy-4- phenylpropyl	3,4,5-Trimethoxyphenyl	2	0.25

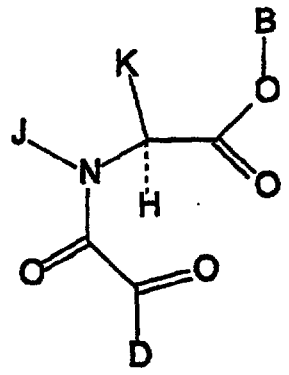
TABLE 1b



(formula 1b)

B	U	n	K_i
Benzyl	3,4-Methylenedioxyphenyl	1	3
Benzyl	3,4-Methylenedioxyphenyl	2	3
Benzyl	4-Methoxyphenyl	1	6
Benzyl	4-Methoxyphenyl	2	4
Benzyl	2,5-Dimethoxyphenyl	1	10
Benzyl	2,4,5-Trimethoxyphenyl	1	25
Benzyl	3,4,5-Trimethoxyphenyl	1	450
Benzyl	4-Dimethylaminophenyl	2	20
Benzyl	4-Nitrophenyl	2	14
Benzyl	1-Furyl	2	2.5
Benzyl	2-Furyl	2	2.5
Benzyl	3-Indoyl	2	>60
Benzyl	3-Pyridyl	2	25
Benzyl	Hydrogen	2	300
Benzyl	Phenyl	2	11

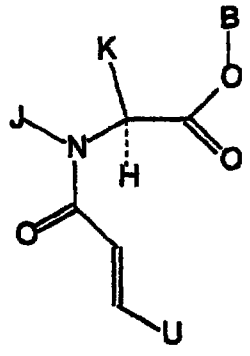
TABLE 1c



(formula Ic)

B	D	J	K	K_i (μM)
Benzyl	Methoxy	Methyl	Hydrogen	1000
Benzyl	Methoxy	Methyl	S-methyl	400
Benzyl	Methoxy	Methyl	S-isopropyl	170
Ethyl	Methoxy	Benzyl	Hydrogen	>1200
tert-Butyl	Methoxy	Ethyl	S-Methyl	>400

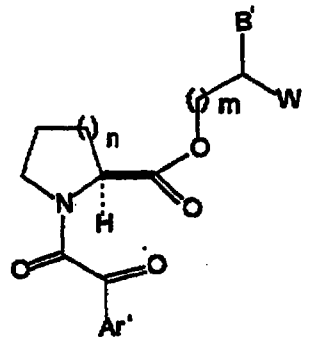
TABLE 1d



(formula 1d)

B	U	J	K	K_i (μM)
Benzyl	4-methoxyphenyl	Methyl	S-Methyl	80
Benzyl	4-methoxyphenyl	Methyl	S-Isopropyl	30
Benzyl	3,4-Methylenedioxyphenyl	Methyl	S-Methyl	50
Benzyl	3,4-Methylenedioxyphenyl	Hydrogen	S-Methyl	60

TABLE 2



(formula II')

Cpd.	n	m	B'	W	Ar'	K_i (nM)
2	1	0	3-(Pyridin-2-yl) propyl	3-Phenylpropyl	3,4,5-Trimethoxyphenyl	95.
3	2	0	3-Phenylpropyl	3-Phenylpropyl	3,4,5-Trimethoxyphenyl	1.
4	2	0	3-Phenoxyphenyl	3-Phenylpropyl	3,4,5-Trimethoxyphenyl	220.
5	2	0	Phenyl	3-Phenoxyphenyl	3,4,5-Trimethoxyphenyl	4,000.
6	2	0	Phenyl	3-Phenylpropyl	3,4,5-Trimethoxyphenyl	80.
7	2	0	2-(Pyridin-3-yl) ethyl	3-Phenylpropyl	3,4,5-Trimethoxyphenyl	3.
8	2	0	E-3-[trans-(4-Hydroxycyclo-hexyl)]-2-methyl-eth-2-enyl	3-Phenylpropyl	3,4,5-Trimethoxyphenyl	27.
9	2	0	3-(Pyridin-3-yl)propyl	3-Phenylpropyl	3,4,5-Trimethoxyphenyl	0.5
10	2	0	Benzyl	3-Phenylpropyl	3,4,5-Trimethoxyphenyl	32.
11	2	0	Benzyl	3-(Indol-3-yl) propyl	3,4,5-Trimethoxyphenyl	24.
12	2	0	2-Phenylethyl	3-Phenylpropyl	3,4,5-Trimethoxyphenyl	83.
13	2	0	2-(4-Methoxy-phenyl)ethyl	3-Phenylpropyl	3,4,5-Trimethoxyphenyl	3.5
14	2	0	2-(4-Methoxy-phenyl)ethyl	3-Phenylpropyl	Phenyl	270.
15	2	0	3-(N-Benzimidazolyl)propyl	3-Phenylpropyl	3,4,5-Trimethoxyphenyl	5.
16	2	1	Benzyl	2-Phenylethyl	3,4,5-Trimethoxyphenyl	57.
17	2	0	3-(4-Methoxy-phenyl)propyl	3-Phenylpropyl	3,4,5-Trimethoxyphenyl	3.
18	2	0	3-(Pyridin-3-yl)-propyl	3-Phenylpropyl	Phenyl	56.
19	2	0	3-(Pyridin-2-yl)-propyl	3-Phenylpropyl	Phenyl	50.
20	2	0	3-(Pyridin-2-yl)-propyl	3-Phenylpropyl	3,4,5-Trimethoxyphenyl	6.5
21	2	0	3-(Pyridin-2yl)-propyl	3-Phenylpropyl	tert-Butyl	36.
22	2	0	3-(Pyridin-3-yl)-propyl-N-oxide	3-Phenylpropyl	3,4,5-Tdmethoxyphenyl	7.
23	2	0	3-IN-(7-Azaindolyl)-propyl	3-Phenylpropyl	3,4,5-Trimethoxyphenyl	9.
24	2	0	3-(Pyridin-3-yl)-propyl	3-(4-Methoxy-phenyl)-propyl	3,4,5-Trimethoxyphenyl	ND
25	2	0	3-(N-Purinyl) propyl	3-Phenylpropyl	3,4,5-Trimethoxyphenyl	2.2
26	2	0	3-(4-Hydroxy-methylphenyl) propyl	3-Phenylpropyl	3,4,5-Trimethoxyphenyl	4.
27	2	0	3-(Pyridin-3-yl)-propyl	3-Phenylpropyl	3-Benzyloxyphenyl	15.
28	2	0	3-(Pyridin-3-yl)-propyl	3-Phenylpropyl	3-Allyloxyphenyl	11.
29	2	0	3-(Pyridin-3-yl)-propyl	3-Phenylpropyl	3-Isopropoxyphenyl	2.
30	2	0	3-(Thiophen-2-yl)-propyl	3-Phenylpropyl	3,4,5-Trimethoxyphenyl	4.

