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Use of flecainide as an anti-connexin agent and method for potentiating the effects of a psychotropic drug

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KROEMER, H. K. et al., "Flecainide enantiomers: Disposition in human subjects and electrophysiologic actions in vitro", Clinical Pharmacology & Therapeutics. 1989, vol. 46, no. 5, pages 584-590
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(54) **Title**: USE OF FLECAINIDE AS AN ANTI-CONNEXIN AGENT AND METHOD FOR POTENTIATING THE EFFECTS OF A PSYCHOTROPIC DRUG

(57) **Abstract**: The present invention relates to the use of flecainide as an anti-connexin agent. This anti-connexin agent is advantageously used to potentiate the therapeutic effectof various psychotropic drugs. More specifically, the invention provides a combination product containing flecainide and modafinil.

USE OF FLECAINIDE AS AN ANTI-CONNEXIN AGENT AND METHOD FOR POTENTIATING THE EFFECTS OF A PSYCHOTROPIC DRUG

Summary of the invention

The present invention relates to the use of flecainide as an anti-connexin agent. This anti-connexin agent is advantageously used to potentiate the therapeutic effect of various psychotropic drugs. More specifically, the invention provides a combination product containing flecainide and modafinil.

Background of the invention

Gap junctions are involved in intercellular communication, which is important for maintaining tissue and organ homeostasis. Gap junctions connect the cell cytoplasm, enabling the exchange of ions (Ca^+ and K^+), second messengers (AMPc, GMPc, IP3), several small metabolites (glucose) and ensuring electrical and metabolic coupling between the cells. The gap junctions are junctions with a selective permeability, formed by protein channels contained in the plasma membrane, and formed by connexin hexamers. Connexin hexamers might as well form hemichannel, linked the intracellular space to extracellular one.

Connexins are integral proteins of the plasma membrane, which are synthesized by practically every cell type, regardless of the position of a multicellular organism in the phylogenesis of the animal world. In vertebrates, occasional cells not producing connexins are adult striated muscle cells, spermatozoids and circulating blood cells. Unlike numerous membrane proteins, connexins have a short half-life (between 3 and 6 hours), are not glycosylated and do not have an enzymatic activity. At present, at least thirteen distinct connexins have been identified in mammals; corresponding, in humans, to 21 isoforms. In practice, various types of connexins can be present in a plurality of tissues, and most of the cells synthesize a plurality of connexins. Before reaching the cell membrane, the connexins assemble in groups of six molecules to form hollow tubular structures called connexons,

which join the plasma membrane by means of Golgi vesicles. When cell contact is established, the connexons of a cell align end-to-end with those of the neighboring cell, establishing a continuous hydrophilic channel around 10 nm long. This junctional channel establishes direct contact between the cytoplasms of the two cells in contact, over the intercellular space.

Connexins are involved in a huge number of physiological processes, and several applications of connexin blocking agents (also called hereafter "connexin blocking agents" or "anti-connexin agents") have been described.

For example, anti-connexin agents have been proposed for treating and/or preventing the following conditions:

- cancers (WO2006/134494 and WO2006/049157),
- some cardiovascular diseases (WO2006/134494),
- wounds (WO2006/134494 and WO2009/097077),
- pain (WO2009/148613),
- migraines (Durham and Garrett, 2009),
- epilepsy (Juszczak and Swiergiel, 2009),
- neurological conditions (WO2006/134494) and neurodegenerative diseases (Takeuchi et al. 2011),
- ischemia (Davidson et al, 2013),
- drug-induced liver injury (Patel et al, 2012)
- infectious diseases (WO2011/067607),
- cytotoxicity induced by chemotherapeutic agents (Tong X. et al, 2013)

and

- inflammatory disorders (WO2006/134494).

Furthermore, the present inventors previously described that anti-connexin agents are able to potentiate the therapeutic effects of psychotropic drugs (WO 2010/029131). In particular, they described that administration of anti-connexin agents such as meclofenamic acid (MFA) increases the therapeutic effects of various psychotropic molecules, enabling to reduce the active doses and thus the undesirable effects of these psychotropic molecules. These synergistic effects have been observed with a wide range of

psychotropic molecules (clozapine, paroxetine, modafinil, diazepam, venlafaxine, escitalopram, bupropion and sertraline).

Identifying new anti-connexin agents is therefore of primary importance to highlight new therapeutic tools aiming to treat various diseases and disorders, in particular in combination with psychotropic drugs.

In this context, the inventors have now demonstrated that the well-known antiarrhythmic agent flecainide, has a broad anti-connexin activity. This is a very surprising result, since flecainide had been described so far to interfere with sodium channels, in particular on heart muscle cells, and these channels are not related with brain gap junctions. Moreover, flecainide had been shown not to influence junctional resistance of cardiac myocyte cell pairs (Daleau et al, 1998).

Detailed description of the invention

In the context of the invention, "flecainide" designates a compound of formula *N*-(piperidin-2-ylmethyl)-2,5-bis(2,2,2-trifluoroethoxy) benzamide. As used herein, this term designates any form of this compound, such as a salt thereof. Preferably, said salt is the flecainide acetate. This term may also encompass the flecainide precursors which can be metabolized in the human body and/or its derivatives (for example, chemical derivatives resulting from one or several halogen substitutions and/or from addition of protective groups).

As disclosed on figure 5A and 5B, flecainide possesses a chiral center implying the existence of an R and S enantiomers (S-(+)-flecainide and R-(-)-flecainide). Figure 5 shows the formulas of R-flecainide (Fig. 5A, (*R*)-*N*-(piperidin-2-ylmethyl)-2,5-bis(2,2,2-trifluoroethoxy)benzamide) and S-flecainide (Fig. 5B, (*S*)-*N*-(piperidin-2-ylmethyl)-2,5-bis(2,2,2-trifluoroethoxy)benzamide).

As used herein, the term "flecainide" designates the racemate form of *N*-(piperidin-2-ylmethyl)-2,5-bis(2,2,2-trifluoroethoxy) benzamide, as well as the R and S enantiomers thereof ((*R*)-*N*-(piperidin-2-ylmethyl)-2,5-bis(2,2,2-trifluoroethoxy)benzamide and (*S*)-*N*-

(piperidin-2-ylmethyl)-2,5-bis(2,2,2-trifluoroethoxy)benzamide, respectively). In a preferred embodiment of the invention, the R enantiomer of flecainide ((*R*)-*N*-(piperidin-2-ylmethyl)-2,5-bis(2,2,2-trifluoroethoxy)benzamide) will be used.

Flecainide is currently administered as a racemate (Kroemer et al, 1989; Lie et al, 1989). The pharmacokinetic parameters of the two enantiomers of flecainide have been largely described, after administration in human and rodents, as described below:

In 1989, Kroemer et al. published a study in 13 patients receiving long-term oral flecainide therapy. S-flecainide and R-flecainide plasma levels were determined, and plasma concentrations of R-flecainide were significantly higher than those of the S-flecainide enantiomer (R/S ratio = 1.10), suggesting that the flecainide drug undergoes modest enantioselective disposition [Kroemer et al, 1989].

In 1989, Gross et al. compared the disposition of the two enantiomers in two human populations: extensive (EM) and five poor (PM) metabolizers of sparteine/debrisoquine after administration of 50mg of racemic flecainide acetate [Gross et al, 1989]. Gross et al. presented data indicating that the half-life of R-flecainide (12.9h) was longer ($P< 0.03$) than that of S-flecainide (9.8h). The renal clearance of the two enantiomers was, however, comparable and similar to that observed in the EM subjects. The urinary recovery of R-flecainide (15.6± 3.7mg) was greater ($P< 0.03$) than that of the S-enantiomer (12.0 ± 3.7 mg). The enantioselective disposition observed in PMs is therefore due to greater impairment in the metabolism of R-flecainide than S-flecainide.

In 1991, Alessi-Severini et al. summarized key findings on pharmacokinetics and concluded that there was no evidence of enantioselective disposition of flecainide in human [Alessi-Severini et al., 1991], citing three reports on stereoselective therapeutic monitoring, which found R/S ratio ranges of 0.67-1.39 (mean 1.03 ± 0.16), 0.75-1.44 (mean 1.04), and 0.89-1.32 (mean 1.10 ± 0.13), and that Gross et al. 1989 study was not relevant on the total population.

In 1998, Hanada et al. demonstrated an absence of enantioselective distribution of the two enantiomers of flecainide in several tissue, after intravenous administration of flecainide racemate in rats [Hanada et al, 1998].

As reviewed in [Mehvar et al, 2002], it appears that the renal clearances of the enantiomers of flecainide are not stereoselective in both healthy volunteers and patients.

Literature is thus globally coherent on the absence of stereoselective effects of flecainide on pharmacokinetics and metabolism.

The physicochemical properties of the two enantiomers of flecainide have been also described. In particular, Turgeon et al. described a stereoselective analytical method for the determination of the antiarrhythmic agent flecainide in human plasma. The resolution of the enantiomers is achieved by high-performance liquid chromatography (HPLC) on a normal phase silica column following derivatization with the optically active reagent (-)-methyl chloroformate [Turgeon et al., 1990].

Moreover, Alessi-Severini et al. described a stereospecific high-performance liquid chromatographic method for the determination of (R,S)-flecainide acetate in human plasma and urine. Flecainide diastereomers were separated after i) a single-step extraction of alkalinized samples performed with distilled diethyl ether, ii) the organic layer was evaporated and the drug was derivatized with 1-[(4-nitrophenyl)sulfonyl]-L-propyl chloride at 80 degrees C for 2 h and iii) by high-performance liquid chromatography (HPLC) on a C18 reversed-phase column with a mobile phase consisting of acetonitrile:water:triethylamine (45:55:0.2) at a flow rate of 1 mL/min [Alessi-Severini et al., 1990].

Racemic flecainide acetate is a widely used class 1c antiarrhythmic agent, which is indicated for treating various types of arrhythmias. More specifically, it is used to regulate the rate and rhythm of the heart. The heart's pumping action is controlled by electrical signals that pass through the heart muscle. These electrical signals cause the two pairs of heart chambers (left and right arteria and ventricles) to contract in a regular manner to produce regular heartbeats. If the electrical activity in the heart is disturbed for any reason, irregular heartbeats (arrhythmias) of various types can result. Flecainide helps to treat arrhythmias by decreasing the sensitivity of the heart muscle cells to electrical impulses. This regulates the electrical conduction in the heart muscle and reduces disturbances in the heart rhythm. As a class I antiarrhythmic agent, flecainide interferes with the sodium channel.

Importantly, several studies have demonstrated that these cardiovascular effects are not mediated by a single enantiomer, both of them contributing to cardiovascular functions:

Antiarrhythmic effects of flecainide and its enantiomers were assessed in two different animal models, chloroform-induced ventricular fibrillation in mice and ouabain-induced ventricular tachycardia in dogs. The two enantiomers were highly effective in suppressing both of these experimental arrhythmias and appeared to be essentially equipotent. No significant differences were found either between the two enantiomers or between the enantiomers and racemic flecainide [Banitt et al, 1986].

The effects of the enantiomers on action potential characteristics in canine cardiac Purkinje fibers were assessed, and they were shown to exert similar electrophysiological effects [Kroemer et al, 1989].

The effects of flecainide acetate racemate and its two enantiomers on voltage-operated sodium and potassium channels and on the sodium pump activity of non-myelinated fibers of the guinea-pig vagus nerve were studied with the sucrose-gap method. There was no significant difference in the effect caused by the enantiomers separately [Lie et al, 1989].

The effects of the enantiomers were evaluated in isolated canine Purkinje fibers using standard microelectrode techniques. The results suggest there is no significant difference between the effects of flecainide enantiomers on basic electro- physiological parameters of canine Purkinje fibers [Smallwood et al, 1989].

To conclude, all those studies have provided no evidence to indicate that administration of a single enantiomer, rather than the racemic drug, would offer any advantage.

According to a first aspect, the present invention therefore pertains to the use of flecainide, *in vitro* and *in vivo*, as an anti-connexin agent. In particular, the present invention relates to flecainide for use as an anti-connexin agent, or, in other words, for blocking gap junctions.

There are 21 genes coding for different connexin isoforms in humans, and different combinations of connexin monomers involved in the composition of the gap junctions are described. In particular, the connexins 26 (Cx 26), 30 (Cx 30), 30.2 (Cx30.2), 32 (Cx 32),

36 (Cx 36), 37 (Cx 37), 40 (Cx 40), 43 (Cx 43), 45 (Cx 45), 46 (Cx 46), and 47 (Cx 47) are expressed in human on cells of the Central or Peripheral Nervous System (Nakase & Naus, 2004).

The present inventors observed that flecainide is effective for inhibiting gap junctions made of all connexin they tested. In particular, and as disclosed in the experimental part below, flecainide is effective for inhibiting gap junctions made of connexin Cx40, Cx26, Cx30, Cx32, and /or Cx43. Importantly, this anti-connexin effect is similar to the one observed for well-known anti-connexin agents such as mefloquine and meclofenamic acid (MFA) (Juszczak & Swiergiel, 2009; Cruikshank et al, 2004; Harks et al, 2001). Higher inhibition levels were even reached for glial connexins Cx26, Cx30 and Cx43 (see figure 1).

The present invention therefore relates to the *in vitro* use of flecainide as an anti-connexin agent. Preferably, this agent can be used to inhibit gap junctions made of the connexins selected in the group consisting of: Cx23 (SEQ ID NO:1), Cx25 (SEQ ID NO:2), Cx26 (SEQ ID NO:3), Cx 30 (SEQ ID NO:4), Cx30.2 (SEQ ID NO:5), Cx30.3 (SEQ ID NO:6), Cx31 (SEQ ID NO:7), Cx31.1 (SEQ ID NO:8), Cx31.9 (SEQ ID NO:9), Cx32 (SEQ ID NO:10), Cx36 (SEQ ID NO:11), Cx37(SEQ ID NO:12), Cx40 (SEQ ID NO:13), Cx40.1 (SEQ ID NO:14), Cx43 (SEQ ID NO:15), Cx45 (SEQ ID NO:16), Cx46 (SEQ ID NO:17), Cx47 (SEQ ID NO:18), Cx50 (SEQ ID NO:19), Cx59 (SEQ ID NO:20), and Cx62 (SEQ ID NO:21).

In a preferred embodiment of the invention, flecainide is used for blocking one or more of the connexins expressed in human cells of the Central or Peripheral Nervous System, that are selected in the group consisting of: Cx 26 (SEQ ID NO:3), Cx 30 (SEQ ID NO:4), Cx 30.2 (SEQ ID NO:5), Cx 32 (SEQ ID NO:10), Cx 36 (SEQ ID NO:11), Cx 37 (SEQ ID NO:12), Cx 40 (SEQ ID NO:13), Cx 43 (SEQ ID NO:15), Cx 45 (SEQ ID NO:16), Cx 46 (SEQ ID NO:17) and Cx 47 (SEQ ID NO:18).

In a more preferred embodiment, flecainide is used for blocking one or more of the connexins selected in the group consisting of: Cx40 (SEQ ID NO:13), Cx26 (SEQ ID NO:3), Cx30 (SEQ ID NO:4), Cx32 (SEQ ID NO:10), and Cx43 (SEQ ID NO:15).

In an even more preferred embodiment, flecainide is used for blocking one or more of the connexins selected in the group consisting of: Cx26 (SEQ ID NO:3), Cx30 (SEQ ID NO:4) and Cx43 (SEQ ID NO:15).

Due to its anti-connexin activity, flecainide can be used for the treatment of a number of disorders and conditions known to benefit from treatment by anti-connexin molecules.

These disorders and conditions include, but are not limited to: cancers, cardiovascular diseases, wounds, pain, migraines, epilepsy, neurological conditions and neurodegenerative diseases, infectious diseases, drug-induced liver injury, cytotoxicity induced by chemotherapeutic agents, ischemia and inflammatory disorders.

More preferably, flecainide can be used for the prevention and/or the treatment of cancers, wounds, migraines, epilepsy, infectious diseases, drug-induced liver injury, cytotoxicity induced by chemotherapeutic agents, ischemia and inflammatory disorders.

Even more preferably, flecainide can be used for the prevention and/or the treatment of wounds, migraines, infectious diseases, drug-induced liver injury, cytotoxicity induced by chemotherapeutic agents, and ischemia.

Even more preferably, flecainide can be used for the prevention and/or the treatment of drug-induced liver injury, cytotoxicity induced by chemotherapeutic agents, and ischemia.