Cpd.	n	m	B'	W	Ar'	K_i (nM)
31	2	0	3-(4-Carboxyphenyl)propyl	3-Phenylpropyl	3,4,5-Trimethoxyphenyl	2.
32	2	0	3-Phenylbutyl	3-Phenylpropyl	3,4,5-Trimethoxyphenyl	20.
33	2	0	2-Hydroxymethylphenyl	3-Phenylpropyl	3,4,6-Trimethoxyphenyl	89.
34	2	0	2-Allyloxyphenyl	3-Phenylpropyl	3,4,5-Trimethoxyphenyl	150.
35	2	0	3-(3-Hydroxymethylphenyl) propyl	3-Phenylpropyl	3,4,5-Trimethoxyphenyl	1.
36	2	0	3-(3-Carboxyphenyl)propyl	3-Phenylpropyl	3,4,5-Trimethoxyphenyl	4.
37	2	0	3-Hydroxymethylphenyl	3-Phenylpropyl	3,4,5-Trimethoxyphenyl	6.8
38	2	0	2-Hydroxyphenyl	3-Phenylpropyl	3,4,5-Trimethoxyphenyl	ND
39	2	0	Pyridin-3-yl	3-Phenylpropyl	3,4,5-Trimethoxyphenyl	ND
40	2	0	3-(Thiopen-2-yl)-propyl	4-Phenylbutyl	3,4,5-Trimethoxyphenyl	1,100.
41	2	0	5-Phenylpentyl	3-Phenylpropyl	3,4,5-Trimethoxyphenyl	45.
42	2	0	3-Allyloxypropyl	3-Phenylpropyl	3,4,5-Trimethoxyphenyl	ND
43	2	0	3-[4-(N,N-Dimethylamine-carbonyl)-phenyl] propyl	3-Phenylpropyl	3,4,5-Trimethoxyphenyl	5.
44	2	0	3-[4-(Morpholine-4-carbonyl)phenyl]-propyl	3-Phenylpropyl	3,4,5-Trimethoxyphenyl	6.
45	2	0	4-Allyoxybutyl	3-Phenylpropyl	3,4,5-Trimethoxyphenyl	7.
46	2	0	3-Allyloxy-prop-1-ynyl	3-Phenylpropyl	3,4,5-Trimethoxyphenyl	5.
47	2	0	3-[4-(Piperidine-1-carbonyl)phenyl]-propyl	3-Phenylpropyl	3,4,5-Trimethoxyphenyl	7.
48	2	0	5-Allyloxynonyl	3-Phenylpropyl	3,4,5-Trimethoxyphenyl	ND
49	2	0	Methyl	3,5-Bis(benzyloxy)phenyl	3,4,5-Trimethoxyphenyl	3,400.
50	2	0	2-Allyloxyethyl	3-Phenylpropyl	3,4,5-Trimethoxyphenyl	11.
51	2	0	3-Allyloxy-(E)-prop-1-ynyl	3-Phenylpropyl	3,4,5-Trimethoxyphenyl	2.8
52	2	0	3-[3-(Morpholine-4-carbonyl) phenyl]propyl	3-Phenylpropyl	3,4,5-Trimethoxyphenyl	1.5
53	2	0	Dec-9-enyl	3-Phenylpropyl	3,4,5-Trimethoxyphenyl	ND
54	2	0	3-[4-(N-Benzyl-aminecarbonyl)-phenyl]propyl	3-Phenylpropyl	3,4,5-Trimethoxyphenyl	1.6
55	2	0	3-[4-(Thiomorpholine-4-carbonyl)\phenyl]propyl	3-Phenylpropyl	3,4,5-Trimethoxyphenyl	2.4
56	2	0	3-(Morpholine-4-carbonyl)phenyl-	3-Phenylpropyl	3,4,5-Trimethoxyphenyl	6.1
57	2	0	3-[4-(1-Methyl-piperazine-4-carbonyl)phenyl] propyl	3-Phenylpropyl	3,4,5-Trimethoxyphenyl	5.6
58	2	0	3-[4-(1-Benzyl-piperazine-4-carbonyl)phenyl] propyl	3-Phenylpropyl	3,4,5-Trimethoxyphenyl	30.
59	2	0	3-[3-(N-Benzyl-amine-carbonyl)phenylpropyl	3-Phenylpropyl	3,4,5-Trimethoxyphenyl	40.
60	2	0	3-[4-(N-Pyridin-2-ylaminecarbon-yl)-phenyl]propyl	3-Phenylpropyl	3,4,5-Trimethoxyphenyl	2.
61	2	0	Pyridin-3-yl	3-(Pyridin-3-yl)-propyl	3,4,5-Trimethoxyphenyl	10.
62	2	0	Prop-2-enyl	3,4-Bis-(Pyridin-4-ylmethoxy)phenyl	3,4,5-Trimethoxyphenyl	62.
63	2	0	Pyridin-3-yl	3-(Pyridin-4-yl-methoxy)phenyl	3,4,5-Trimethoxyphenyl	13.
64	2	0	3-Phenylpropyl	3-(Pyridin-4-yl-methoxy)phenyl	3,4,5-Trimethoxyphenyl	1.4