According to a particular aspect of the present invention, flecainide is used as an agent for potentiating the effects of a psychotropic drug. These potentiating effects are illustrated below by experiments performed with modafinil (see figures 2 to 4). As an anti-connexin agent, flecainide can potentiate the effects of any psychotropic drug (as shown in WO 2010/029131 and US 2011/172188, incorporated by reference).

The term "potentiate" in this case means that flecainide significantly increases the therapeutic effects of the psychotropic drug administered to the same patient. Thus, the combination of the psychotropic drug with flecainide makes it possible to reduce the doses of said psychotropic drug and therefore to limit the adverse effects of said psychotropic drug, and/or to obtain a stronger therapeutic effect without increasing the dose of said psychotropic drug.

In the present text, a "psychotropic drug" or "psychotropic agent" refers to any substance that acts primarily on the state of the central nervous system by modifying certain cerebral biochemical and physiological processes. Examples of psychotropic drugs which can be used in the context of the present invention include anesthetics, analgesics such as opioids, antipyretics and antimigraine preparations, anti-epileptics, anti-Parkinson drugs such as anti-cholinergic and dopaminergic anti-Parkinson agents, psycholeptics such as antipsychotics, anxiolytics, hypnotics and sedatives, psychoanaleptics such as antidepressants, psychostimulants and anti-dementia drugs, as well as parasymptomimetics, anti-addiction drugs, antivertigo preparations *etc*. Non-limitative examples of specific molecules which can be advantageously used as psychotropic drugs according to the invention are listed in Table 1 below.

Therapeutic category	Pharmacological sub-class	Chemical sub-class	Active agent
Anesthetics	***1.*** General anesthetics	***2.*** Ethers	***3.*** diethyl ether; vinyl ether
		4. Halogenated hydrocarbons	***5.*** halothane; chloroform; enflurane; trichloroethylene; isoflurane; desflurane; sevoflurane
		6. Barbiturates, plain	*7.* methohexital; hexobarbital;
		8. Barbiturates in combination with other drugs	***9.*** narcobarbital
		10. Opioid anesthetics	***11.*** fentanyl; alfentanil; sufentanil; phenoperidine; anileridine; remifentanil;
		12. Other general anesthetics	***13.*** droperidol; ketamine; propanidid; alfaxalone; etomidate; propofol; sodium oxybate; nitrous oxide; esketamine; xenon;
	14. Local anesthetics	***15.*** Esters of aminobenzoic acid	***16.*** metabutethamine; procaine; tetracaine; chloroprocaine; benzocaine;
		17. Amides	***18.*** bupivacaine; lidocaine; mepivacaine; prilocaine; butanilicaine; cinchocaine; etidocaine; articaine;ropivacaine; levobupivacaine ; bupivacaine ;
		19. Esters of benzoic acid	20. cocaine
		21. Other local anesthetics	***22.*** ethyl chloride; dyclonine; phenol; capsaicin

Analgesics	***23.*** Opioids	***24.*** Natural opium alkaloids	***25.*** opium; hydromorphone; nicomorphine; oxycodone; dihydrocodeine; diamorphine; papaveretum; morphine; codeine,
		26. Phenylpiperidine derivatives	***27.*** ketobemidone; pethidine;
		28. Diphenylpropylamine derivatives	***29.*** dextromoramide; piritramide; dextropropoxyphene; bezitramide; methadone,
		30. Benzomorphan derivatives	***31.*** pentazocine; phenazocine
		32. Morphinan derivatives	***33.*** butorphanol; nalbuphine
		34. Other opioids	***35.*** tilidine; tramadol; dezocine; meptazinol; tapentadol;
	36. Other analgesics and antipyretics	***37.*** Salicylic acid and derivatives	***38.*** acetylsalicylic acid; aloxiprin; choline salicylate; sodium salicylate; salicylamide; salsalate; ethenzamide; morpholine salicylate; dipyrocetyl; benorilate; diflunisal; potassium salicylate; guacetisal; carbasalate calcium; imidazole salicylate
		39. Pyrazolones	***40.*** phenazone; metamizole sodium; aminophenazone ; propyphenazone; nifenazone;
		41. Anilides	***42.*** paracetamol; phenacetin; bucetin; propacetamol ;
		43. Other analgesics and antipyretics	***44.*** rimazolium; glafenine; floctafenine; viminol; nefopam; ziconotide; methoxyflurane; nabiximols
	45. Antimigraine Preparations	***46.*** Ergot alkaloids	***47.*** Dihydroergotamine; ergotamine; methysergide; lisuride;
		48. Corticosteroid derivatives	***49.*** flumedroxone
		50. Selective serotonin (5HT1) agonists	***51.*** sumatriptan; naratriptan; zolmitriptan; rizatriptan; almotriptan; eletriptan; frovatriptan
		52. Other antimigraine preparations	***53.*** pizotifen; clonidine; iprazochrome; dimetotiazine ; oxetorone
Anti-epileptics	***54.*** Antiepileptics	***55.*** Barbiturates and derivatives	***56.*** methylphenobarbital; Phenobarbital; primidone; barbexaclone; metharbital
		57. Hydantoin derivatives	***58.*** ethotoin; phenytoin; amino(diphenylhydantoin) valeric

			acid; mephenytoin; fosphenytoin;
		59. Oxazolidine derivatives	***60.*** paramethadione; trimethadione; ethadione
		61. Succinimide derivatives	***62.*** Ethosuximide; phensuximide; mesuximide;
		63. Benzodiazepine derivatives	***64.*** clonazepam
		65. Carboxamide derivatives	***66.*** carbamazepine; oxcarbazepine; rufinamide; eslicarbazepine
		67. Fatty acid derivatives	***68.*** valproic acid; valpromide; aminobutyric acid; vigabatrin; progabide; tiagabine
		69. Other antiepileptics	***70.*** sultiame; phenacemide; lamotrigine; felbamate; topiramate; gabapentin; pheneturide; levetiracetam; zonisamide; pregabalin; stiripentol; lacosamide; carisbamate; retigabine;beclamide
Anti-Parkinson drugs	***71.*** Anticholinergic agents	***72.*** Tertiary amines	***73.*** Trihexyphenidyl; biperiden; metixene; procyclidine; profenamine; dexetimide; phenglutarimide; mazaticol; bornaprine; tropatepine
		74. Ethers chemically close to antihistamines	***75.*** etanautine; orphenadrine
		76. Ethers of tropine or tropine derivatives	***77.*** benzatropine; etybenzatropine
	78. Dopaminergic agents	***79.*** Dopa and dopa derivatives	***80.*** levodopa; decarboxylase inhibitor; COMT inhibitor; melevodopa ; etilevodopa
		81. Adamantane derivatives	***82.*** amantadine
		83. Dopamine agonists	***84.*** bromocriptine; pergolide; dihydroergocryptine; esylate; ropinirole; pramipexole; cabergoline; apomorphine; piribedil; rotigotine
		85. Monoamine oxidase B inhibitors	***86.*** selegiline; rasagiline
		87. Other dopaminergic agents	***88.*** olcapone; entacapone; budipine
Psycho-leptics	***89.*** Antipschotics	***90.*** Phenothiazines with	***91.*** chlorpromazine; levomepromazine; promazine;

		aliphatic side-chain	acepromazine; triflupromazine; cyamemazine; chlorproethazine
		92. Phenothiazines with piperazine structure	***93.*** dixyrazine; fluphenazine; perphenazine; prochlorperazine; thiopropazate; trifluoperazine; acetophenazine; thioproperazine; butaperazine; perazine
		94. Phenothiazines with piperidine structure	***95.*** periciazine; thioridazine; mesoridazine; pipotiazine
		96. Butyrophenone derivatives	***97.*** Haloperidol; trifluperidol; melperone; moperone; pipamperone; bromperidol; benperidol; droperidol; fluanisone
		98. Indole derivatives	***99.*** oxypertine; molindone; sertindole; ziprasidone
		100. Thioxanthene derivatives	***101.*** flupentixol; clopenthixol; chlorprothixene; tiotixene; zuclopenthixol
		102. Diphenylbutylpiperidine derivatives	***103.*** fluspirilene; pimozide; penfluridol
		104. Diazepines, oxazepines, thiazepines and oxepines	***105.*** loxapine; clozapine; olanzapine; quetiapine; asenapine; clotiapine
		106. Benzamides	***107.*** sulpiride; sultopride; tiapride; remoxipride; amisulpride; veralipride; levosulpiride
		108. Lithium	***109.*** lithium
		110. Other antipsychotics	***111.*** prothipendyl; risperidone; mosapramine; zotepine; aripiprazole; paliperidone
	112. Anxiolytics	***113.*** Benzodiazepine derivatives	***114.*** chlordiazepoxide; medazepam; oxazepam; potassium clorazepate; lorazepam; adinazolam; bromazepam; clobazam; ketazolam; prazepam; alprazolam; halazepam; pinazepam camazepam; nordazepam; fludiazepam; ethyl loflazepate; etizolam; clotiazepam; cloxazolam; tofisopam ;
		115. Diphenylmethane derivatives	***116.*** hydroxyzine; captodiame;
		117. Carbamates	118. meprobamate; emylcamate; mebutamate;

		119. Dibenzo-bicyclo-octadiene derivatives	***120.*** benzoctamine
		121. Azaspirodecanedione derivatives	***122.*** buspirone
		123. Other anxiolytics	***124.*** Mephenoxalone; gedocarnil; etifoxine
	125. Hypnotics and sedatives	***126.*** Barbiturates, plain	***127.*** Pentobarbital; amobarbital; butobarbital; barbital; aprobarbital; secobarbital; talbutal; vinylbital; vinbarbital; cyclobarbital; heptabarbital; reposal; methohexital; thiopental; etallobarbital; allobarbital; proxibarbal
		128. Aldehydes and derivatives	***129.*** chloral hydrate; chloralodol; acetylglycinamide; dichloralphenazone; paraldehyde
		130. Benzodiazepine derivatives	***131.*** flurazepam; nitrazepam; flunitrazepam; estazolam; triazolam; lormetazepam; temazepam; midazolam; brotizolam; quazepam; loprazolam; doxefazepam; cinolazepam
		132. Piperidinedione derivatives	***133.*** glutethimide; methyprylon; pyrithyldione
		134. Benzodiazepine related drugs	***135.*** zopiclone; zolpidem; zaleplon; eszopiclone
		136. Melatonin receptor agonists	137. melatonin; ramelteon
		138. Other hypnotics and sedatives	***139.*** methaqualone; clomethiazole; bromisoval; carbromal; scopolamine; propiomazine; triclofos ethchlorvynol; valerian; hexapropymate; bromides; apronal; valnoctamide; methylpentynol; niaprazine; dexmedetomidine
		140. Hypnotics and sedatives in combination, excl. barbiturates	***141.*** emepronium; dipiperonylaminoethanol
Psychoanaleptics	***142.*** Antidepressants	***143.*** Non-selective monoamine reuptake inhibitors	***144.*** desipramine; imipramine; imipramine oxide; clomipramine; opipramol; trimipramine; lofepramine; dibenzepin; amitriptyline; nortriptyline;

			protriptyline; doxepin; iprindole; melitracen; butriptyline; dosulepin; amoxapine; dimetacrine; amineptine ; maprotiline; quinupramine
		145. Selective serotonin reuptake inhibitors	***146.*** zimeldine; fluoxetine; citalopram; paroxetine; sertraline; alaproclate; fluvoxamine; etoperidone; escitalopram
		147. Monoamine oxidase inhibitors, non-selective	***148.*** isocarboxazid; nialamide; phenelzine; tranylcypromine; iproniazide; iproclozide
		149. Monoamine oxidase A inhibitors	***150.*** moclobemide; toloxatone
		151. Other antidepressants	***152.*** oxitriptan; tryptophan; mianserin; nomifensine; trazodone; nefazodone; minaprine; bifemelane; viloxazine; oxaflozane; mirtazapine; bupropion; medifoxamine; tianeptine; pivagabine; venlafaxine; milnacipran; reboxetine; gepirone; duloxetine; agomelatine; desvenlafaxine
	153. Psychostimulants, agents used for ADHD and nootropics	***154.*** Centrally acting sympathomimetics	***155.*** amphetamine; dexamfetamine; metamfetamine; methylphenidate; pemoline; fencamfamin; modafinil; armodafinil; fenozolone; atomoxetine; fenetylline ; exmethylphenidate; lisdexamfetamine
		156. Xanthine derivatives	***157.*** caffeine; propentofylline
		158. Other psychostimulants and nootropics	***159.*** meclofenoxate; pyritinol; piracetam; deanol; fipexide; citicoline; oxiracetam; pirisudanol; linopirdine; nizofenone; aniracetam; acetylcarnitine; idebenone; prolintane; pipradrol; pramiracetam; adrafinil; vinpocetine ; pitolisant ;
	160. Anti-dementia drugs	***161.*** Anticholinesterases	***162.*** tacrine; donepezil; rivastigmine; galantamine
		163. Other anti-dementia drugs	***164.*** memantine; ginkgo biloba
Other nervous	***165.*** Parasympat	***166.*** Anticholines	***167.*** neostigmine; pyridostigmine;

system drugs	homimetics	terases	distigmine; ambenonium;
		168. Choline esters	***169.*** carbachol; bethanechol
		170. Other parasympathomimetics	***171.*** pilocarpine; choline alfoscerate; cevimeline
	172. Drugs used in addictive disorders	***173.*** Drugs used in nicotine dependence	***174.*** nicotine; varenicline
		175. Drugs used in alcohol dependence	***176.*** disulfiram; calcium carbimide; acamprosate; naltrexone; baclofene
		177. Drugs used in opioid dependence	***178.*** buprenorphine; levacetylmethadol ; lofexidine;
	179. Antivertigo preparations	***180.*** Antivertigo preparations	***181.*** betahistine; cinnarizine; flunarizine; acetylleucine
	182. Other nervous system drugs	***183.*** Other nervous system drugs	***184.*** tirilazad; riluzole; xaliproden ; amifampridine; tetrabenazine; fampridine; mazindol

Table 1: Psychotropic molecules

Preferably, the said psychotropic drug is selected in the group consisting of: dopaminergic, GABAergic, adrenergic, acetylcholinergic, serotoninergic, opioidergic, adenosinergic, ionotropic, histaminergic, IMAO, Catechol-O-methyl transferase, DOPA decarboxylase, noradrenergic and glutamatergic psychotropic effectors, as well as molecules having an effect on the hypocretin/orexin system (including hypocretin-1 and hypocretin-2).

The term "effector" herein refers to any substance activating or inhibiting, directly or indirectly, one or more neuroreceptors, as well as any substance that modifies the concentration of said neurotransmitter; therefore, an effector according to the present invention can be an agonist or an antagonist of said receptors.

It is shown in the examples below that said psychotropic drug is advantageously modafinil.

As a matter of fact, the present inventors have shown that flecainide potentiates the promnesiant and/or awakening effects of modafinil (see figures 2 and 3), and that the modafinil/flecainide combination shows promising effects by reducing cataplectic-like events in mice. The precise mechanism of modafinil action has not been completely

elucidated yet. In fact, it is known that modafinil acts on several molecular receptors, in particular on the dopamine, norepinephrine, serotonine, glutamate, GABA, orexine and histamine receptors (Ishizuka et al, 2012; Minzenberg et al, 2008). Therefore, modafinil acts as a GABAergic, dopaminergic, norepinephrinergic, serotoninergic, histaminergic, and glutamatergic effectors, and it has an effect on the hypocretin/orexin system (including hypocretin-1 and hypocretin-2).

Any compound modulating the same molecular receptors as modafinil can be advantageously associated with flecainide.

Thus, in a preferred embodiment, the psychotropic drug which is associated with flecainide acts on the very same receptors as modafinil does. The psychrotropic drug associated with flecainide is therefore preferably selected in the group consisting of: GABAergic, dopaminergic, norepinephrinergic, serotoninergic, histaminergic, and glutamatergic effectors. Also, it may have an effect on the hypocretin/orexin system (including hypocretin-1 and hypocretin-2).

According to a specific embodiment, the said psychotropic drug is a dopaminergic effector selected in the group consisting of: ADX-N05 (formely "YKP10A", having the formula: (R)- (beta-amino-benzenepropyl) carbamate mono- hydrochloride), amphetamine, loxapine, acepromazine, methylphenidate, pergolide, lisuride, bromocriptine, dopamine, ropinirole, apomorphine, aripiprazole, sulpiride, amisulpride, sultopride, tiapride, pimozide, risperidone, haloperidol, penfluridol, zuclopenthixol or bupropion.

According to another specific embodiment, the said psychotropic drug is a GABAergic effector selected in the group consisting of: tiagabine, topiramate, clorazepate, diazepam, clonazepam, oxazepam, lorazepam, bromazepam, lormetazepam, nitrazepam, clotiazepam, aiprozolam, estazolam, triazolam, loprazolam, etifoxin, meprobamate, zopiclone, zolpidem, pregabaline, gabapentine, phenobarbital, felbamate and vigabatrin.

According to another specific embodiment, the said psychotropic drug is a serotoninergic effector selected in the group consisting of: chlorpromazine, trimipramine, clozapine, olanzapine, cyamemazine, flupentixol, nefopam, fluvoxamine, clomipramine, sertraline, fluoxetine, citalopram, escitalopram, paroxetine, amitriptyline, duloxetine, venlafaxine, buspirone, carpipramine, zolmitriptan, sumatriptan, naratriptan, indoramine, ergotamine,

ergotamine tartrate, pizotifene, pipamperone, methysergide, pizotyline, milnacipran,, viloxazine, tianeptine, hypericum and lithium.

According to another specific embodiment, the said psychotropic drug is a histaminergic effector selected in the group consisting of: acrivastine, alimemazine, antazoline, astemizole, azatadine, azelastine, brompheniramine, buclizine, carbinoxamine, carebastine, cetirizine, chlorcyclizine, chlorpheniramine, cinnarizine, clemastine, clemizole, clocinizine, clonidine, cyclizine, cyproheptadine, descarboethoxyloratidine, dexchlorpheniramine, dimenhydrinate, dimethindene, dimethothiazine, diphenhydramine, diphenylpyraline, doxylamine, ebastine, efletirizine, epinastine, fexofenadine,hydroxyzine, ketotifen, levocabastine, loratidine, meclizine, mequitazine, methdilazine, mianserin, mizolastine, niaprazine, noberastine, norastemizole, oxatomide, oxomemazine, phenbenzamine, pheniramine, picumast, promethazine, pyrilamine, temelastine, terfenadine, trimeprazine, tripelennamine, triprolidine, ranitidine, cimetidine, famotidine, nizatidine, tiotidine, zolantidine, ciproxifan, pitolisant and ritanserine.

According to another specific embodiment, the said psychotropic drug is a hypocretin/orexin modulator selected in the group consisting of: EMPA, SB-334867, SB-674042, SB-408124, GSK1059865, almorexant, suvorexant, MK-6096, DORA-1, DORA-22, DORA-12, SB-649868, JNJ-1037049 (described in Gotter et al, 2012)).

According to another specific embodiment, the said psychotropic drug is a norepinephrinergic effector selected in the group consisting of: (R)-3-nitrobiphenyline, 2-fluoronorepinephrine, 4-NEMD, 5-fluoronorepinephrine, 6-fluoronorepinephrine, abediterol, albuterol, amibegron, amidephrine, amitraz, anisodamine, anisodine, apraclonidine, arbutamine, arformoterol, arotinolol, bambuterol, befunolol, bitolterol, brimonidine, bromoacetylalprenololmenthane, broxaterol, buphenine, cannabivarin, carbuterol, cimaterol, cirazoline, clenbuterol, denopamine, deterenol, detomidine, dexmedetomidine, dihydroergotamine, dipivefrine, dobutamine, dopexamine, ephedrine, epinephrine , esproquin, etafedrine, ethylnorepinephrine, etilefrine, fenoterol, formoterol, guanabenz, guanfacine, guanoxabenz, hexoprenaline, higenamine, indacaterol, indanidine, isoetarine, isoprenaline, isoproterenol, isoxsuprine, labetalol, levonordefrin, levosalbutamol, lofexidine, mabuterol, medetomidine, metaraminol, methoxamine, methoxyphenamine, methyldopa, midodrine, mivazerol, n-isopropyloctopamine,

naphazoline, norepinephrine, octopamine, orciprenaline, oxyfedrine, oxymetazoline, phenylephrine, phenylpropanolamine, piperoxan, pirbuterol, prenalterol, procaterol, pseudoephedrine, ractopamine, reproterol, rilmenidine, rimiterol, ritodrine, romifidine, salbutamol, salmeterol, solabegron, synephrine, talipexole, terbutaline, tetrahydrozoline, tizanidine, tolonidine, tretoquinol, tulobuterol, urapidil, xamoterol, xylazine, xylometazoline, zilpaterol, and zinterol.

According to another specific embodiment, the said psychotropic drug is a glutamatergic effector selected in the group consisting of: memantine, amantadine, MK-801, ketamine, norketamine, dextromethorphan, levometorphan, dextrorphan, levorphanol, phencyclidine, PCA, CNS-1102, remacemide, pentamidine, and 9-aminoacridine (described in Traynelis et al, 2010).

Preferably, said psychotropic drug is not flupirtine.

The potentiating effects of flecainide can be achieved by administrating same to a patient, either before, at the same time, of after administration of the psychotropic drug to said patient.

Consequently, the present invention describes a method for treating a patient with psychiatric and/or neurodegenerative disorders, including the administration to said patient of a) flecainide and b) at least one psychotropic drug as mentioned above, in which said compounds a) and b) are administered simultaneously, separately or spread out over time.

Patients needing this treatment may have psychiatric, neurologic and/or neurodegenerative disorders included in the group consisting of: excessive daytime sleepiness (EDS), sleep disorders, insufficient sleep time, central sleep apnea, narcolepsy (with or without cataplexy), obstructive sleep apnea/hypopnea (SAHOS), idiopathic hypersomnia, Kleine-Levin syndrome, circadian rhythm disorders, shift work sleep disorder, jet-lag, disorders after sleep restriction or sleep deprivation (attention disorders, alertness disorders, sleepiness), restless legs syndrome (RLS) and Periodic Lim Movement Disorders (PLMD), insomnia, parasomnia, attention deficit hyperactivity disorder (ADHD), post-traumatic stress disorder (PTSD), disorders commonly associated with somnolence or sleepiness (such as Parkinson disease, multiple sclerosis, stroke, neuromuscular disorders or structural brain disorders, respiratory disorders, chronic renal failure, liver failure, rheumatologic

disorders), medication-induced somnolence (due to benzodiazepines, barbiturates, sleeping pills, antidepressants, anti-psychotics…), mood disorders, anxiety disorders, schizophrenia, tinnitus, depression, malaise, dementia, bipolar disorder, obesity, hyperphagia, manic episode, obsessive-compulsive disorder, senility, dependence or addiction (to games, drugs, alcohol, tobacco, etc.), fecal or urinary incontinence, premature ejaculation, breathing difficulty and fatigue, notably due to cancer, neurodegenerative disorders, menopause, traumatic brain injuries, viral infection or post-myelitis, or to fibromyalgia.

Excessive daytime sleepiness (EDS) occurs daily, recurring typically every 2 h, although this can vary widely. Sleepiness is exacerbated when the patient is physically inactive. The sleep episodes have several characteristics (Dauvilliers I. et al, 2007 and Boulos et al, 2010):

- They are often irresistible, despite the individual making desperate efforts to fight the urge to sleep;
- They are usually short, although their length can vary with environmental factors (eg, the duration can increase with passive activities such as watching television);
- They are frequently associated with dreaming;
- They typically restore normal wakefulness for up to several hours.

EDS characterizes several conditions or diseases: insufficient sleep time, central sleep apnea, narcolepsy (with or without cataplexy), obstructive sleep apnea/hypopnea (SAHOS), idiopathic hypersomnia, recurrent hypersomnia (Kleine-Levin syndrome), circadian rhythm disorders (jet lag), disorders after sleep restriction or sleep deprivation (attention disorders, alertness disorders, sleepiness), restless legs syndrome (RLS) and Periodic Lim Movement Disorders (PLMD), neurological conditions commonly associated with sleepiness (such as Parkinson disease, multiple sclerosis, stroke, neuromuscular disorders or structural brain disorders), medical conditions commonly associated with sleepiness (respiratory disorders, chronic renal failure, liver failure, rheumatologic disorders), mood disorders, anxiety disorders, schizophrenia, or medication-induced somnolence (due to benzodiazepines, barbiturates, sleeping pills, antidepressants, anti-psychotics…).

Cataplexy is characterized by a sudden drop of muscle tone triggered by emotional factors, most often by positive emotions such as laughter, repartee, pleasant surprise (e.g., seeing friends in the street or scoring a goal), or by anger, but almost never by stress, fear, or physical effort. Many neurophysiological and pharmaceutical studies indicate that cataplexy shares common neurophysiological mechanisms with REM sleep atonia (Dauvilliers I. et al, 2007).

In the case of simultaneous use, the two components of the treatment are administered to the patient simultaneously. According to this embodiment of the present invention, the two components can be packaged together, in the form of a mixture, or separately, then mixed spontaneously before being administered together to the patient. Alternatively, the two components are administered simultaneously, but separately. In particular, the routes of administration of the two components may be different. The administration can also be performed at different sites. In another embodiment, the two components are administered sequentially or spaced apart over time, for example in the same day or at an interval ranging from several minutes to several days.

Since flecainide potentiates the effects of psychotropic drugs, it can advantageously be used for reducing the doses of said psychotropic drug, thereby limiting the adverse effects of said psychotropic drug, and/or reducing the risks of failure and withdrawal.

The effective equivalent dose of a psychotropic drug, *i.e.*, the psychotropic drug dose that, when administered in combination with flecainide, induces a physiological effect or a pharmacological signature similar or identical to that of the psychotropic drug alone administered at the active pharmacological dose, can be determined by the methods disclosed in WO2010/029131 and US 2011/172188.

According to another aspect, the present invention pertains to a composition, especially a pharmaceutical composition, comprising flecainide and at least one psychotropic drug. This composition is preferably formulated for patients with psychiatric and/or neurodegenerative disorders, as disclosed above. In addition to flecainide and to said psychotropic drug, the composition can comprise any pharmaceutical vehicle, stabilizer, adjuvant and the like as frequently used in the art.

Examples of pharmaceutically acceptable vehicles include, but are not limited to: water; aqueous vehicles such as, but not limited to, sodium chloride solution, Ringer's solution, dextrose solution, dextrose and sodium chloride solution, and lactated Ringer's solution; water-miscible vehicles such as, but not limited to, ethyl alcohol, polyethylene glycol, and polypropylene glycol; and nonaqueous vehicles such as, but not limited to, corn oil, cottonseed oil, peanut oil, sesame oil, ethyl oleate, isopropyl myristate, and benzyl benzoate.

According to a preferred embodiment, this composition is formulated for oral administration (including buccal cavity or sublingually). Other interesting formulations include formulations for intraperitoneal (i.p.), intravenous (i.v.), subcutaneous (s.c.), intramuscular (i.m.), transcutaneous, transdermal, intrathecal and intracranial administrations. Still other formulations include epidural, submucosal, intranasal, ocular cul-de-sac and rectal routes of administration, as well as administration by pulmonary inhalation.

A variety of administration means, including but not limited to capsules, tablets, syrups, creams and ointments, suppositories, patches or any reservoir capable of containing and dispensing flecainide and the psychotropic drug, can be used for formulating the above-described compositions.

In the compositions according to the invention, the psychotropic drug is as described above.

In a preferred embodiment, said psychotropic drug is used for treating narcolepsy and is therefore selected in the group consisting of: caffeine, mazindol, sodium oxybate, pitolisant, amphetamine, methylphenidate, (R)- (beta-amino-benzenepropyl) carbamate mono- hydrochloride, modafinil and armodafinil.

In a preferred embodiment, the composition of the invention contains between 1 to 1000 mg, preferably 5 to 800 mg of the psychotropic drug, depending of its nature. A preferred posology would be to administer to the patient between 1 to 1000 mg/day, more preferably between 5 to 800 mg/day of the psychotropic drug.

According to another preferred embodiment, the composition of the invention contains between 1 to 200, preferably 1 to 100 mg of flecainide. A preferred posology would be to administer to the patient between 1 to 200, preferably 1 to 100 mg/day of flecainide.

More preferably, said flecainide is the R enantiomer disclosed on figure 5A.

In a more preferred embodiment, flecainide is associated with the psychotropic drug modafinil.

By "modafinil" is herein meant the 2-[(diphenylmethyl) sulfinyl] acetamide (Provigil, see figure 5C), as well as its precursors or prodrugs such as adrafinil (Dubey et al, 2009) which can be metabolized in the human body and its active derivatives. More precisely, the term "Modafinil" herein designates any form of modafinil (racemate, R-modafinil, S- modafinil, *etc.*), as well as its precursors which can be metabolized in the human body and its derivatives. Figure 5 shows the formulas of R-Modafinil (Fig. 5C) and S-Modafinil (Fig. 5D).

Modafinil is an analeptic drug prescribed essentially for the treatment of narcolepsy, shift work sleep disorder, and excessive daytime sleepiness associated with obstructive sleep apnea. Besides these wake-promoting properties, modafinil also improves working memory and episodic memory, and other processes dependent on prefrontal cortex and cognitive control (Minzenberg MJ et al, 2008).

The present inventors have shown that, surprisingly, flecainide strongly potentiates *in vivo* the waking effects of Modafinil, whereas it has no effect on wake duration on its own (example 2). Moreover, flecainide strongly potentiates *in vivo* the cognitive activity of Modafinil, whereas it has no promnesiant effect on its own (example 3). This synergistic activity could be explained by the fact that flecainide strongly extends the duration of Modafinil treatment (example 4). On the other hand, the present inventors herein describes that the flecainide / modafinil combination has a synergistic effect on cataplectic-like phenotype in narcoleptic mice (example 5) and is all the more surprising than either flecainide or modafinil has no effect on this phenotype (figure 6B). In a preferred embodiment, the present invention thus pertains to flecainide, for use for potentiating the promnesiant and/or awakening effects of modafinil, and/or for improving its safety, and/or for increasing the duration of action of modafinil in patients in need thereof, especially in

patients suffering from: excessive daytime sleepiness (EDS), sleep disorders, insufficient sleep time, central sleep apnea, narcolepsy (with or without cataplexy), obstructive sleep apnea/hypopnea (SAHOS), idiopathic hypersomnia, Kleine-Levin syndrome, circadian rhythm disorders, shift work sleep disorder, jet-lag, disorders after sleep restriction or sleep deprivation (attention disorders, alertness disorders, sleepiness), restless legs syndrome (RLS) and Periodic Lim Movement Disorders (PLMD), insomnia, parasomnia, attention deficit hyperactivity disorder (ADHD), post-traumatic stress disorder (PTSD), disorders commonly associated with somnolence or sleepiness (such as Parkinson disease, multiple sclerosis, stroke, neuromuscular disorders or structural brain disorders, respiratory disorders, chronic renal failure, liver failure, rheumatologic disorders), medication-induced somnolence (due to benzodiazepines, barbiturates, sleeping pills, antidepressants, anti-psychotics…), mood disorders, anxiety disorders, schizophrenia, tinnitus, depression, malaise, dementia, bipolar disorder, obesity, hyperphagia, manic episode, obsessive-compulsive disorder, senility, dependence or addiction (to games, drugs, alcohol, tobacco, etc.), fecal or urinary incontinence, premature ejaculation, breathing difficulty and fatigue, notably due to cancer, neurodegenerative disorders, menopause, traumatic brain injuries, viral infection or post-myelitis, or to fibromyalgia, which have been proposed to be treated by modafinil.

In a more preferred embodiment, the present invention specifically pertains to flecainide, for use for potentiating the awakening effects of modafinil, and/or for improving its safety, and/or for increasing the duration of action of modafinil in patients suffering from: excessive daytime sleepiness (EDS), sleep disorders, insufficient sleep time, central sleep apnea, narcolepsy (with or without cataplexy), obstructive sleep apnea/hypopnea (SAHOS), idiopathic hypersomnia, Kleine-Levin syndrome, circadian rhythm disorders, shift work sleep disorder, jet-lag, disorders after sleep restriction or sleep deprivation (attention disorders, alertness disorders, sleepiness), restless legs syndrome (RLS) and Periodic Lim Movement Disorders (PLMD), insomnia, parasomnia, attention deficit hyperactivity disorder (ADHD), post-traumatic stress disorder (PTSD), disorders commonly associated with somnolence or sleepiness (such as Parkinson disease, multiple sclerosis, stroke, neuromuscular disorders or structural brain disorders, respiratory disorders, chronic renal failure, liver failure, rheumatologic disorders), medication-induced somnolence (due to benzodiazepines, barbiturates, sleeping pills, antidepressants, anti-

psychotics…), mood disorders, anxiety disorders, schizophrenia, tinnitus, depression, malaise, dementia, bipolar disorder, obesity, hyperphagia, manic episode, obsessive-compulsive disorder, senility, dependence or addiction (to games, drugs, alcohol, tobacco, etc.), fecal or urinary incontinence, premature ejaculation, breathing difficulty and fatigue, notably due to cancer, neurodegenerative disorders, menopause, traumatic brain injuries, viral infection or post-myelitis, or to fibromyalgia, for which modafinil has been proposed or authorized.