Cpd.	n	m	B'	W	Ar'	K_i (nM)
65	2	0	3-Phenylpropyl	3,4-Bis-(Pyridin-4-ylmethoxy)phenyl	3,4,5-Trimethoxyphenyl	4.1
66	2	0	Methyl	3,4-Bis-(Pyridin-4-ylmethoxy)phenyl	3,4,5-Trimethoxyphenyl	35.
67	2	0	3-Phenylpropyl	2,3,4-Tris-(Pyridin-4-ylmethoxy)phenyl	3,4,5-Trimethoxyphenyl	46.
68	2	0	3-Phenylpropyl	3-(Morpholine-4-carbonyl)-4-(Pyridin-4-ylmethoxy)phenyl	3,4,5-Trimethoxyphenyl	2.
69	2	0	Methyl	3,4,5-Tris-(Pyridin-4-ylmethoxy)phenyl	3,4,5-Trimethoxyphenyl	36.
70	2	0	3-Phenylpropyl	3,4,5-Tris-(Pyridin-4-ylmethoxy)phenyl	3,4,5-Trimethoxyphenyl	5.
71	2	0	Methyl	3,5-Bis-(Pyridin-4-ylmethoxy)phenyl	3,4,5-Trimethoxyphenyl	14.
72	2	0	3,5-Bis-(Pyridin-4-ylmethoxy) phenyl	Methyl	3,4,5-Trimethoxyphenyl	12.
73	2	0	Methyl	3,5-Bis-(Pyridin-4-yl(methoxy)-4-Methyl-phenyl	3,4,5-Trimethoxyphenyl	36.
74	2	0	Ethyl	3,4,5-Tris-(Pyridin-4-ylmethoxy)phenyl	3,4,5-Trimethoxyphenyl	18.
75	2	0	3,4,5-Tris-(Pyridin-4-yl-methoxy)phenyl	Ethyl	3,4,5-Trimethoxyphenyl	12.
76	2	0	Prop-2-enyl	3,4,5-Tris-(Pyridin-4-ylmethoxy)phenyl	3,4,5-Trimethoxyphenyl	14.
77	2	0	Methyl	3,4,6-Tris-(Pyridin-4-ylmethoxy)phenyl	3,4-Dimethoxyphenyl	24.
78	2	0	Ethenyl	3,4,5-Tris-(Pyridin-4-ylmethoxy)phenyl	3,4,5-Trimethoxyphenyl	73.
79	2	0	3,4,5-Tris-(Pyridin-4-ylmethoxy)phenyl	Ethenyl	3,4,5-Trimethoxyphenyl	2.3
80	2	0	Propyl	3,4,5-Tris-(Pyridin-4-ylmethoxy)phenyl	3,4,5-Trimethoxyphenyl	17.
81	2	0	3,4,5-Tris-(Pyridin-4-ylmethoxy)phenyl	Propyl	3,4,5-Trimethoxyphenyl	5.
82	2	0	Methyl	3,4,5-Tris-(Thiophen-3-ylmethoxy)phenyl	3,4,5-Trimethoxyphenyl	>5000
83	2	0	3,4,5-Tris-(Thio-phen-3-ylmethoxy)-phenyl	Methyl	3,4,5-Trimethoxyphenyl	>1000
84	2	0	Methyl	2-Isopropoxy-3,4-Bis-(Pyridin-4-ylmethoxy)-phenyl	3,4,5-Trimethoxyphenyl	54.
85	2	0	2-Isopropoxy-3,4-Bis-(Pyridin-4-yl-methoxy) phenyl	Methyl	3,4,5-Trimethoxyphenyl	3.5
86	1	0	Methyl	3,4,5-Tris-(Pyridin-4-ylmethoxy)phenyl	3,4,5-Trimethoxyphenyl	280.
87	1	0	3,4,5-Tris-(Pyridin-4-ylmethoxy)phenyl	Methyl	3,4,5-Trimethoxyphenyl	360.
88	2	0	Methyl	3,4,5-Tris-(Pyrimidin-4-ylmethoxy)phenyl	3,4,5-Trimethoxyphenyl	19.
89	2	0	Benzyloxymethyl	Benzyloxyphenyl	3,4,5-Trimethoxyphenyl	5.
90	2	0	Methyl	3,4,5-Tris-(Benzyloxy)phenyl	3,4,5-Trimethoxyphenyl	2,600.

Cpd.	n	m	B'	W	Ar'	K_i (nM)
91	2	0	3-Phenylpropyl	3-(Pyridin-3-yl-carbonyl)phenyl	3,4,5-Trimethoxyphenyl	24.
92	2	0	3-(Pyridin-3-yl-carbonyl)phenyl	3-Phenylpropyl	3,4,5-Trimethoxyphenyl	9.
93	2	0	3-Phenylpropyl	3-(Pyridin-4-yl-methoxy)phenyl	3,4-Dimethoxyphenyl	7.5
94	2	0	3-Phenylpropyl	3-(Pyridin-4-yl-carbonyl)phenyl	4-Benzyloxy-3,5-Di-methoxyphenyl	25.
95	2	0	3-Phenylpropyl	3-(Pyridin-4-yl-carbonyl)phenyl	4-Allyloxy-3,5-Di-methoxyphenyl	3.6
96	2	0	3-Phenylpropyl	3-(Pyridin-4-yl-carbonyl)phenyl	3-Benzyloxy-4-methoxyphenyl	25.
97	2	0	3-Phenylpropyl	3-(Pyridin-4-yl-carbonyl)phenyl	3-Allyloxy-4-methoxyphenyl	17.
98	2	0	3-Phenylpropyl	3-(Pyridin-4-yl-carbonyl)phenyl	3-[3-Phenyl-(E)-prop-2-enyl]-4-methoxyphenyl	380.
99	2	0	3-Phenylpropyl	4-(Pyridin-4-yl-carbonyl)phenyl	4-Benzyloxy-3,5-Di-methoxyphenyl	15,000.
100	2	0	3-Phenylpropyl	4-(Pyridin-4-yl-carbonyl)phenyl	3-Benzyloxy-4-methoxyphenyl	>5000
101	2	0	3-Phenylpropyl	3-(Pyridin-4-yl-carbonyl)phenyl	3,4,5-Trimethoxyphenyl	ND
102	2	0	3-Phenylpropyl	3-(Pyridin-4-yl-carbonyl)phenyl	3,4-Dimethoxyphenyl	ND
103	2	0	3-Phenylpropyl	Phenyl	3-Benzyloxy-4-methoxyphenyl	24,000.
104	2	0	3-Phenylpropyl	Phenyl	4-Benzyloxy-3,5-Dimethoxyphenyl	1,700.
105	1	0	3-(Pyridin-3-yl)-propyl	3-Phenylpropyl	tert-Butyl	340.
106	2	0	3-(Pyridin-3-yl)-propyl	3-(Pyridin-3-yl)-propyl	3,4,5-Trimethoxyphenyl	3.7
107	1	0	Benzyloxymethyl	Benzyloxymethyl	3,4,5-Trimethoxyphenyl	75,000.
108	1	0	3-(Pyridin-3-yl)-propyl	3-(Pyridin-3-yl)-propyl	3,4,5-Trimethoxyphenyl	89.
109	2	0	3-(Pyridin-3-yl)-propyl	3-(Pyridin-3-yl)-propyl	Isopropyl	1,500.
110	2	0	3-(Pyridin-3-yl)-	3-(Pyridin-3-yl)-	Thiophen-2-yl	ND
111	2	0	3-(Pyridin-3-yl)-propyl	3-(Pyridin-3-yl)-propyl	3,4-Methylenedioxy-phenyl	ND
112	2	0	3-(Pyridin-3-yl)-prop-2-ynyl	3-(Pyridin-3-yl)-prop-2-ynyl	3,4-Methylenedioxy phenyl	ND
113	2	0	3-(Pyridin-3-yl)-prop-2-ynyl	3-(Pyridin-3-yl)-prop-2-ynyl	3,4,5-Trimethoxyphenyl	ND
114	2	0	3-(Pyridin-2-yl)-propyl	3-(Pyridin-2-yl)-propyl	3,4,5-Trimethoxyphenyl	ND
115	2	0	Isopropyl	3,4,5-Tris-(Pyridin-4-ylmethoxy)phenyl	3,4,5-Trimethoxyphenyl	0.39
116	2	0	3,4,5-Tris-(Pyridin-4-ylmethoxy)phenyl	Isopropyl	3,4,5-Trimethoxyphenyl	13.
118	2	0	3,4,5-Tris-(Pyridin-4-ylmethoxy)phenyl	Prop-2-enyl	3,4,5-Trimethoxyphenyl	12.

EXAMPLE 2

Assay of Neurite Outgrowth in PC12 Cultures

In order to directly determine the neurotrophic

activity of the FKBP12 binding compounds utilized in this invention, the assay described by W. E. Lyons et al., Proc. Natl. Acad. Sci. USA, 91, pp. 3191-95 (1994) is carried out.

PC12 rat pheochromocytoma cells are maintained at 37°C and 5% CO_2 in Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% heat-inactivated horse serum (HS) and 5% heat-inactivated fetal bovine serum (FBS). The cells are then plated at 10^5 per 35mm culture well coated with 5 $\mu g/cm^2$ rat tail collagen and allowed to attach. The medium is then replaced with DMEM + 2% HS and 1% FBS, NGF (1-100 ng/ml) and varying concentrations of an FKBP12 binding compound (0.1 nM - 10 µM). Control cultures are administered NGF without FKBP12 binding compound.

The FKBP12 binding compounds utilized in this invention cause a significant increase in neurite outgrowth over control cultures.

EXAMPLE 3

Assay of Neurite Outgrowth in Dorsal Root Ganglion Culture

Another way to directly determine the neurotrophic activity of the FKBP12 binding compounds utilized in this invention is the dorsal root ganglion culture assay also described by W. E. Lyons et al., Proc. Natl. Acad. Sci. USA, 91, pp. 3191-95 (1994).

In this assay, dorsal root ganglia are dissected from 16 day rat embryos and cultured in collagen-coated 35mm dishes with N2 medium at 37°C in a 15% CO_2 environment. Sensory ganglia are then treated with various concentrations of NGF (0 - 100 ng/ml) and an FKB12 binding compound (0.1 nM - 10 µM). Ganglia are observed every two days under a phase contrast microscope and axon lengths are measured. Control cultures either

lack FKBP12 binding compound or lack FKBP12 binding compound and NGF.

The FKBP12 binding compounds utilized in this invention cause a significant increase in neurite outgrowth over control cultures which lack such compounds in both the presence and absence of NGF.

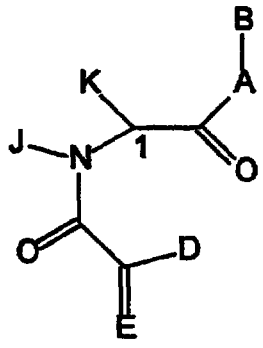
While I have hereinbefore presented a number of embodiments of this invention, it is apparent that my basic construction can be altered to provide other embodiments which utilize the methods of this invention. Therefore, it will be appreciated that the scope of this invention is to be defined by the claims appended hereto rather than the specific embodiments which have been presented hereinbefore by way of example.

CLAIMS

I claim:

1. A pharmaceutically acceptable composition comprising:

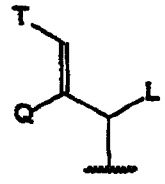
a) a neurotrophic amount of a compound with affinity for FKBP12 having the formula (I):



(I)

and pharmaceutically acceptable derivatives thereof, wherein A in O, NH, or N-(C1-C4 alkyl);

wherein B is hydrogen, CHL-Ar, (C1-C6)-straight or branched alkyl, (C2-C6)-straight or branched alkenyl, (C5-C7)-cycloalkyl, (C5-C7)-cycloalkenyl or Ar substituted (C1-C6)-alkyl or (C2-C6)-alkenyl, or



wherein L and Q are independently hydrogen, (C1-C6)-straight or branched alkyl or (C2-C6)-straight or branched alkenyl; and

T is Ar or substituted cyclohexyl with substituents at positions 3 and 4 which are independently selected from the group consisting of

hydrogen, hydroxyl, O-(C1-C4)-alkyl or O-(C2-C4)-alkenyl and carbonyl;

wherein Ar is selected from the group consisting of 1-naphthyl, 2-naphthyl, 2-furyl, 3-furyl, 2-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl and phenyl having one to three substituents which are independently selected from the group consisting of hydrogen, halo, hydroxyl, nitro, CF_3, (C1-C6)-straight or branched alkyl or (C2-C6)-straight or branched alkenyl, O-(C1-C4)-straight or branched alkyl or O-((C2-C4)-straight or branched alkenyl), O-benzyl, O-phenyl, amino and phenyl;

D is U;

E is either oxygen or CH-U, provided that if D is hydrogen, then E is CH-U or if E is oxygen then D is not hydrogen;

wherein each U is independently selected from hydrogen, O-(C1-C4)-straight or branched alkyl or O-((C2-C4)-straight or branched alkenyl), (C1-C6)-straight or branched alkyl or (C2-C6)-straight or branched alkenyl, (C5-C7)-cycloalkyl or (C5-C7)-cycloalkenyl substituted with (C1-C4)-straight or branched alkyl or (C2-C4)-straight or branched alkenyl, 2-indolyl, 3-indolyl, [(C1-C4)-alkyl or (C2-C4)-alkenyl]-Ar or Ar;

J is hydrogen or C1 or C2 alkyl;

K is (C1-C4)-straight or branched alkyl, benzyl or cyclohexylmethyl; or J and K are taken together to form a 5-7 membered heterocyclic ring which may contain an O, S, SO or SO_2 substituent therein; and

the stereochemistry at carbon position 1 is R or S;

b) a neurotrophic factor; and

c) a pharmaceutically suitable carrier.

2. The composition according to claim 1, wherein:

A is oxygen;

J is hydrogen or C1 or C2 alkyl;

K is (C1-C4)-straight or branched alkyl, benzyl or cyclohexylmethyl; or J and K are taken together to form pyrrolidyl or piperidyl; and

the stereochemistry at carbon position 1 is S.

3. The composition according to claim 2, wherein:

J and K are taken together to form pyrrolidyl or piperidyl; and

E is CH-U; and

U is dimethylaminophenyl, methoxyphenyl, dimethoxyphenyl, trimethoxyphenyl, nitrophenyl, furyl, indolyl, pyridyl, or methylenedioxyphenyl.