In a preferred embodiment, the present invention specifically pertains to flecainide, for use for potentiating the awakening effects of modafinil, and/or for improving its safety, and/or for increasing the duration of action of modafinil in patients suffering from excessive daytime sleepiness (EDS).

In another preferred embodiment, the present invention relates to flecainide, for use for potentiating the awakening effects of modafinil, and/or for improving its safety, and/or for increasing the duration of action of modafinil in patients suffering from conditions or diseases involving EDS, that are for example: insufficient sleep time, central sleep apnea, narcolepsy (with or without cataplexy), obstructive sleep apnea/hypopnea (SAHOS), idiopathic hypersomnia, recurrent hypersomnia (Kleine-Levin syndrome), circadian rhythm disorders (jet lag), disorders after sleep restriction or sleep deprivation (attention disorders, alertness disorders and sleepiness), restless legs syndrome (RLS) and Periodic Lim Movement Disorders (PLMD), neurological conditions commonly associated with sleepiness (such as Parkinson disease, multiple sclerosis, stroke, neuromuscular disorders or structural brain disorders), medical conditions commonly associated with sleepiness (respiratory disorders, chronic renal failure, liver failure, rheumatologic disorders), mood disorders, anxiety disorders, schizophrenia, or medication-induced somnolence (due to benzodiazepines, barbiturates, sleeping pills, antidepressants, anti-psychotics…).

In another preferred embodiment, the present invention relates to a modafinil/flecainide combination product, for use for treating cataplexy in narcoleptic patients.

It is to be noted that the potentiation of the effects of modafinil by flecainide enables a reduction of the dose of modafinil, and hence a reduction of its side-effects. As a consequence, some applications of modafinil, for which this drug was not approved because of its side-effects and possible risks associated thereto, can now be envisioned,

such as its use as a performance-enhancing and/or brain-boosting agent. According to a particular embodiment, the present invention thus pertains to a performance-enhancing product comprising flecainide and modafinil.

In another preferred embodiment, the present invention specifically pertains to the use of flecainide and modafinil for enhancing the memory of healthy subjects and/or to maintain them awake for long-lasting periods of time and/or to treat cataplexy in narcoleptic patients. These subjects can be for example individuals that need to memorize a lot of information and/or to remain awake for long lasting periods. In a preferred embodiment, said subjects are humans (e.g., security agents, students, etc.).

In a particular embodiment, the present invention also relates to a composition comprising flecainide and modafinil, which can advantageously be used for treating diseases and conditions including but not limited to excessive daytime sleepiness (EDS), narcolepsy (with or without cataplexy), obstructive sleep apnea/hypopnea (SAHOS), shift work sleep disorder, disorders after sleep restriction or sleep deprivation (attention disorders, alertness disorders, sleepiness), restless leg syndrome, hypersomnia, idiopathic hypersomnia and fatigue, notably due to cancer, jet-lag, neurodegenerative disorders, menopause, traumatic brain injuries, viral infection or post-myelitis, or to fibromyalgia. In particular, this composition can be used for treating cataplexy in narcoleptic patients.

This composition can also be used for enhancing the memory of healthy subjects and/or for maintaining them awake for long-lasting periods of time. Typical periods of time are for example 6 hours, preferably 12 hours.

The present invention moreover relates specifically to the use of flecainide and modafinil in the preparation of a medicament that is intended to be used for treating diseases and conditions such as excessive daytime sleepiness (EDS), narcolepsy (with or without cataplexy), obstructive sleep apnea/hypopnea (SAHOS), shift work sleep disorder, restless leg syndrome, hypersomnia, idiopathic hypersomnia and fatigue, notably due to cancer, neurodegenerative disorders, menopause, traumatic brain injuries, viral infection or post-myelitis, or to fibromyalgia.

In a preferred embodiment, the present invention relates to the use of flecainide and modafinil in the preparation of a medicament that is intended to be used for treating cataplexy in narcoleptic patients.

In addition to modafinil and flecainide, the composition / medicament of the invention can comprise other agents such as vitamin C, vitamin B6, magnesium, L-arginine, L-glutamine, L-citrulline, taurine, caffeine, etc. According to a particular embodiment, this product can be sold over-the-counter. It can be formulated, for example, as an OTC medicine or as a food supplement.

In a preferred embodiment, the composition of the invention contains between 1 to 1000 mg, preferably between 5 to 800 mg, and more preferably between 5 to 600 mg of the modafinil. According to another preferred embodiment, the composition of the invention is formulated so that 5 to 800, preferably 5 to 600 mg/day of modafinil are administered to a patient in need thereof, in one, two or more takings.

According to another preferred embodiment, the composition of the invention contains between 1 to 200, preferably 1 to 100 mg of flecainide. According to another preferred embodiment, the composition of the invention is formulated so that 1 to 200, preferably 1 to 100 mg/day of flecainide are administered to a patient in need thereof, in one, two or more takings. In a more preferred embodiment, said flecainide is the R enantiomer disclosed on figure 5A.

In a final aspect, the present invention relates to a combination product comprising flecainide and modafinil, for simultaneous, separated or staggered use for preventing and/or treating excessive daytime sleepiness (EDS), narcolepsy (with or without cataplexy), obstructive sleep apnea/hypopnea (SAHOS), shift work sleep disorder, restless leg syndrome, hypersomnia, idiopathic hypersomnia and fatigue, notably due to cancer, jet-lag, neurodegenerative disorders, menopause, traumatic brain injuries, viral infection or post-myelitis, or to fibromyalgia. This combination product is preferably used for preventing and/or treating cataplexy in narcoleptic patients.

Other characteristics of the invention will also become apparent in the course of the description which follows of the biological assays which have been performed in the framework of the invention and which provide it with the required experimental support, without limiting its scope.

Legends to the figures

Figure 1: Inhibition of the human connexins functionality by flecainide. Rin-Cx26 cells, Rin-Cx30 cells, Rin-Cx32 cells, Rin-CX40 cells and Rin-Cx43 cells are cultured in the presence of flecainide (280µM), mefloquine (10 µM) and MFA (100 µM) for 4 hours. The transfer of fluorochrome by gap junctions (composed of connexins) is evaluated by flow cytometry (1A and 1B). Viability of the cells treated with flecainide is shown on figure 1B.

Figure 2: Efficiency of flecainide for potentiating the awakening effect of modafinil. Mice (n = 8 per batch) were orally treated by either modafinil (32 mg/kg) or modafinil (32mg/kg) and flecainide (1mg/kg) (figure 2A) or flecainide alone (1mg/kg) (figure 2B) and replaced in their home cage. The wake duration was measured using polygraphic analyses.

Figure 3: Efficacy of flecainide for potentiating the promnesiant effect of modafinil. Mice (n = 6 to 23 per batch) are tested in the T-maze. They were intraperitoneally treated by either modafinil (64 mg/kg or 128mg/kg) or modafinil (64mg/kg) and flecainide (1mg/kg) or flecainide alone (1mg/kg). The graphic represents the percentage of alternation after 6 trials, 50% corresponding to a random alternation.

Figure 4 : Efficacy of flecainide for potentiating the locomotor effect of modafinil. Mice (n=8 per batch) were orally treated by either modafinil (64 mg/kg) or modafinil (64mg/kg) and flecainide (1mg/kg) or flecainide alone (1mg/kg) and replaced in their home cage. The locomotor activity was measured using videotracking device.

Figure 5: Molecular structure of A. R-flecainide; B. S-flecainide; C. R-Modafinil, D. S-Modafinil.

Figure 6: Number of episodes of OREM/DREM phases in narcoleptic mice (Ox-/-) treated by modafinil/flecainide (A) or flecainide alone (B). (A). Oral treatment of Ox-/- male mice with modafinil 64 mg/kg with flecainide 1 mg/kg was compared to Modafinil 64 mg/kg and vehicle. **: $p<0,01$; ***:$p<0,005$, Two-Way ANOVA. (B) Oral treatment of Ox-/- male mice with flecainide 1 mg/kg was compared to vehicle.

Figure 7: Number of episodes of OREM/DREM phases in narcoleptic mice (Ox-/-) treated by the combination between modafinil and one of the two enantiomers of flecainide (R-flecainide and S-flecainide). Oral treatment with modafinil 64 mg/kg with R-flecainide 1 mg/kg or S-flecainide 1 mg/kg was compared to vehicle.

EXAMPLES

Example 1: Effect of Flecainide on gap junctions

1.1. Materials and methods

Cell culture

The rat insulinoma RIN cell line, deficient in GJIC (del Corsso et al, 2006), was grown in OptiMem medium, supplemented with 10% fetal calf serum. GJB6 (Cx30), GJB1 (Cx32), GJB2 (Cx26), GJA5 (Cx40) and GJA1 (Cx43) open reading frames were amplified from human cDNA. The open reading frames were cloned in pcDNA3.1/V5-His-TOPO (Invitrogen). Cells were transfected using Lipofectamine and further selected using geneticin.

Dye transfer experiments

Cells were seeded and loaded with two fluorochromes, calcein acetoxymethyl ester, a gap junction permeable dye, and Vybrant DiI, a membrane lipophilic dye. The next day, cells were dissociated and incubated for four hours in presence of previously seeded non-loaded cells and in the presence of flecainide racemate 70, 140 or 280 µM, mefloquine 10 µM or meclofenamic acid (MFA) 100 µM. Flow cytometry was conducted on a FACScan.

Inhibition was quantified as the relative number of receiver cells that gained fluorescence to the total number of receiver cells (non GJ-mediated dye transfer was then substracted to these ratio based on connexin non-expressing RIN cells, defined at background dye transfer ratio). This ratio of cellular coupling was then normalized, after each treatment, on the vehicle one.

Toxicity analysis

Twenty thousand RIN were seeded in 100 µl of culture medium in 96-wells plates. After 48h culture, cells were treated for 4 hours with previously identified chemical compounds at several concentrations. Cells were rinsed in PBS and grown 24h in fresh medium. Cell viability was measured by using WST-1 (Roche).

1.2. Experimental results

Cellular models were validated by using two classical inhibitors described in litterature, meclofenamic acid (MFA) (Dhein, 2004) (100 µM) and mefloquine (Cruikshank et al, 2004) (10 µM). Results are shown on figure 1A. Flecainide is as efficient in blocking connexin as the other anti-connexin agents.

Cell viability tests (using WST-1, dotted curve on Figure 1B) after one day of treatment, indicate that flecainide has no cell toxicity at the dose inhibiting cerebral connexins.

In addition, flecainide inhibits all the tested isoforms of cerebral connexin using dye-transfer cell-parachute assay (Cx30, Cx32, Cx26, Cx40, Cx43) (it is estimated that a more than a significant 10% reduction in gap junction cellular is considered as physiologically relevant). In addition, higher inhibition levels are reached for glial connexins Cx26, Cx30 and Cx43.

Example 2: Flecainide potentiates the waking effects of Modafinil

Preclinical and clinical data indicated that modafinil modifies sleep-cycle rhythm and promotes wake phases (Lin et al, 2008). Here we tested in rodents whether such activity was potentiated by flecainide after oral challenge with modafinil, using polysomnographic analysis on implanted mice. Using a sub-efficient dosage of modafinil (32 mg/kg), the

inventors demonstrated a new feature of the combination of modafinil and flecainide since it significantly increases the total duration of wake episodes.

2.1. Materials and Methods

Wild-type C57bl/6 male mice (n=9/groups) were implanted with EEG/EMG/EOG electrodes for polysomnographic analyses. After a two-week recovery period, mice were orally treated with vehicle, Modafinil 32 mg/kg and Modafinil 32 mg/kg + flecainide racemate 1 mg/kg and wake periods were quantified using Spike2 scripts. Here the inventors represented the duration of wake during the first three hours (after a one-hour period post-administration). **: $p<0,01$ in a One-Way ANOVA analysis.

2.2. Results

Modafinil is a molecule that promotes wakefulness in humans and mice, increasing in mice their activity in a dose-dependent manner (Simon et al, 1994). The activity of mice treated with modafinil at 32 mg/kg was compared with that of mice treated with the combination modafinil 32 mg/kg + flecainide 1 mg/kg or vehicle.

Figure 2A shows that flecainide significantly increases the waking effects of modafinil. Figure 2B shows that this effect is not mediated by flecainide alone.

Thus, flecainide significantly potentiates modafinil waking activity in wild type mice, while being devoid of own effect on wake duration.

Exemple 3: Flecainide significantly enhances modafinil cognitive activity

Modafinil induces a cognitive enhancing effect (Beracochea et al, 2003), such property can be assessed using the alternating sequential test, a widely used apparatus to assess spatial working memory in mice (Beracochea & Jaffard, 1987). Spontaneous alternation is the innate tendency of rodents to alternate their choices to enter into the compartments of arrival of a T-maze device, over successive trials. To alternate during a given trial N, the animal must remember the choice made selectively in test N-1, and the response in alternating is performance measure. Acute administration of modafinil before entering the maze, can improve the performance of mice in this test (Beracochea et al, 2001). The

inventors' results showed that flecainide significantly potentiates the promnesiant effect of a subefficient dose of modafinil, while flecainide alone is devoid of any own promnesiant effect.

3.1. Materials and methods

The alternating sequential test is widely used to assess spatial working memory in mice (Beracochea & Jaffard, 1987). Spontaneous alternation is the innate tendency of rodents to alternate their choices to entry into the compartments of arrival of a T-maze device, over successive trials. To alternate during a given trial N, the animal must remember the choice made selectively in test N-1, so the decline in alternating will reflect the phenomenon of oblivion. The response in alternating is performance measure. Sequential alternating assesses more specifically the sensitivity to interference, a major factor in oblivion.

The experiment takes place in a T-maze (50 cm x 10 cm x 25 cm). All the subjects were given 7 successive trials separated by a 120-s intertrial interval. To begin a trial, the mouse was placed in the start box for 120 s before the door to the stem was opened. When the subject entered one of the goal arms, the door to that arm was closed. The chosen arm and the time that elapsed between opening the door and the arrival to the end of the chosen arm (task achievement time) were registered. Following a 30-s confinement period (fixed and invariant) in the chosen arm, the animal was removed and placed in the start box for a new trial. Between each test, the unit is cleaned with a cloth soaked in water and alcohol to avoid olfactory detection. The index memory is represented by the average of alternating percentage (number of alternation choices / total number of tests X 100). (n=6 to 23 for each group). Mice were intraperitoneally treated by either modafinil (64 mg/kg or 128mg/kg) or modafinil (64mg/kg) and flecainide racemate (1mg/kg) or flecainide racemate alone (1mg/kg) or vehicle.

# $p<0,05$ in one sample t-test vs random 50% alternance ; * $p<0,05$ One way ANOVA followed by Tukey's multiple comparison vs modafinil group.

3.2.Results

The T-maze is a device for assessing working memory in mice. Acute administration of modafinil before entering the maze, can improve the performance of mice in this test (Beracochea et al, 2001).

The validity of the test was performed by comparing the responses of mice intraperitoneally treated with an effective dose of modafinil alone (128 mg/kg), a dose of flecainide alone (1 mg/kg) and a sub-effective dose of modafinil (64 mg/kg) with or without flecainide alone (1 mg/kg). The results are shown in Figure 3.

These results show that flecainide significantly potentiates modafinil promnesiant activity, while flecainide alone shows no own cognitive effect.

Exemple 4: Flecainide significantly prolongs modafinil activity

Modafinil is a molecule that promotes wakefulness in humans and mice, increasing in mice their activity in a dose-dependent manner (Simon et al, 1994). The inventors' results showed that flecainide significantly potentiates the locomotor effect of a subefficient dose of modafinil, while flecainide alone is devoid of any own locomotor effect in rodents.