4. The composition according to claim 2, wherein:

J and K are taken together to form pyrrolidyl or piperidyl;

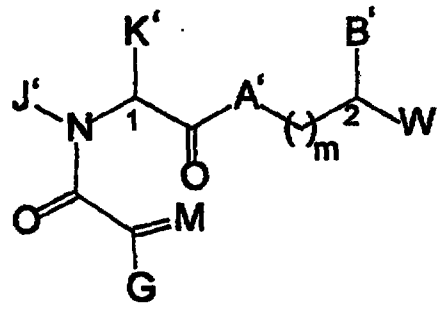
E is oxygen:

B is benzyl, naphthyl, tert-butyl, hydrogen, E-3-phenyl-2-methyl-prop-2-enyl, E-3-(4-hydroxyphenyl) 2-methyl-prop-2-enyl, E-3-[trans(4-hydroxycyclohexyl)]-2-methyl-prop-2-enyl, cyclohexylethyl, cyclohexylpropyl, cyclohexylbutyl, cyclopentylopropyl, E-3-(4-methoxyphenyl)-2-methyl-prop-2-enyl, E-3-(3,4-dimethoxyphenyl)-2-methyl-prop-2-enyl or E-3-[cis(4-hydroxycyclohexyl)]-2-methyl-prop-2-enyl; and

D is phenyl, methoxyphenyl, cyclohexyl, ethyl, methoxy, nitrobenzyl, thiophenyl, indolyl, furyl, pyridyl, pyridyl-N-oxide, nitrophenyl, fluorophenyl, trimethoxyphenyl or dimethoxyphenyl.

5. A pharmaceutically acceptable composition comprising:

a) a neurotrophic amount of a compound with affinity for FKBP12 having the formula (II):



(II)

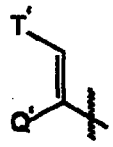
and pharmaceutically acceptable derivatives thereof, wherein A' is CH_2, oxygen, NH or N-(C1-C4 alkyl);

B' and W are independently:

(i) hydrogen, Ar', (C1-C10)-straight or branched alkyl, (C2-C10)-straight or branched alkenyl or alkynyl, (C5-C7)-cycloalkyl substituted (C1-C6)-straight or branched alkyl, (C2-C6)-straight or branched alkenyl or alkynyl, (C5-C7)-cycloalkenyl substituted (C1-C6)-straight or branched alkyl, (C2-C6)-straight or branched alkenyl or alkynyl, or Ar' substituted (C1-C6)-straight or branched alkyl, (C2-C6)-straight or branched alkenyl or alkynyl wherein, in each case, any one of the CH_2 groups of said alkyl, alkenyl or alkynyl chains may be optionally replaced by a heteroatom selected from the group consisting of O, S, SO, SO_2, N, and NR,

wherein R is selected from the group consisting of hydrogen, (C1-C4)-straight or branched alkyl, (C2-C4)-straight or branched alkenyl or alkynyl, and (C1-C4) bridging alkyl wherein a bridge is formed between the nitrogen and a carbon atom of said

heteroatom-containing chain to form a ring, and wherein said ring is optionally fused to an Ar' group; or



(ii)

wherein Q' is hydrogen, (C1-C6)-straight or branched alkyl or (C2-C6)-straight or branched alkenyl or alkynyl; and

T' is Ar' or substituted 5-7 membered cycloalkyl with substituents at positions 3 and 4 which are independently selected from the group consisting of oxo, hydrogen, hydroxyl, O-(C1-C4)-alkyl, and O-(C2-C4)-alkenyl;

wherein Ar' is a carbocyclic aromatic group selected from the group consisting of phenyl, 1-naphthyl, 2-naphthyl, indenyl, azulenyl, fluorenyl, and anthracenyl; or a heterocyclic aromatic group selected from the group consisting of 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, 1,2,3-oxadiazolyl, 1,2,3-triazolyl, 1,3,4-thiadiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,3,5-triazinyl, 1,3,5-trithianyl, indolizinyl, indolyl, isoindolyl, 3H-indolyl, indolinyl, benzo[b]furanyl, benzo[b]thiophenyl, 1H-indazolyl, benzimidazolyl, benzthiazolyl, purinyl, 4H-quinolizinyl, quinolinyl, isoquinolinyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, 1,8-naphthyridinyl, pteridinyl,

carbazolyl, acridinyl, phenazinyl, phenothiazinyl, and phenoxazinyl; and

wherein Ar' may contain one to three substituents which are independently selected from the group consisting of hydrogen, halogen, hydroxyl, hydroxymethyl, nitro, trifluoromethyl, trifluoromethoxy, (C1-C6)-straight or branched alkyl, (C2-C6)-straight or branched alkenyl, O-[(C1-C4)-straight or branched alkyl], O-[(C2-C4)-straight or branched alkenyl], O-benzyl, O-phenyl, 1,2-methylenedioxy, amino, carboxyl, N-[(C1-C5)-straight or branched alkyl or (C2-C5)-straight or branched alkenyl)carboxamides, N,N-di-[(C1-C5)-straight or branched alkyl or (C2-C5)-straight or branched alkenyl)]carboxamides, N-morpholinocarboxamide, N-benzylcarboxamide, N-thiomorpholinocarboxamide, N-picolinoylcarboxamide, O-X, CH_2-$(CH_2)_q$-X, O-$(CH_2)_q$-X, $(CH_2)_q$-O-X, and CH=CH-X;

wherein X is 4-methoxyphenyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrazyl, quinolyl, 3,5-dimethylisoxazoyl, isoxazoyl, 2-methylthiazoyl, thiazoyl, 2-thienyl, 3-thienyl, or pyrimidyl; and

q is 0-2;

G is U';

M is either oxygen or CH-U';

provided that if G is hydrogen, then M is CH-U' or if M is oxygen, then G is U';

wherein U' is hydrogen, O-[(C1-C4)-straight or branched alkyl] or O-[(C2-C4)straight or branched alkenyl], (C1-C6)-straight or branched alkyl or (C2-C6)-straight or branched alkenyl,

(C5-C7)-cycloalkyl or (C5-C7)-cycloalkenyl substituted with (C1-C4)-straight or branched alkyl or (C2-C4)-straight or branched alkenyl, [(C1-C4)-alkyl or (C2-C4)-alkenyl]-Y or Y;

wherein Y is selected from the group consisting of phenyl, 1-naphthyl, 2-naphthyl, indenyl, azulenyl, fluorenyl, anthracenyl, 2-pyrrolinyl, 3-pyrrolinyl, pyrolidinyl, 1,3-dioxolyl, 2-imidazolinyl, imidazolidinyl, 2H-pyranyl, 4H-pyranyl, piperidyl, 1,4-dioxanyl, morpholinyl, 1,4-dithianyl, thiomorpholinyl, piperazinyl, quinuclidinyl, and heterocyclic aromatic groups as defined for Ar' above; and

wherein Y may contain one to three substituents which are independently selected from the group consisting of hydrogen, halogen, hydroxyl, hydroxymethyl, nitro, trifluoromethyl, trifluoromethoxy, (C1-C6)-straight or branched alkyl, (C2-C6)-straight or branched alkenyl, O-[(C1-C4)-straight or branched alkyl], O-[(C2-C4)-straight or branched alkenyl], O-benzyl, O-phenyl, 1,2-methylenedioxy, amino, and carboxyl;

J is hydrogen, (C1-C2) alkyl or benzyl;

K is (C1-C4)-straight or branched alkyl, benzyl or cyclohexylmethyl, or J' and K are taken together to form a 5-7 membered heterocyclic ring which may contain a heteroatom selected from the group consisting of O, S, SO and SO_2;

m is 0-3; and

wherein said compound is not a compound of formula (I);

b) a neurotrophic factor; and

c) a pharmaceutically suitable carrier.

6. The composition according to claim 6, wherein:

B' and W are independently:

(i) hydrogen, Ar', (C1-C10)-straight or branched alkyl, (C2-C10)-straight or branched alkenyl or alkynyl, (C5-C7)-cycloalkyl substituted (C1-C6)-straight or branched alkyl, (C2-C6)-straight or branched alkenyl or alkynyl, (C5-C7)-cycloalkenyl substituted (C1-C6)-straight or branched alkyl, (C2-C6)-straight or branched alkenyl or alkynyl, or Ar' substituted (C1-C6)-straight or branched alkyl, (C2-C6)-straight or branched alkenyl or alkynyl wherein, in each case, any one of the CH_2 groups of said alkyl, alkenyl or alkynyl chains may be optionally replaced by a heteroatom selected from the group consisting of O, S, SO, SO_2; or



(ii)

Ar may contain one to three substituents which are independently selected from the group consisting of hydrogen, halogen, hydroxyl, hydroxymethyl, nitro, trifluoromethyl, trifluoromethoxy, (C1-C6)-straight or branched alkyl, (C2-C6)-straight or branched alkenyl, O-[(C1-C4)-straight or branched alkyl], O-[(C2-C4)-straight or branched alkenyl], O-benzyl, O-phenyl, 1,2-methylenedioxy, amino and carboxyl; and

Y is selected from the group consisting of phenyl, 1-naphthyl, 2-naphthyl, indenyl, azulenyl, fluorenyl, anthracenyl and heterocyclic aromatic groups as defined for Ar' above.

7. The composition according to claim 5, wherein:

at least one of B' or W is independently selected from the group consisting of (C2-C10)-straight or branched alkynyl; (C5-C7)-cycloalkyl substituted (C2-C6)-straight or branched alkynyl; (C5-C7)-cycloalkenyl substituted (C2-C6)-straight or branched alkynyl; and Ar' substituted (C2-C6)-straight or branched alkynyl.

8. The composition according to claim 5, wherein:

at least one of B' or W is independently represented by the formula $-(CH_2)_r-(Z)-(CH_2)_s-Ar'$, wherein:

Z is independently selected from the group consisting of CH_2, O, S, SO, SO_2, N, and NR;

r is 0-4;

s is 0-1.

9. The composition according to claim 5, wherein:

at least one of B' or W is independently selected from the group consisting of Ar', Ar'-substituted (C1-C6)-straight or branched alkyl, and Ar'-substituted (C2-C6)-straight or branched alkenyl or alkynyl;

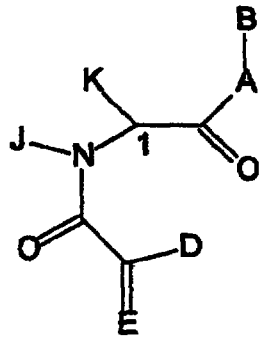
wherein Ar' is substituted with one to three substituents which are independently selected from the group consisting of N-(straight or branched (C1-C5)-alkyl or (C2-C5)-alkenyl) carboxamides, N,N-di-(straight or branched (C1-C5)-alkyl or (C2-C5)-alkenyl)carboxamides, N-morpholinocarboxamide, N-benzylcarboxamide, N-thiomorpholinocarboxamide, N-picolinoylcarboxamide, O-X, $CH_2-(CH_2)_q-X$, $O-(CH_2)_q-X$, $(CH_2)_q-O-X$, and CH=CH-X.

10. The composition according to claim 1 or 5, wherein said neurotrophic factor is selected from nerve

growth factor (NGF), insulin growth factor (IGF) and active truncated derivatives thereof, acidic fibroblast growth factor (aFGF), basic fibroblast growth factor (bFGF), platelet-derived growth factors (PDGF), brain-derived neurotrophic factor (BDNF), ciliary neurotrophic factors (CNTF), glial cell line-derived neurotrophic factor (GDNF), neurotrophin-3 (NT-3) and neurotrophin 4/5 (NT-4/5).

11. The composition according to claim 10, wherein said neurotrophic factor is NGF.

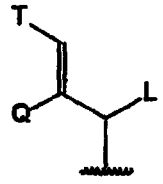
12. A method for stimulating neurite growth in nerve cells comprising the step of contacting said nerve cells with a composition comprising a neurotrophic amount of a compound with affinity for FKBP12 having the formula (I):



(I)

and pharmaceutically acceptable derivatives thereof, wherein A in O, NH, or N-(C1-C4 alkyl);

B is hydrogen, CHL-Ar, (C1-C6)-straight or branched alkyl, (C2-C6)-straight or branched alkenyl, (C5-C7)-cycloalkyl, (C5-C7)-cycloalkenyl or Ar substituted (C1-C6)-alkyl or (C2-C6)-alkenyl, or



wherein L and Q are independently hydrogen, (C1-C6)-straight or branched alkyl or (C2-C6)-straight or branched alkenyl; and

T is Ar or substituted cyclohexyl with substituents at positions 3 and 4 which are independently selected from the group consisting of hydrogen, hydroxyl, O-(C1-C4)-alkyl or O-(C2-C4)-alkenyl;

wherein Ar is selected from the group consisting of 1-naphthyl, 2-naphthyl, 2-furyl, 3-furyl, 2-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl and phenyl having one to three substituents which are independently selected from the group consisting of hydrogen, halo, hydroxyl, nitro, CF_3, (C1-C6)-straight or branched alkyl or (C2-C6)-straight or branched alkenyl, O-(C1-C4)-straight or branched alkyl or O-((C2-C4)-straight or branched alkenyl), O-benzyl, O-phenyl, amino and phenyl;

D is U;

E is either oxygen or CH-U, provided that if D is hydrogen, then E is CH-U or if E is oxygen then D is not hydrogen;

wherein each U is independently selected from hydrogen, O-(C1-C4)-straight or branched alkyl or O-((C2-C4)-straight or branched alkenyl), (C1-C6)-straight or branched alkyl or (C2-C6)-straight or branched alkenyl, (C5-C7)-cycloalkyl or (C5-C7)-cycloalkenyl substituted with (C1-C4)-straight or branched alkyl or (C2-C4)-straight or branched

alkenyl, 2-indolyl, 3-indolyl, [(C1-C4)-alkyl or (C2-C4)-alkenyl]-Ar or Ar;

J is hydrogen or C1 or C2 alkyl;

K is (C1-C4)-straight or branched alkyl, benzyl or cyclohexylmethyl; or J and K are taken together to form a 5-7 membered heterocyclic ring which may contain an O, S, SO or SO_2 substituent therein; and

the stereochemistry at carbon position 1 is R or S.