4.1. Materials and methods

Mice (n=8 per batch) were orally treated by either modafinil (64 mg/kg) or modafinil (64mg/kg) and flecainide racemate (1mg/kg) or flecainide racemate alone (1mg/kg) or vehicle and replaced in their home cage. Locomotor activity is evaluated by video tracking. Videos have been analyzed using Ethovision XT software (Noldus®).*: $p<0,01$ in a Two-Way ANOVA analysis

4.2.Results

The activity of mice treated with modafinil at 64 mg/kg was compared with that of mice treated with the combination modafinil 64 mg/kg + flecainide 1 mg/kg. Figure 4 shows that flecainide significantly increases the duration of effect of modafinil on the activity of mice.

To conclude, the above results show that Flecainide significantly inhibits the functionality of gap junctions, without inducing cellular toxicity. In addition, this compound potentiates the efficacy and duration of effect of modafinil, notably in its promnesiant and awakening side.

Exemple 5: Modafinil/Flecainide combination has a surprising efficient profile on DREM cataplectic-like phenotype in narcoleptic mice.

5.1. Material and methods

Animals

Prepro-orexin knockout (KO) mice were offspring of the mouse strain generated by Chemelli et al. [1999] and kept on C57BL/6J genomic background. After backcrossing male orexin-/- mice and female wild-type (WT) mice for nine generations, the obtained orexin+/- mice were crossed to produce heterozygote and homozygote WT and KO littermates. To determine their genotypes with respect to orexin gene, tail biopsies were performed at the age of 4 weeks for DNA detection using PCR.

Surgery

At the age of 12 weeks and with a body weight of 30±2 g, mice used for EEG and sleep–wake studies were chronically implanted, under deep gas anesthesia using isoflurane (2%, 200 ml/min) and a TEM anesthesia system (Bordeaux, France), with six cortical electrodes (gold-plated tinned copper wire, Ø = 0.4 mm, Filotex, Draveil, France) and three muscle electrodes (fluorocarbon-coated gold-plated stainless steel wire, Ø = 0.03 mm, Cooner Wire Chatworth, CA, U.S.A.) to record the electroencephalogram (EEG) and electromyogram (EMG) and to monitor the sleep–wake cycle. All electrodes were previously soldered to a multi-channel electrical connector and each was separately insulated with a covering of heat-shrinkable polyolefin/polyester tubing. Cortical electrodes were inserted into the dura through 3 pairs of holes made in the skull, located

respectively in the frontal (1 mm lateral and anterior to the bregma), parietal (1 mm lateral to the midline at the midpoint between the bregma and lambda), and occipital (2 mm lateral to the midline and 1 mm anterior to the lambda) cortex. Muscle electrodes were inserted into the neck muscles. Finally, the electrode assembly was anchored and fixed to the skull with Super-Bond (Sun Medical Co., Shiga, Japan) and dental cement. This implantation allows stable and long-lasting polygraphic recordings [Parmentier et al, 2002].

Polygraphic recording in the mouse and data acquisition and analysis

After surgery, the animals were housed individually, placed in an insulated sound-proof recording room maintained at an ambient temperature of 23±1 °C and on a 12 h light/dark cycle (lights-on at 7 a.m.). After a 7-day recovery period, mice were habituated to the recording cable for 7 days before polygraphic recordings were started. Direct REM sleep onset (DREMs) episodes, also called narcoleptic episodes or sleep onset REM periods by some authors [Chemelli et al, 1999; Mignot et al, 2005; Fujiki et al, 2006], were defined as the occurrence of REM sleep directly from wake, namely a REM episode that follows directly a wake episode lasting more than 60 s without being preceded by any cortical slow activity of more that 5 s during the 60 s.

Drug administration and experimental procedures in the mouse

After recovery from the surgery and habituation to the recording cables, each mouse was subjected to a recording session of two continuous days, beginning at 7 a.m. Administrations were performed at 6:45 p.m. just before lights-off (7:00 p.m.), since orexin-/- mice display narcoleptic attacks only during lights-off phase [Chemelli et al, 1999]. The order of administration was randomized. Polygraphic recordings were made immediately after administration and were maintained during the whole lights-off period (12 h). Two administrations were separated by a period of 7 days (washout). Mice (n=8 per batch) were orally treated by either modafinil (64 mg/kg) or modafinil (64mg/kg) and flecainide racemate (1mg/kg) or flecainide racemate alone (1mg/kg) or vehicle.

5.2. Results

Orexins (also known as hypocretins) are two hypothalamic neuropetides identified in 1998 [Sakurai et al, 1998; De Lecea L. et al, 1998]. Neurons containing orexins have been identified in the hypothalamic dorsolateral and peri-fornical areas, these neurons play a key role in behavioral arousal. A large body of evidence indicates that an orexin deficiency is responsible for the pathogenesis of human and animal narcolepsy [Lin et al, 1999; Chemelli et al, 1999]. It has been recently shown that the most major phenotypes of orexin KO mice are a behavior/motor deficit during waking and the occurrence, during the dark phase, of episodes of sleep onset REM (DREM, as known as SOREM) - defined on EEG, EMG and video recordings as sudden onset of paradoxical sleep directly from wakefulness [Anaclet et al, 2009]. Thus SOREM/DREM constitutes a main phenotype of murine narcolepsy which is frequently seen in narcoleptic patients [Lin et al, 20011]. Using this model, it was shown that modafinil allows DREM episodes to persist [Lin et al, 2008], a situation similar to that in the clinic in which modafinil improves excessive daytime sleepiness without clear effect in cataplexy.

Moreover, as disclosed on figure 6B, flecainide racemate (alone), at 1 mg/kg dose, has no effect on DREM cataplectic-like phenotype in narcoleptic Ox-/- mice.

However, and importantly, the results disclosed on figure 6A show that modafinil/flecainide combination decreases the occurrence of DREM episode.

Hence, flecainide and modafinil do not have any significant effect on a DREM cataplectic-like phenotype when used alone, whereas their combination importantly decreases the DREM cataplectic-like phenotype.

These results highlight the synergy existing between flecainide and modafinil, said synergy being due to the potentiation of the modafinil efficiency by flecainide, since no effect is seen with either modafinil or flecainide alone in narcoleptic mice.

Exemple 6: Modafinil/R-flecainide is surprisingly more efficient than Modafinil/S-flecainide on DREM cataplectic-like phenotype in narcoleptic mice

The same materials and methods than in example 5 were used, except that the flecainide racemate has been replaced by the R-flecainide enantiomer.

As disclosed on figure 7, R-flecainide enantiomer combined with modafinil is more efficient on DREM cataplectic-like phenotype in narcoleptic Ox-/- mice than the S-flecainide enantiomer combined with modafinil.

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2014295030 12 May 2017

CLAIMS

1. A therapeutic composition comprising flecainide and at least one psychotropic drug, wherein said psychotropic drug is modafinil.

2. The therapeutic composition according to claim 1, for use for treating excessive daytime sleepiness (EDS), sleep disorders, insufficient sleep time, central sleep apnea, narcolepsy (with or without cataplexy), obstructive sleep apnea/hypopnea (SAHOS), idiopathic hypersomnia, Kleine-Levin syndrome, circadian rhythm disorders, shift work sleep disorder, jet-lag, disorders after sleep restriction or sleep deprivation (attention disorders, alertness disorders, sleepiness), restless legs syndrome (RLS) and Periodic Lim Movement Disorders (PLMD), insomnia, parasomnia, attention deficit hyperactivity disorder (ADHD), post-traumatic stress disorder (PTSD), disorders commonly associated with somnolence or sleepiness (such as Parkinson disease, multiple sclerosis, stroke, neuromuscular disorders or structural brain disorders, respiratory disorders, chronic renal failure, liver failure, rheumatologic disorders), medication-induced somnolence (due to benzodiazepines, barbiturates, sleeping pills, antidepressants, anti-psychotics...), mood disorders, anxiety disorders, schizophrenia, tinnitus, depression, malaise, dementia, bipolar disorder, obesity, hyperphagia, manic episode, obsessive-compulsive disorder, senility, dependence or addiction (to games, drugs, alcohol, tobacco, etc.), fecal or urinary incontinence, premature ejaculation, breathing difficulty and fatigue, notably due to cancer, neurodegenerative disorders, menopause, traumatic brain injuries, viral infection or post-myelitis, or to fibromyalgia.

3. The therapeutic composition of claims 1 or 2, for use for enhancing the memory of healthy subjects and/or for maintaining them awake for long-lasting periods of time.

4. The therapeutic composition of claims 1 or 2, for use for treating cataplexy in narcoleptic patients.

5. The therapeutic composition of any one of claims 1 to 4, for use for treating somnolence or sleepiness associated with Parkinson disease.

6. Simultaneous, separated or staggered use of flecainide and modafinil for preventing and/or treating excessive daytime sleepiness (EDS), sleep disorders, insufficient sleep time, central sleep apnea, narcolepsy (with or without cataplexy), obstructive sleep apnea/hypopnea (SAHOS), idiopathic hypersomnia, Kleine-Levin syndrome, circadian rhythm disorders, shift work sleep disorder, jet-lag, disorders after sleep restriction or sleep deprivation (attention disorders, alertness disorders, sleepiness), restless legs syndrome (RLS) and Periodic Lim Movement Disorders (PLMD), insomnia, parasomnia, attention deficit hyperactivity disorder (ADHD), post-traumatic stress disorder (PTSD), disorders commonly associated with somnolence or sleepiness (such as Parkinson disease, multiple sclerosis, stroke, neuromuscular disorders or structural brain disorders, respiratory disorders, chronic renal failure, liver failure, rheumatologic disorders), medication-induced somnolence (due to benzodiazepines, barbiturates, sleeping pills, antidepressants, anti-psychotics...), mood disorders, anxiety disorders, schizophrenia, tinnitus, depression, malaise, dementia, bipolar disorder, obesity, hyperphagia, manic episode, obsessive-compulsive disorder, senility, dependence or addiction (to games, drugs, alcohol, tobacco, etc.), fecal or urinary incontinence, premature ejaculation, breathing difficulty and fatigue, notably due to cancer, neurodegenerative disorders, menopause, traumatic brain injuries, viral infection or post-myelitis, or to fibromyalgia.

7. The use of claim 6, for use for enhancing the memory of healthy subjects and/or for maintaining them awake for long-lasting periods of time.

8. The use of claim 6, for use for treating cataplexy in narcoleptic patients.

9. The use of any one of claims 6 to 8, for treating somnolence or sleepiness associated with Parkinson disease.

10. A method of potentiating the effects of a psychotropic drug, preferably for increasing the efficacy and/or safety and/or the duration of action of a psychotropic drug comprising aministering flecainide.

11. A method according to claim 10, wherein said psychotropic drug is selected from the group consisting of: GABAergic, dopaminergic, norepinephrinergic, serotoninergic, histaminergic, and glutamatergic effectors, and those having an effect on the hypocretin/orexin system.

12. A method according to claim 10 or 11, wherein said psychotropic drug is selected in the group consisting of: caffeine, mazindol, sodium oxybate, pitolisant, amphetamine, methylphenidate, (R)- (beta-amino-benzenepropyl) carbamate mono- hydrochloride, modafinil and armodafinil.

13. A method according to any one of claims 10 to 12 wherein the effect is the promnesiant effect and/or the awakening effect of the psychotropic drug.

14. A method according to any of claims 10 to 13, for increasing the efficacy and/or the duration of action of a psychotropic drug selected in the group consisting of caffeine, mazindol, sodium oxybate, pitolisant, amphetamine, methylphenidate, (R)- (beta-amino-benzenepropyl) carbamate mono- hydrochloride, modafinil and armodafinil.

15. A method according to any of claims 10 to 14, wherein said psychotropic drug is modafinil.

16. A method according to claim 15, for potentiating the promnesiant effect and/or the awakening effect of modafinil in patients suffering from Parkinson disease associated with somnolence or sleepiness.

17. A therapeutic composition comprising flecainide and at least one psychotropic drug, wherein said psychotropic drug is not flupirtine.

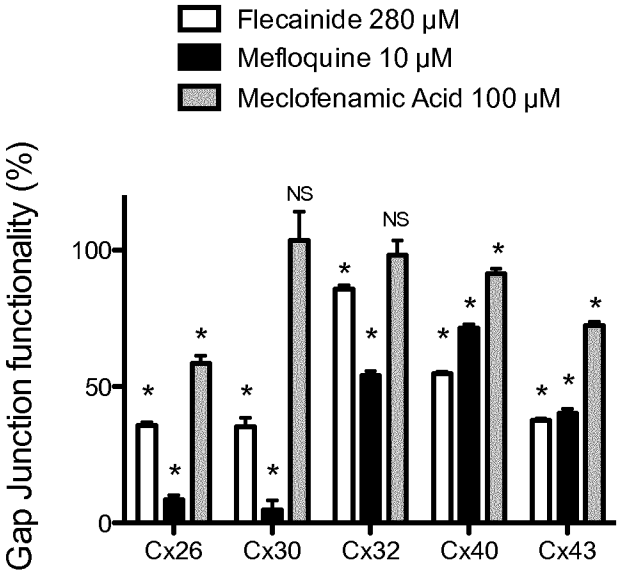
18. The therapeutic composition according to claim 17, wherein said psychotropic drug is selected from the group consisting of: GABAergic, dopaminergic, norepinephrinergic, serotoninergic, histaminergic, and glutamatergic effectors, and those having an effect on the hypocretin/orexin system, caffeine, mazindol, sodium oxybate, pitolisant, amphetamine, methylphenidate, (R)- (beta-amino-benzenepropyl) carbamate mono- hydrochloride, modafinil and armodafinil.

19. The therapeutic composition according to claim 18, wherein said psychotropic drug is modafinil.

20. A method of treating a disorder selected from the group consisting of wounds, migraines, infectious diseases, drug-induced liver injury, cytotoxicity induced by chemotherapeutic agents, and ischemia comprising administering flecainide.

Figure 1

A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Mefloquine 10 µM
Meclofenamic Acid 100 µM
Gap Junction functionality (%)
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NS
NS
*
Cx26
Cx30
Cx32
Cx40
Cx43

B

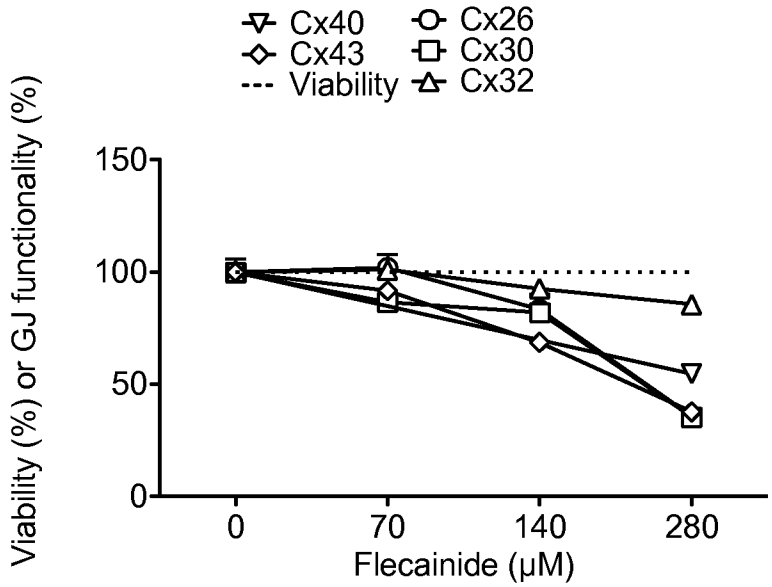
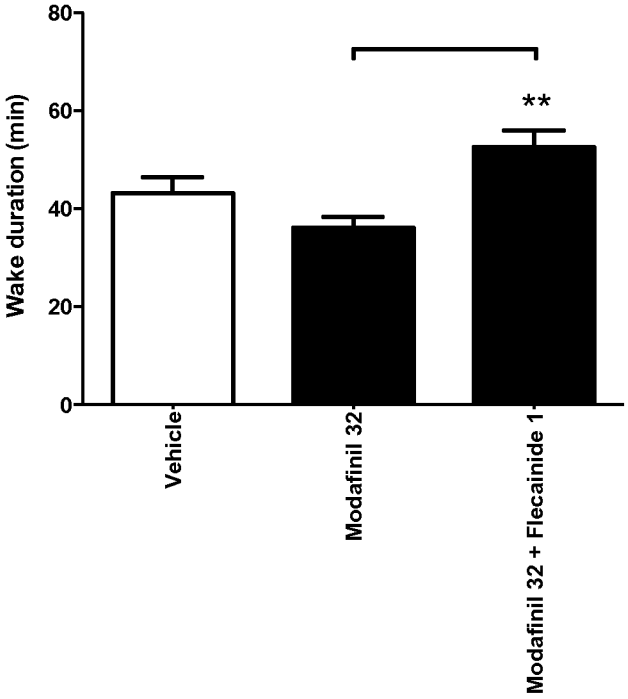

Cx40
Cx43
Viability
Cx26
Cx30
Cx32
Viability (%) or GJ functionality (%)
150
100
50
0
0
70
140
280
Flecainide (µM)

Figure 2

A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60
40
20
0
Wake duration (min)
**
Vehicle
Modafinil 32
Modafinil 32 + Flecainide 1

B

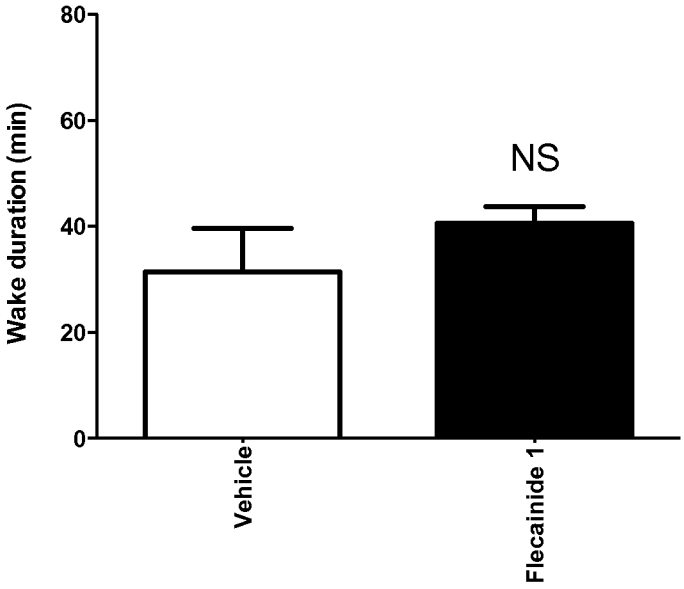
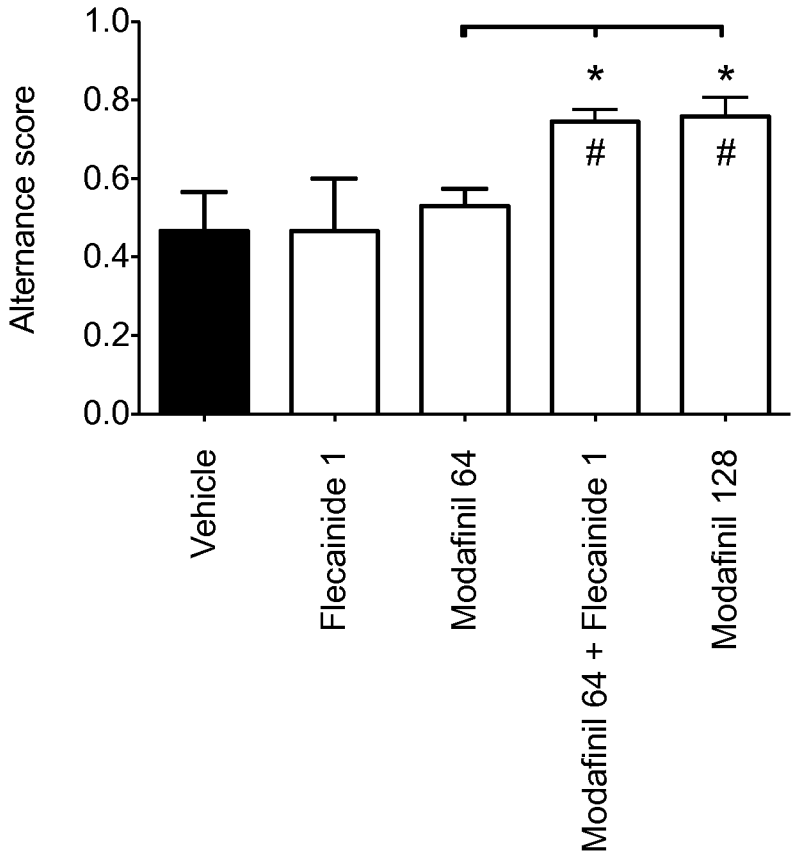

80
60
40
20
0
Wake duration (min)
NS
Vehicle
Flecainide 1

Figure 3


Alternance score
1.0
0.8
0.6
0.4
0.2
0.0
*
*
#
#
Vehicle
Flecainide 1
Modafinil 64
Modafinil 64 + Flecainide 1
Modafinil 128

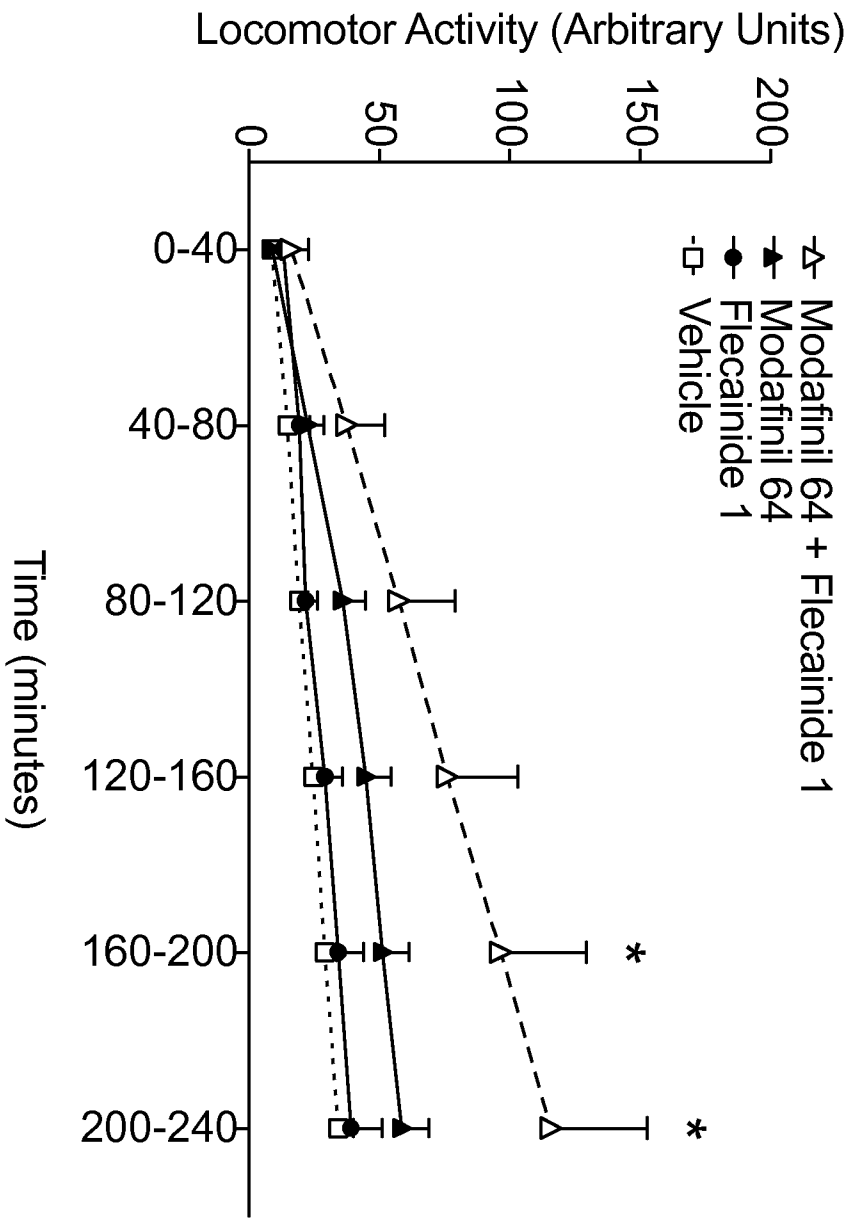
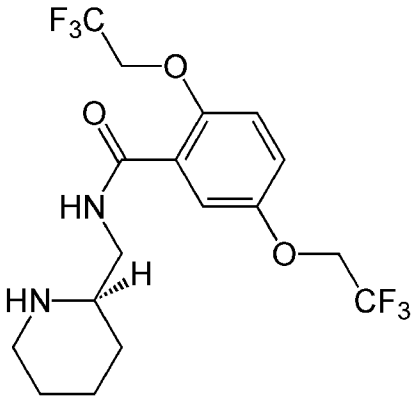

Locomotor Activity (Arbitrary Units)
0
50
100
150
200
Time (minutes)
0-40
40-80
80-120
120-160
160-200
200-240
Modafinil 64 + Flecainide 1
Modafinil 64
Flecainide 1
Vehicle
*
*

Figure 4

Figure 5



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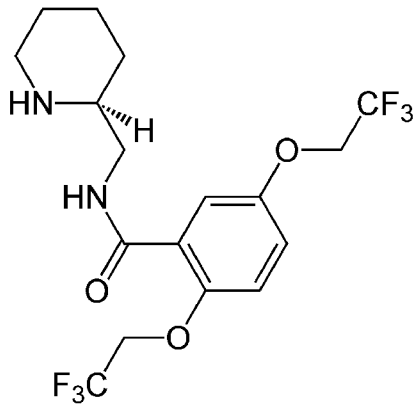

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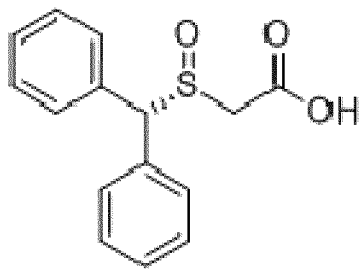

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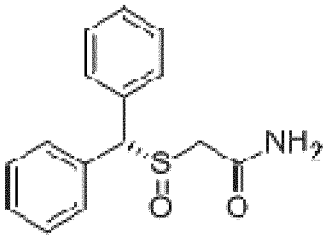

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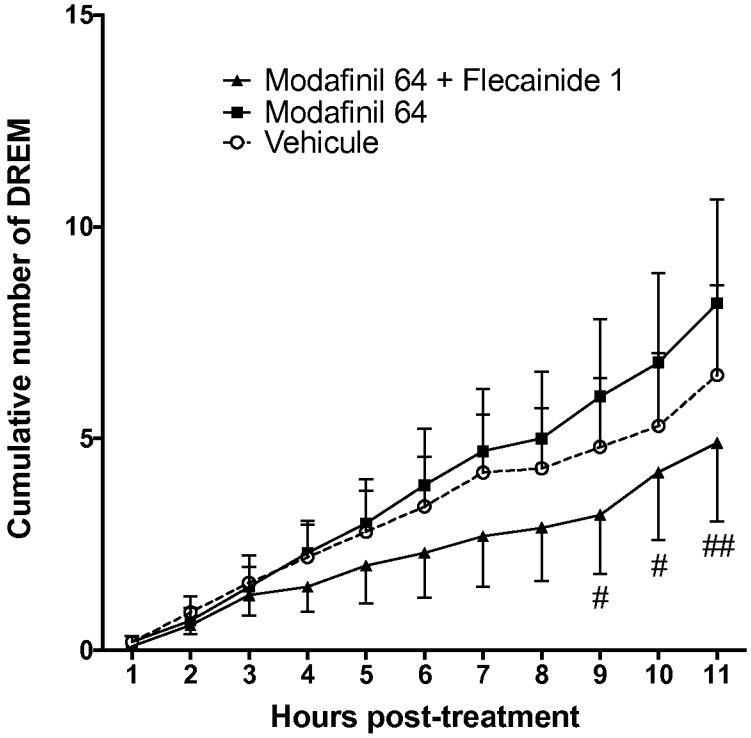
Figure 6

A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Modafinil 64
Vehicule
Cumulative number of DREM
Hours post-treatment
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10
15
1
2
3
4
5
6
7
8
9
10
11
#
#
##

B

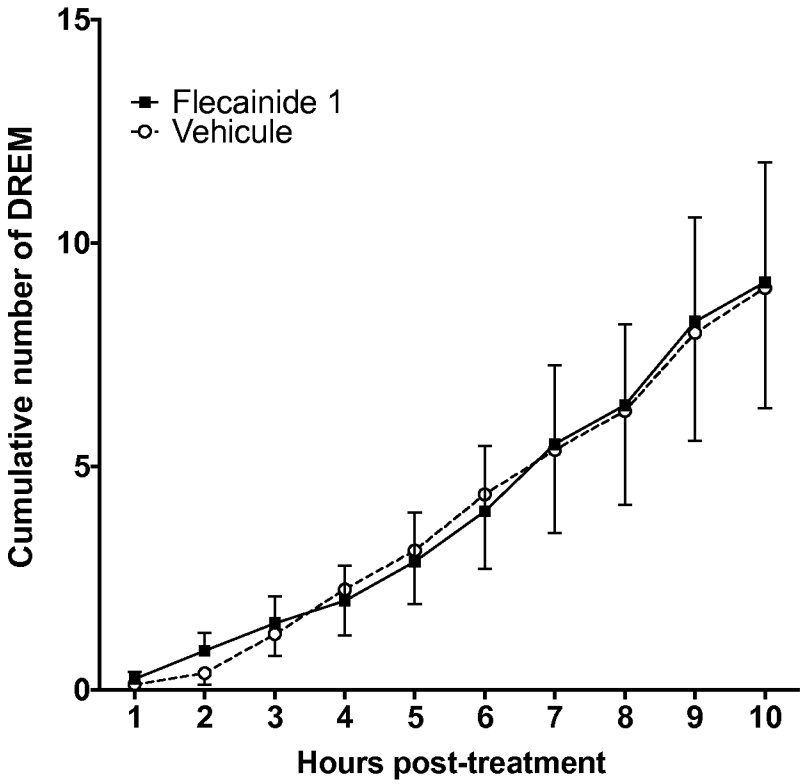
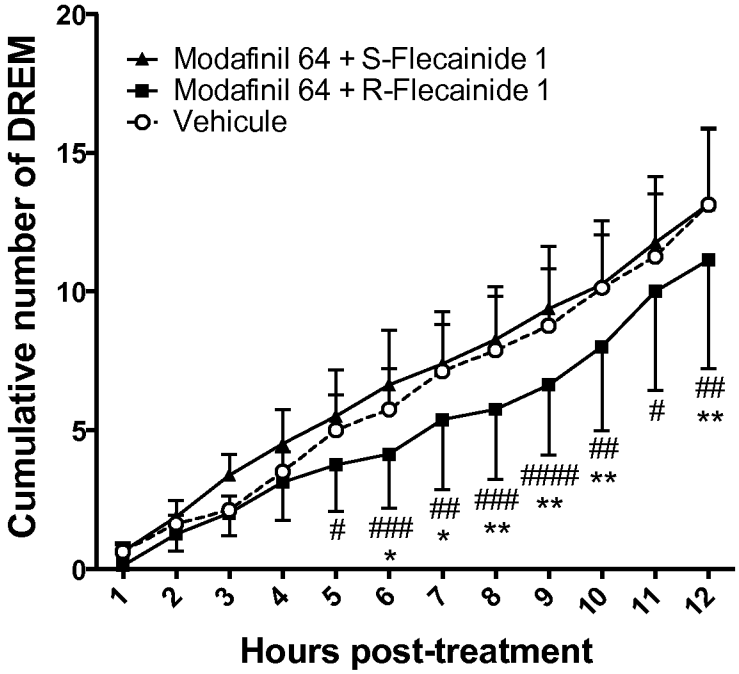

Flecainide 1
Vehicule
Cumulative number of DREM
Hours post-treatment
0
5
10
15
1
2
3
4
5
6
7
8
9
10

Figure 7



Two-way ANOVA, repeated measures by both factors
*p<0,05 vs Vehicule
#p<0,05 vs Modafinil 64

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Asn Thr Phe Thr Thr Ile Thr Ile Leu Leu Phe Val Ala Glu Ile Phe
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    50                  55                  60


Phe Asp Asp Phe Phe Pro Ile Ser Gln Val Arg Leu Trp Ala Leu Gln
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Leu Ile Met Val Ser Thr Pro Ser Leu Leu Val Val Leu His Val Ala
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Ile Val Lys Thr Gly Phe Glu Ile Gly Phe Leu Val Leu Phe Tyr Lys
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50 55 60