13. The method according to claim 12, wherein in said compound with affinity for FKBP12:

A is oxygen;

J is hydrogen or C1 or C2 alkyl;

K is (C1-C4)-straight or branched alkyl, benzyl or cyclohexylmethyl; or J and K are taken together to form pyrrolidyl or piperidyl; and

the stereochemistry at carbon position 1 is S.

14. The method according to claim 13, wherein in said compound with affinity for FKBP12:

J and K are taken together to form pyrrolidyl or piperidyl; and

E is CH-U; and

U is dimethylaminophenyl, methoxyphenyl, dimethoxyphenyl, trimethoxyphenyl, nitrophenyl, furyl, indolyl, pyridyl, or methylenedioxyphenyl.

15. The method according to claim 13, wherein in said compound with affinity for FKBP12:

J and K are taken together to form pyrrolidyl or piperidyl;

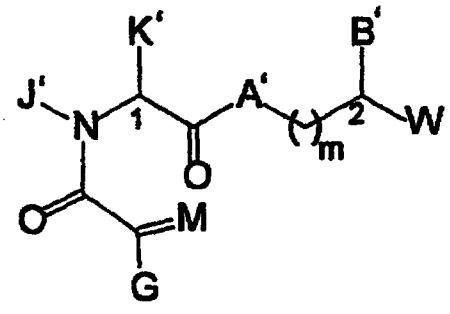
E is oxygen:

B is benzyl, naphthyl, tert-butyl, hydrogen, E-3-phenyl-2-methyl-prop-2-enyl, E-3-(4-hydroxyphenyl) 2-methyl-prop-2-enyl, E-3-[trans(4-hydroxycyclohexyl)]-2-

methyl-prop-2-enyl, cyclohexylethyl, cyclohexylpropyl, cyclohexylbutyl, cyclopentylopropyl, E-3-(4-methoxyphenyl)-2-methyl-prop-2-enyl, E-3-(3,4-dimethoxyphenyl)-2-methyl-prop-2-enyl or E-3-[cis(4-hydroxycyclohexyl)]-2-methyl-prop-2-enyl; and

D is phenyl, methoxyphenyl, cyclohexyl, ethyl, methoxy, nitrobenzyl, thiophenyl, indolyl, furyl, pyridyl, pyridyl-N-oxide, nitrophenyl, fluorophenyl, trimethoxyphenyl or dimethoxyphenyl.

16. A method for stimulating neurite growth in nerve cells comprising the step of contacting said nerve cells with a composition comprising a neurotrophic amount of a compound with affinity for FKBP12 having the formula (II):



(II)

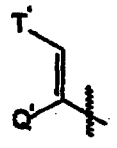
and pharmaceutically acceptable derivatives thereof, wherein A' is CH_2, oxygen, NH or N-(C1-C4 alkyl);

B' and W are independently:

(i) hydrogen, Ar', (C1-C10)-straight or branched alkyl, (C2-C10)-straight or branched alkenyl or alkynyl, (C5-C7)-cycloalkyl substituted (C1-C6)-straight or branched alkyl, (C2-C6)-straight or branched alkenyl or alkynyl, (C5-C7)-cycloalkenyl substituted (C1-C6)-straight or branched alkyl, (C2-C6)-straight or branched alkenyl or alkynyl, or Ar' substituted

-(C1-C6)-straight or branched alkyl, (C2-C6)-straight or branched alkenyl or alkynyl wherein, in each case, any one of the CH_2 groups of said alkyl, alkenyl or alkynyl chains may be optionally replaced by a heteroatom selected from the group consisting of O, S, SO, SO_2, N, and NR,

wherein R is selected from the group consisting of hydrogen, (C1-C4)-straight or branched alkyl, (C2-C4)-straight or branched alkenyl or alkynyl, and (C1-C4) bridging alkyl wherein a bridge is formed between the nitrogen and a carbon atom of said heteroatom-containing chain to form a ring, and wherein said ring is optionally fused to an Ar' group; or



(ii)

wherein Q' is hydrogen, (C1-C6)-straight or branched alkyl or (C2-C6)-straight or branched alkenyl or alkynyl; and

T' is Ar' or substituted 5-7 membered cycloalkyl with substituents at positions 3 and 4 which are independently selected from the group consisting of oxo, hydrogen, hydroxyl, O-(C1-C4)-alkyl, and O-(C2-C4)-alkenyl;

wherein Ar' is a carbocyclic aromatic group selected from the group consisting of phenyl, 1-naphthyl, 2-naphthyl, indenyl, azulenyl, fluorenyl, and anthracenyl; or a heterocyclic aromatic group selected from the group consisting of 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrrolyl, oxazolyl, thiazolyl,

imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, 1,2,3-oxadiazolyl, 1,2,3-triazolyl, 1,3,4-thiadiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,3,5-triazinyl, 1,3,5-trithianyl, indolizinyl, indolyl, isoindolyl, 3H-indolyl, indolinyl, benzo[b]furanyl, benzo[b]thiophenyl, 1H-indazolyl, benzimidazolyl, benzthiazolyl, purinyl, 4H-quinolizinyl, quinolinyl, isoquinolinyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, 1,8-naphthyridinyl, pteridinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, and phenoxazinyl; and

wherein Ar' may contain one to three substituents which are independently selected from the group consisting of hydrogen, halogen, hydroxyl, hydroxymethyl, nitro, trifluoromethyl, trifluoromethoxy, (C1-C6)-straight or branched alkyl, (C2-C6)-straight or branched alkenyl, O-[(C1-C4)-straight or branched alkyl], O-[(C2-C4)-straight or branched alkenyl], O-benzyl, O-phenyl, 1,2-methylenedioxy, amino, carboxyl, N-[(C1-C5)-straight or branched alkyl or (C2-C5)-straight or branched alkenyl)carboxamides, N,N-di-[(C1-C5)-straight or branched alkyl or (C2-C5)-straight or branched alkenyl)]carboxamides, N-morpholinocarboxamide, N-benzylcarboxamide, N-thiomorpholinocarboxamide, N-picolinoylcarboxamide, O-X, CH_2-$(CH_2)_q$-X, O-$(CH_2)_q$-X, $(CH_2)_q$-O-X, and CH=CH-X;

wherein X is 4-methoxyphenyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrazyl, quinolyl, 3,5-dimethylisoxazoyl,

isoxazoyl, 2-methylthiazoyl, thiazoyl, 2-thienyl, 3-thienyl, or pyrimidyl; and

q is 0-2;