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    130                 135                 140

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Phe Ser Met Gln Arg Leu Val Lys Cys Asn Ala Trp Pro Cys Pro Asn
                165                 170                 175

Thr Val Asp Cys Phe Val Ser Arg Pro Thr Glu Lys Thr Val Phe Thr
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Val Phe Met Ile Ala Val Ser Gly Ile Cys Ile Leu Leu Asn Val Thr
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        35                  40                  45

Glu Asp Phe Val Cys Asn Thr Leu Gln Pro Gly Cys Lys Asn Val Cys
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Tyr Asp His Phe Phe Pro Val Ser His Ile Arg Leu Trp Ala Leu Gln
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Asn Asp Phe Lys Asp Ile Glu Asp Ile Lys Lys Gln Lys Val Arg Ile
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            180                 185                 190

Ile Phe Met Ile Ser Ala Ser Val Ile Cys Met Leu Leu Asn Val Ala
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Phe Asp Ala Phe His Pro Leu Ser Pro Leu Arg Phe Trp Val Phe Gln
65                  70                  75                  80

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Tyr His Val Ile Trp His Trp Glu Leu Ser Gly Lys Gly Lys Glu Glu
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Glu Thr Leu Ile Gln Gly Arg Glu Gly Asn Thr Asp Val Pro Gly Ala
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Leu Ile Leu Val Thr Cys Pro Ser Leu Leu Val Val Met His Val Ala
85 90 95

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Lys Asp Phe Asp Cys Asn Thr Lys Gln Pro Gly Cys Thr Asn Val Cys
    50                  55                  60

Tyr Asp Asn Tyr Phe Pro Ile Ser Asn Ile Arg Leu Trp Ala Leu Gln
65                  70                  75                  80

Leu Ile Phe Val Thr Cys Pro Ser Leu Leu Val Ile Leu His Val Ala
                85                  90                  95

Tyr Arg Glu Glu Arg Glu Arg Arg His Arg Gln Lys His Gly Asp Gln
            100                 105                 110
```

```
Cys Ala Lys Leu Tyr Asp Asn Ala Gly Lys Lys His Gly Gly Leu Trp
        115                 120                 125

Trp Thr Tyr Leu Phe Ser Leu Ile Phe Lys Leu Ile Ile Glu Phe Leu
    130                 135                 140

Phe Leu Tyr Leu Leu His Thr Leu Trp His Gly Phe Asn Met Pro Arg
145                 150                 155                 160

Leu Val Gln Cys Ala Asn Val Ala Pro Cys Pro Asn Ile Val Asp Cys
                165                 170                 175

Tyr Ile Ala Arg Pro Thr Glu Lys Lys Ile Phe Thr Tyr Phe Met Val
            180                 185                 190

Gly Ala Ser Ala Val Cys Ile Val Leu Thr Ile Cys Glu Leu Cys Tyr
        195                 200                 205

Leu Ile Cys His Arg Val Leu Arg Gly Leu His Lys Asp Lys Pro Arg
    210                 215                 220

Gly Gly Cys Ser Pro Ser Ser Ser Ala Ser Arg Ala Ser Thr Cys Arg
225                 230                 235                 240

Cys His His Lys Leu Val Glu Ala Gly Glu Val Asp Pro Asp Pro Gly
                245                 250                 255

Asn Asn Lys Leu Gln Ala Ser Ala Pro Asn Leu Thr Pro Ile
            260                 265                 270
```

<210> 8
<211> 273
<212> PRT
<213> homo sapiens

<220>
<221> MISC_FEATURE
<223> Cx31.1 (NP_005259.1)

<400> 8

```
Met Asn Trp Ser Ile Phe Glu Gly Leu Leu Ser Gly Val Asn Lys Tyr
1               5                   10                  15

Ser Thr Ala Phe Gly Arg Ile Trp Leu Ser Leu Val Phe Ile Phe Arg
            20                  25                  30

Val Leu Val Tyr Leu Val Thr Ala Glu Arg Val Trp Ser Asp Asp His
        35                  40                  45
```

```
Lys Asp Phe Asp Cys Asn Thr Arg Gln Pro Gly Cys Ser Asn Val Cys
    50                  55                  60

Phe Asp Glu Phe Phe Pro Val Ser His Val Arg Leu Trp Ala Leu Gln
65                  70                  75                  80

Leu Ile Leu Val Thr Cys Pro Ser Leu Leu Val Val Met His Val Ala
                85                  90                  95

Tyr Arg Glu Val Gln Glu Lys Arg His Arg Glu Ala His Gly Glu Asn
            100                 105                 110

Ser Gly Arg Leu Tyr Leu Asn Pro Gly Lys Lys Arg Gly Gly Leu Trp
        115                 120                 125

Trp Thr Tyr Val Cys Ser Leu Val Phe Lys Ala Ser Val Asp Ile Ala
    130                 135                 140

Phe Leu Tyr Val Phe His Ser Phe Tyr Pro Lys Tyr Ile Leu Pro Pro
145                 150                 155                 160

Val Val Lys Cys His Ala Asp Pro Cys Pro Asn Ile Val Asp Cys Phe
                165                 170                 175

Ile Ser Lys Pro Ser Glu Lys Asn Ile Phe Thr Leu Phe Met Val Ala
            180                 185                 190

Thr Ala Ala Ile Cys Ile Leu Leu Asn Leu Val Glu Leu Ile Tyr Leu
        195                 200                 205

Val Ser Lys Arg Cys His Glu Cys Leu Ala Ala Arg Lys Ala Gln Ala
    210                 215                 220

Met Cys Thr Gly His His Pro His Gly Thr Thr Ser Ser Cys Lys Gln
225                 230                 235                 240

Asp Asp Leu Leu Ser Gly Asp Leu Ile Phe Leu Gly Ser Asp Ser His
                245                 250                 255

Pro Pro Leu Leu Pro Asp Arg Pro Arg Asp His Val Lys Lys Thr Ile
            260                 265                 270

Leu
```

<210> 9

<211> 294
<212> PRT
<213> homo sapiens

<220>
<221> misc_feature
<223> Cx31.9 (NP_689343.3)

<400> 9

```
Met Gly Glu Trp Ala Phe Leu Gly Ser Leu Leu Asp Ala Val Gln Leu
1               5                   10                  15

Gln Ser Pro Leu Val Gly Arg Leu Trp Leu Val Val Met Leu Ile Phe
            20                  25                  30

Arg Ile Leu Val Leu Ala Thr Val Gly Gly Ala Val Phe Glu Asp Glu
        35                  40                  45

Gln Glu Glu Phe Val Cys Asn Thr Leu Gln Pro Gly Cys Arg Gln Thr
    50                  55                  60

Cys Tyr Asp Arg Ala Phe Pro Val Ser His Tyr Arg Phe Trp Leu Phe
65                  70                  75                  80

His Ile Leu Leu Leu Ser Ala Pro Pro Val Leu Phe Val Val Tyr Ser
                85                  90                  95

Met His Arg Ala Gly Lys Glu Ala Gly Gly Ala Glu Ala Ala Ala Gln
            100                 105                 110

Cys Ala Pro Gly Leu Pro Glu Ala Gln Cys Ala Pro Cys Ala Leu Arg
        115                 120                 125

Ala Arg Arg Ala Arg Arg Cys Tyr Leu Leu Ser Val Ala Leu Arg Leu
    130                 135                 140

Leu Ala Glu Leu Thr Phe Leu Gly Gly Gln Ala Leu Leu Tyr Gly Phe
145                 150                 155                 160

Arg Val Ala Pro His Phe Ala Cys Ala Gly Pro Pro Cys Pro His Thr
                165                 170                 175

Val Asp Cys Phe Val Ser Arg Pro Thr Glu Lys Thr Val Phe Val Leu
            180                 185                 190

Phe Tyr Phe Ala Val Gly Leu Leu Ser Ala Leu Leu Ser Val Ala Glu
        195                 200                 205
```

```
Leu Gly His Leu Leu Trp Lys Gly Arg Pro Arg Ala Gly Glu Arg Asp
    210                 215                 220

Asn Arg Cys Asn Arg Ala His Glu Glu Ala Gln Lys Leu Leu Pro Pro
225                 230                 235                 240

Pro Pro Pro Pro Pro Pro Pro Pro Ala Leu Pro Ser Arg Arg Pro Gly
                245                 250                 255

Pro Glu Pro Cys Ala Pro Pro Ala Tyr Ala His Pro Ala Pro Ala Ser
            260                 265                 270

Leu Arg Glu Cys Gly Ser Gly Arg Gly Lys Ala Ser Pro Ala Thr Gly
        275                 280                 285

Arg Arg Asp Leu Ala Ile
    290


<210>  10
<211>  283
<212>  PRT
<213>  homo sapiens


<220>
<221>  MISC_FEATURE
<223>  Cx32 (NP_000157.1)

<400>  10

Met Asn Trp Thr Gly Leu Tyr Thr Leu Leu Ser Gly Val Asn Arg His
1               5                   10                  15

Ser Thr Ala Ile Gly Arg Val Trp Leu Ser Val Ile Phe Ile Phe Arg
            20                  25                  30

Ile Met Val Leu Val Val Ala Ala Glu Ser Val Trp Gly Asp Glu Lys
        35                  40                  45

Ser Ser Phe Ile Cys Asn Thr Leu Gln Pro Gly Cys Asn Ser Val Cys
    50                  55                  60

Tyr Asp Gln Phe Phe Pro Ile Ser His Val Arg Leu Trp Ser Leu Gln
65                  70                  75                  80

Leu Ile Leu Val Ser Thr Pro Ala Leu Leu Val Ala Met His Val Ala
                85                  90                  95

His Gln Gln His Ile Glu Lys Lys Met Leu Arg Leu Glu Gly His Gly
            100                 105                 110
```

```
Asp Pro Leu His Leu Glu Glu Val Lys Arg His Lys Val His Ile Ser
        115                 120                 125

Gly Thr Leu Trp Trp Thr Tyr Val Ile Ser Val Val Phe Arg Leu Leu
    130                 135                 140

Phe Glu Ala Val Phe Met Tyr Val Phe Tyr Leu Leu Tyr Pro Gly Tyr
145                 150                 155                 160

Ala Met Val Arg Leu Val Lys Cys Asp Val Tyr Pro Cys Pro Asn Thr
                165                 170                 175

Val Asp Cys Phe Val Ser Arg Pro Thr Glu Lys Thr Val Phe Thr Val
            180                 185                 190

Phe Met Leu Ala Ala Ser Gly Ile Cys Ile Ile Leu Asn Val Ala Glu
        195                 200                 205

Val Val Tyr Leu Ile Ile Arg Ala Cys Ala Arg Arg Ala Gln Arg Arg
    210                 215                 220

Ser Asn Pro Pro Ser Arg Lys Gly Ser Gly Phe Gly His Arg Leu Ser
225                 230                 235                 240

Pro Glu Tyr Lys Gln Asn Glu Ile Asn Lys Leu Leu Ser Glu Gln Asp
                245                 250                 255

Gly Ser Leu Lys Asp Ile Leu Arg Arg Ser Pro Gly Thr Gly Ala Gly
            260                 265                 270

Leu Ala Glu Lys Ser Asp Arg Cys Ser Ala Cys
        275                 280


<210>  11
<211>  321
<212>  PRT
<213>  homo sapiens


<220>
<221>  MISC_FEATURE
<223>  Cx36 (NP_065711.1)

<400>  11

Met Gly Glu Trp Thr Ile Leu Glu Arg Leu Leu Glu Ala Ala Val Gln
1               5                   10                  15

Gln His Ser Thr Met Ile Gly Arg Ile Leu Leu Thr Val Val Val Ile
            20                  25                  30
```

```
Phe Arg Ile Leu Ile Val Ala Ile Val Gly Glu Thr Val Tyr Asp Asp
        35                  40                  45

Glu Gln Thr Met Phe Val Cys Asn Thr Leu Gln Pro Gly Cys Asn Gln
    50                  55                  60

Ala Cys Tyr Asp Arg Ala Phe Pro Ile Ser His Ile Arg Tyr Trp Val
65                  70                  75                  80

Phe Gln Ile Ile Met Val Cys Thr Pro Ser Leu Cys Phe Ile Thr Tyr
                85                  90                  95

Ser Val His Gln Ser Ala Lys Gln Arg Glu Arg Arg Tyr Ser Thr Val
            100                 105                 110

Phe Leu Ala Leu Asp Arg Asp Pro Pro Glu Ser Ile Gly Gly Pro Gly
        115                 120                 125

Gly Thr Gly Gly Gly Gly Ser Gly Gly Gly Lys Arg Glu Asp Lys Lys
    130                 135                 140

Leu Gln Asn Ala Ile Val Asn Gly Val Leu Gln Asn Thr Glu Asn Thr
145                 150                 155                 160

Ser Lys Glu Thr Glu Pro Asp Cys Leu Glu Val Lys Glu Leu Thr Pro
                165                 170                 175

His Pro Ser Gly Leu Arg Thr Ala Ser Lys Ser Lys Leu Arg Arg Gln
            180                 185                 190

Glu Gly Ile Ser Arg Phe Tyr Ile Ile Gln Val Val Phe Arg Asn Ala
        195                 200                 205

Leu Glu Ile Gly Phe Leu Val Gly Gln Tyr Phe Leu Tyr Gly Phe Ser
    210                 215                 220

Val Pro Gly Leu Tyr Glu Cys Asn Arg Tyr Pro Cys Ile Lys Glu Val
225                 230                 235                 240

Glu Cys Tyr Val Ser Arg Pro Thr Glu Lys Thr Val Phe Leu Val Phe
                245                 250                 255

Met Phe Ala Val Ser Gly Ile Cys Val Val Leu Asn Leu Ala Glu Leu
            260                 265                 270

Asn His Leu Gly Trp Arg Lys Ile Lys Leu Ala Val Arg Gly Ala Gln
```

275 280 285

Ala Lys Arg Lys Ser Ile Tyr Glu Ile Arg Asn Lys Asp Leu Pro Arg
290 295 300

Val Ser Val Pro Asn Phe Gly Arg Thr Gln Ser Ser Asp Ser Ala Tyr
305 310 315 320

Val

<210> 12
<211> 333
<212> PRT
<213> homo sapiens

<220>
<221> MISC_FEATURE
<223> Cx37 (NP_002051.2)

<400> 12

Met Gly Asp Trp Gly Phe Leu Glu Lys Leu Leu Asp Gln Val Gln Glu
1 5 10 15

His Ser Thr Val Val Gly Lys Ile Trp Leu Thr Val Leu Phe Ile Phe
20 25 30

Arg Ile Leu Ile Leu Gly Leu Ala Gly Glu Ser Val Trp Gly Asp Glu
35 40 45

Gln Ser Asp Phe Glu Cys Asn Thr Ala Gln Pro Gly Cys Thr Asn Val
50 55 60

Cys Tyr Asp Gln Ala Phe Pro Ile Ser His Ile Arg Tyr Trp Val Leu
65 70 75 80

Gln Phe Leu Phe Val Ser Thr Pro Thr Leu Val Tyr Leu Gly His Val
85 90 95

Ile Tyr Leu Ser Arg Arg Glu Glu Arg Leu Arg Gln Lys Glu Gly Glu
100 105 110

Leu Arg Ala Leu Pro Ala Lys Asp Pro Gln Val Glu Arg Ala Leu Ala
115 120 125

Ala Val Glu Arg Gln Met Ala Lys Ile Ser Val Ala Glu Asp Gly Arg
130 135 140

```
Leu Arg Ile Arg Gly Ala Leu Met Gly Thr Tyr Val Ala Ser Val Leu
145                 150                 155                 160

Cys Lys Ser Val Leu Glu Ala Gly Phe Leu Tyr Gly Gln Trp Arg Leu
                165                 170                 175

Tyr Gly Trp Thr Met Glu Pro Val Phe Val Cys Gln Arg Ala Pro Cys
            180                 185                 190

Pro Tyr Leu Val Asp Cys Phe Val Ser Arg Pro Thr Glu Lys Thr Ile
        195                 200                 205

Phe Ile Ile Phe Met Leu Val Val Gly Leu Ile Ser Leu Val Leu Asn
    210                 215                 220

Leu Leu Glu Leu Val His Leu Leu Cys Arg Cys Leu Ser Arg Gly Met
225                 230                 235                 240

Arg Ala Arg Gln Gly Gln Asp Ala Pro Pro Thr Gln Gly Thr Ser Ser
                245                 250                 255