G is U';

M is either oxygen or CH-U';

provided that if G is hydrogen, then M is CH-U' or if M is oxygen, then G is U';

wherein U' is hydrogen, O-[(C1-C4)-straight or branched alkyl] or O-[(C2-C4)straight or branched alkenyl], (C1-C6)-straight or branched alkyl or (C2-C6)-straight or branched alkenyl, (C5-C7)-cycloalkyl or (C5-C7)-cycloalkenyl substituted with (C1-C4)-straight or branched alkyl or (C2-C4)-straight or branched alkenyl, [(C1-C4)-alkyl or (C2-C4)-alkenyl]-Y or Y;

wherein Y is selected from the group consisting of phenyl, 1-naphthyl, 2-naphthyl, indenyl, azulenyl, fluorenyl, anthracenyl, 2-pyrrolinyl, 3-pyrrolinyl, pyrolidinyl, 1,3-dioxolyl, 2-imidazolinyl, imidazolidinyl, 2H-pyranyl, 4H-pyranyl, piperidyl, 1,4-dioxanyl, morpholinyl, 1,4-dithianyl, thiomorpholinyl, piperazinyl, quinuclidinyl, and heterocyclic aromatic groups as defined for Ar' above; and

wherein Y may contain one to three substituents which are independently selected from the group consisting of hydrogen, halogen, hydroxyl, hydroxymethyl, nitro, trifluoromethyl, trifluoromethoxy, (C1-C6)-straight or branched alkyl, (C2-C6)-straight or branched alkenyl, O-[(C1-C4)-straight or branched alkyl], O-[(C2-C4)-straight or branched alkenyl], O-benzyl, O-phenyl, 1,2-methylenedioxy, amino, and carboxyl;

J' is hydrogen, (C1-C2) alkyl or benzyl;

K is (C1-C4)-straight or branched alkyl, benzyl or cyclohexylmethyl, or J' and K are taken together to form a 5-7 membered heterocyclic ring which may contain a heteroatom selected from the group consisting of O, S, SO and SO_2; and

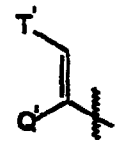
m is 0-3;

wherein said compound is not a compound of formula (I).

17. The method according to claim 16, wherein in said compound with affinity for FKBP12:

B' and W are independently:

(i) hydrogen, Ar', (C1-C10)-straight or branched alkyl, (C2-C10)-straight or branched alkenyl or alkynyl, (C5-C7)-cycloalkyl substituted (C1-C6)-straight or branched alkyl, (C2-C6)-straight or branched alkenyl or alkynyl, (C5-C7)-cycloalkenyl substituted (C1-C6)-straight or branched alkyl, (C2-C6)-straight or branched alkenyl or alkynyl, or Ar' substituted (C1-C6)-straight or branched alkyl, (C2-C6)-straight or branched alkenyl or alkynyl wherein, in each case, any one of the CH_2 groups of said alkyl, alkenyl or alkynyl chains may be optionally replaced by a heteroatom selected from the group consisting of O, S, SO, SO_2; or



(ii)

Ar' may contain one to three substituents which are independently selected from the group consisting of hydrogen, halogen, hydroxyl, hydroxymethyl, nitro, trifluoromethyl, trifluoromethoxy, (C1-C6)-straight or branched alkyl, (C2-C6)-straight or branched alkenyl,

O-[(C1-C4)-straight or branched alkyl], O-[(C2-C4)-straight or branched alkenyl], O-benzyl, O-phenyl, 1,2-methylenedioxy, amino and carboxyl; and

Y is selected from the group consisting of phenyl, 1-naphthyl, 2-naphthyl, indenyl, azulenyl, fluorenyl, anthracenyl and heterocyclic aromatic groups as defined for Ar above.

18. The method according to claim 16, wherein in said compound with affinity for FKBP12:

at least one of B' or W is independently selected from the group consisting of (C2-C10)-straight or branched alkynyl; (C5-C7)-cycloalkyl substituted (C2-C6)-straight or branched alkynyl; (C5-C7)-cycloalkenyl substituted (C2-C6)-straight or branched alkynyl; and Ar' substituted (C2-C6)-straight or branched alkynyl.

19. The method according to claim 16, wherein in said compound with affinity for FKBP12:

at least one of B' or W is independently represented by the formula $-(CH_2)_r-(Z)-(CH_2)_s-Ar'$, wherein:

Z is independently selected from the group consisting of CH_2, O, S, SO, SO_2, N, and NR;

r is 0-4; and

s is 0-1.

20. The method according to claim 16, wherein in said compound with affinity for FKBP12:

at least one of B' or W is independently selected from the group consisting of Ar', Ar'-substituted (C1-C6)-straight or branched alkyl, and Ar'-substituted (C2-C6)-straight or branched alkenyl or alkynyl; and

wherein Ar' is substituted with one to three substituents which are independently selected from

the group consisting of N-(straight or branched (C1-C5)-alkyl or (C2-C5)-alkenyl) carboxamides, N,N-di-(straight or branched (C1-C5)-alkyl or (C2-C5)-alkenyl)carboxamides, N-morpholinocarboxamide, N-benzylcarboxamide, N-thiomorpholinocarboxamide, N-picolinoylcarboxamide, O-X, CH_2-$(CH_2)_q$-X, O-$(CH_2)_q$-X, $(CH_2)_q$-O-X, and CH=CH-X.

21. The method according to claim 12 or 16, wherein said method comprises the additional step of contacting said nerve cells with a neurotrophic factor.

22. The method according to claim 21, wherein said neurotrophic factor is selected from nerve growth factor (NGF), insulin growth factor (IGF) and active truncated derivatives thereof, acidic fibroblast growth factor (aFGF), basic fibroblast growth factor (bFGF), platelet-derived growth factors (PDGF), brain-derived neurotrophic factor (BDNF), ciliary neurotrophic factors (CNTF), glial cell line-derived neurotrophic factor (GDNF), neurotrophin-3 (NT-3) and neurotrophin 4/5 (NT-4/5).

23. The method according to claim 22, wherein said neurotrophic factor is NGF.

24. The method according to claim 12 or 16, wherein said method is used to treat a patient who is suffering from or has suffered from Alzheimer's disease, Parkinson's disease, ALS, stroke and ischemia associated with stroke, neural paropathy, other neural degenerative diseases, motor neuron diseases, sciatic crush, spinal cord injuries or facial nerve crush.

25. The method according to claim 21, wherein said method is used to treat a patient who is suffering from or has suffered from Alzheimer's disease, Parkinson's disease, ALS, stroke and ischemia associated with stroke, neural paropathy, other neural degenerative diseases, motor neuron diseases, sciatic crush, spinal cord injuries or facial nerve crush.