Asp Pro Tyr Thr Asp Gln Val Phe Phe Tyr Leu Pro Val Gly Gln Gly
            260                 265                 270

Pro Ser Ser Pro Pro Cys Pro Thr Tyr Asn Gly Leu Ser Ser Ser Glu
        275                 280                 285

Gln Asn Trp Ala Asn Leu Thr Thr Glu Glu Arg Leu Ala Ser Ser Arg
    290                 295                 300

Pro Pro Leu Phe Leu Asp Pro Pro Pro Gln Asn Gly Gln Lys Pro Pro
305                 310                 315                 320

Ser Arg Pro Ser Ser Ser Ala Ser Lys Lys Gln Tyr Val
                325                 330


<210>  13
<211>  358
<212>  PRT
<213>  homo sapiens


<220>
<221>  MISC_FEATURE
<223>  Cx40 (NP_005257)

<400>  13

Met Gly Asp Trp Ser Phe Leu Gly Asn Phe Leu Glu Glu Val His Lys
1               5                   10                  15
```

```
His Ser Thr Val Val Gly Lys Val Trp Leu Thr Val Leu Phe Ile Phe
            20                  25                  30

Arg Met Leu Val Leu Gly Thr Ala Ala Glu Ser Ser Trp Gly Asp Glu
        35                  40                  45

Gln Ala Asp Phe Arg Cys Asp Thr Ile Gln Pro Gly Cys Gln Asn Val
    50                  55                  60

Cys Tyr Asp Gln Ala Phe Pro Ile Ser His Ile Arg Tyr Trp Val Leu
65                  70                  75                  80

Gln Ile Ile Phe Val Ser Thr Pro Ser Leu Val Tyr Met Gly His Ala
                85                  90                  95

Met His Thr Val Arg Met Gln Glu Lys Arg Lys Leu Arg Glu Ala Glu
            100                 105                 110

Arg Ala Lys Glu Val Arg Gly Ser Gly Ser Tyr Glu Tyr Pro Val Ala
        115                 120                 125

Glu Lys Ala Glu Leu Ser Cys Trp Glu Glu Gly Asn Gly Arg Ile Ala
    130                 135                 140

Leu Gln Gly Thr Leu Leu Asn Thr Tyr Val Cys Ser Ile Leu Ile Arg
145                 150                 155                 160

Thr Thr Met Glu Val Gly Phe Ile Val Gly Gln Tyr Phe Ile Tyr Gly
                165                 170                 175

Ile Phe Leu Thr Thr Leu His Val Cys Arg Arg Ser Pro Cys Pro His
            180                 185                 190

Pro Val Asn Cys Tyr Val Ser Arg Pro Thr Glu Lys Asn Val Phe Ile
        195                 200                 205

Val Phe Met Leu Ala Val Ala Ala Leu Ser Leu Leu Leu Ser Leu Ala
    210                 215                 220

Glu Leu Tyr His Leu Gly Trp Lys Lys Ile Arg Gln Arg Phe Val Lys
225                 230                 235                 240

Pro Arg Gln His Met Ala Lys Cys Gln Leu Ser Gly Pro Ser Val Gly
                245                 250                 255

Ile Val Gln Ser Cys Thr Pro Pro Pro Asp Phe Asn Gln Cys Leu Glu
            260                 265                 270
```

```
Asn Gly Pro Gly Gly Lys Phe Phe Asn Pro Phe Ser Asn Asn Met Ala
        275                 280                 285

Ser Gln Gln Asn Thr Asp Asn Leu Val Thr Glu Gln Val Arg Gly Gln
    290                 295                 300

Glu Gln Thr Pro Gly Glu Gly Phe Ile Gln Val Arg Tyr Gly Gln Lys
305                 310                 315                 320

Pro Glu Val Pro Asn Gly Val Ser Pro Gly His Arg Leu Pro His Gly
                325                 330                 335

Tyr His Ser Asp Lys Arg Arg Leu Ser Lys Ala Ser Ser Lys Ala Arg
            340                 345                 350

Ser Asp Asp Leu Ser Val
        355


<210>  14
<211>  370
<212>  PRT
<213>  homo sapiens


<220>
<221>  misc_feature
<223>  Cx40.1 (NP_699199.2)

<400>  14

Met Glu Gly Val Asp Leu Leu Gly Phe Leu Ile Ile Thr Leu Asn Cys
1               5                   10                  15

Asn Val Thr Met Val Gly Lys Leu Trp Phe Val Leu Thr Met Leu Leu
            20                  25                  30

Arg Met Leu Val Ile Val Leu Ala Gly Arg Pro Val Tyr Gln Asp Glu
        35                  40                  45

Gln Glu Arg Phe Val Cys Asn Thr Leu Gln Pro Gly Cys Ala Asn Val
    50                  55                  60

Cys Tyr Asp Val Phe Ser Pro Val Ser His Leu Arg Phe Trp Leu Ile
65                  70                  75                  80

Gln Gly Val Cys Val Leu Leu Pro Ser Ala Val Phe Ser Val Tyr Val
                85                  90                  95

Leu His Arg Gly Ala Thr Leu Ala Ala Leu Gly Pro Arg Arg Cys Pro
```

```
            100                 105                 110

Asp Pro Arg Glu Pro Ala Ser Gly Gln Arg Arg Cys Pro Arg Pro Phe
        115                 120                 125

Gly Glu Arg Gly Gly Leu Gln Val Pro Asp Phe Ser Ala Gly Tyr Ile
    130                 135                 140

Ile His Leu Leu Leu Arg Thr Leu Leu Glu Ala Ala Phe Gly Ala Leu
145                 150                 155                 160

His Tyr Phe Leu Phe Gly Phe Leu Ala Pro Lys Lys Phe Pro Cys Thr
                165                 170                 175

Arg Pro Pro Cys Thr Gly Val Val Asp Cys Tyr Val Ser Arg Pro Thr
            180                 185                 190

Glu Lys Ser Leu Leu Met Leu Phe Leu Trp Ala Val Ser Ala Leu Ser
        195                 200                 205

Phe Leu Leu Gly Leu Ala Asp Leu Val Cys Ser Leu Arg Arg Arg Met
    210                 215                 220

Arg Arg Arg Pro Gly Pro Pro Thr Ser Pro Ser Ile Arg Lys Gln Ser
225                 230                 235                 240

Gly Ala Ser Gly His Ala Glu Gly Arg Arg Thr Asp Glu Glu Gly Gly
                245                 250                 255

Arg Glu Glu Glu Gly Ala Pro Ala Pro Pro Gly Ala Arg Ala Gly Gly
            260                 265                 270

Glu Gly Ala Gly Ser Pro Arg Arg Thr Ser Arg Val Ser Gly His Thr
        275                 280                 285

Lys Ile Pro Asp Glu Asp Glu Ser Glu Val Thr Ser Ser Ala Ser Glu
    290                 295                 300

Lys Leu Gly Arg Gln Pro Arg Gly Arg Pro His Arg Glu Ala Ala Gln
305                 310                 315                 320

Asp Pro Arg Gly Ser Gly Ser Glu Glu Gln Pro Ser Ala Ala Pro Ser
                325                 330                 335

Arg Leu Ala Ala Pro Pro Ser Cys Ser Ser Leu Gln Pro Pro Asp Pro
            340                 345                 350
```

Pro Ala Ser Ser Ser Gly Ala Pro His Leu Arg Ala Arg Lys Ser Glu
355 360 365

Trp Val
370

<210> 15
<211> 382
<212> PRT
<213> homo sapiens

<220>
<221> MISC_FEATURE
<223> Cx43 (NP_000156.1)

<400> 15

Met Gly Asp Trp Ser Ala Leu Gly Lys Leu Leu Asp Lys Val Gln Ala
1 5 10 15

Tyr Ser Thr Ala Gly Gly Lys Val Trp Leu Ser Val Leu Phe Ile Phe
20 25 30

Arg Ile Leu Leu Leu Gly Thr Ala Val Glu Ser Ala Trp Gly Asp Glu
35 40 45

Gln Ser Ala Phe Arg Cys Asn Thr Gln Gln Pro Gly Cys Glu Asn Val
50 55 60

Cys Tyr Asp Lys Ser Phe Pro Ile Ser His Val Arg Phe Trp Val Leu
65 70 75 80

Gln Ile Ile Phe Val Ser Val Pro Thr Leu Leu Tyr Leu Ala His Val
85 90 95

Phe Tyr Val Met Arg Lys Glu Glu Lys Leu Asn Lys Lys Glu Glu Glu
100 105 110

Leu Lys Val Ala Gln Thr Asp Gly Val Asn Val Asp Met His Leu Lys
115 120 125

Gln Ile Glu Ile Lys Lys Phe Lys Tyr Gly Ile Glu Glu His Gly Lys
130 135 140

Val Lys Met Arg Gly Gly Leu Leu Arg Thr Tyr Ile Ile Ser Ile Leu
145 150 155 160

Phe Lys Ser Ile Phe Glu Val Ala Phe Leu Leu Ile Gln Trp Tyr Ile
165 170 175

```
Tyr Gly Phe Ser Leu Ser Ala Val Tyr Thr Cys Lys Arg Asp Pro Cys
            180                 185                 190

Pro His Gln Val Asp Cys Phe Leu Ser Arg Pro Thr Glu Lys Thr Ile
        195                 200                 205

Phe Ile Ile Phe Met Leu Val Val Ser Leu Val Ser Leu Ala Leu Asn
    210                 215                 220

Ile Ile Glu Leu Phe Tyr Val Phe Phe Lys Gly Val Lys Asp Arg Val
225                 230                 235                 240

Lys Gly Lys Ser Asp Pro Tyr His Ala Thr Ser Gly Ala Leu Ser Pro
                245                 250                 255

Ala Lys Asp Cys Gly Ser Gln Lys Tyr Ala Tyr Phe Asn Gly Cys Ser
            260                 265                 270

Ser Pro Thr Ala Pro Leu Ser Pro Met Ser Pro Pro Gly Tyr Lys Leu
        275                 280                 285

Val Thr Gly Asp Arg Asn Asn Ser Ser Cys Arg Asn Tyr Asn Lys Gln
    290                 295                 300

Ala Ser Glu Gln Asn Trp Ala Asn Tyr Ser Ala Glu Gln Asn Arg Met
305                 310                 315                 320

Gly Gln Ala Gly Ser Thr Ile Ser Asn Ser His Ala Gln Pro Phe Asp
                325                 330                 335

Phe Pro Asp Asp Asn Gln Asn Ser Lys Lys Leu Ala Ala Gly His Glu
            340                 345                 350

Leu Gln Pro Leu Ala Ile Val Asp Gln Arg Pro Ser Ser Arg Ala Ser
        355                 360                 365

Ser Arg Ala Ser Ser Arg Pro Arg Pro Asp Asp Leu Glu Ile
    370                 375                 380


<210>  16
<211>  396
<212>  PRT
<213>  homo sapiens


<220>
<221>  MISC_FEATURE
<223>  Cx45 (NP_001073852.1)
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<400> 16

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Met Ser Trp Ser Phe Leu Thr Arg Leu Leu Glu Glu Ile His Asn His
1               5                  10                  15

Ser Thr Phe Val Gly Lys Ile Trp Leu Thr Val Leu Ile Val Phe Arg
            20                  25                  30

Ile Val Leu Thr Ala Val Gly Gly Glu Ser Ile Tyr Tyr Asp Glu Gln
        35                  40                  45

Ser Lys Phe Val Cys Asn Thr Glu Gln Pro Gly Cys Glu Asn Val Cys
    50                  55                  60

Tyr Asp Ala Phe Ala Pro Leu Ser His Val Arg Phe Trp Val Phe Gln
65                  70                  75                  80

Ile Ile Leu Val Ala Thr Pro Ser Val Met Tyr Leu Gly Tyr Ala Ile
                85                  90                  95

His Lys Ile Ala Lys Met Glu His Gly Glu Ala Asp Lys Lys Ala Ala
            100                 105                 110

Arg Ser Lys Pro Tyr Ala Met Arg Trp Lys Gln His Arg Ala Leu Glu
        115                 120                 125

Glu Thr Glu Glu Asp Asn Glu Glu Asp Pro Met Met Tyr Pro Glu Met
    130                 135                 140

Glu Leu Glu Ser Asp Lys Glu Asn Lys Glu Gln Ser Gln Pro Lys Pro
145                 150                 155                 160

Lys His Asp Gly Arg Arg Arg Ile Arg Glu Asp Gly Leu Met Lys Ile
                165                 170                 175

Tyr Val Leu Gln Leu Leu Ala Arg Thr Val Phe Glu Val Gly Phe Leu
            180                 185                 190

Ile Gly Gln Tyr Phe Leu Tyr Gly Phe Gln Val His Pro Phe Tyr Val
        195                 200                 205

Cys Ser Arg Leu Pro Cys Pro His Lys Ile Asp Cys Phe Ile Ser Arg
    210                 215                 220

Pro Thr Glu Lys Thr Ile Phe Leu Leu Ile Met Tyr Gly Val Thr Gly
225                 230                 235                 240

Leu Cys Leu Leu Leu Asn Ile Trp Glu Met Leu His Leu Gly Phe Gly
```

245 250 255

Thr Ile Arg Asp Ser Leu Asn Ser Lys Arg Arg Glu Leu Glu Asp Pro
260 265 270

Gly Ala Tyr Asn Tyr Pro Phe Thr Trp Asn Thr Pro Ser Ala Pro Pro
275 280 285

Gly Tyr Asn Ile Ala Val Lys Pro Asp Gln Ile Gln Tyr Thr Glu Leu
290 295 300

Ser Asn Ala Lys Ile Ala Tyr Lys Gln Asn Lys Ala Asn Thr Ala Gln
305 310 315 320

Glu Gln Gln Tyr Gly Ser His Glu Glu Asn Leu Pro Ala Asp Leu Glu
325 330 335

Ala Leu Gln Arg Glu Ile Arg Met Ala Gln Glu Arg Leu Asp Leu Ala
340 345 350

Val Gln Ala Tyr Ser His Gln Asn Asn Pro His Gly Pro Arg Glu Lys
355 360 365

Lys Ala Lys Val Gly Ser Lys Ala Gly Ser Asn Lys Ser Thr Ala Ser
370 375 380

Ser Lys Ser Gly Asp Gly Lys Thr Ser Val Trp Ile
385 390 395

<210> 17
<211> 435
<212> PRT
<213> homo sapiens

<220>
<221> MISC_FEATURE
<223> Cx46 (NP_068773.2)

<400> 17

Met Gly Asp Trp Ser Phe Leu Gly Arg Leu Leu Glu Asn Ala Gln Glu
1 5 10 15

His Ser Thr Val Ile Gly Lys Val Trp Leu Thr Val Leu Phe Ile Phe
20 25 30

Arg Ile Leu Val Leu Gly Ala Ala Ala Glu Asp Val Trp Gly Asp Glu
35 40 45

```
Gln Ser Asp Phe Thr Cys Asn Thr Gln Gln Pro Gly Cys Glu Asn Val
    50                  55                  60

Cys Tyr Asp Arg Ala Phe Pro Ile Ser His Ile Arg Phe Trp Ala Leu
65                  70                  75                  80

Gln Ile Ile Phe Val Ser Thr Pro Thr Leu Ile Tyr Leu Gly His Val
                85                  90                  95

Leu His Ile Val Arg Met Glu Glu Lys Lys Lys Glu Arg Glu Glu Glu
            100                 105                 110

Glu Gln Leu Lys Arg Glu Ser Pro Ser Pro Lys Glu Pro Pro Gln Asp
        115                 120                 125

Asn Pro Ser Ser Arg Asp Asp Arg Gly Arg Val Arg Met Ala Gly Ala
    130                 135                 140

Leu Leu Arg Thr Tyr Val Phe Asn Ile Ile Phe Lys Thr Leu Phe Glu
145                 150                 155                 160

Val Gly Phe Ile Ala Gly Gln Tyr Phe Leu Tyr Gly Phe Glu Leu Lys
                165                 170                 175

Pro Leu Tyr Arg Cys Asp Arg Trp Pro Cys Pro Asn Thr Val Asp Cys
            180                 185                 190

Phe Ile Ser Arg Pro Thr Glu Lys Thr Ile Phe Ile Ile Phe Met Leu
        195                 200                 205

Ala Val Ala Cys Ala Ser Leu Leu Leu Asn Met Leu Glu Ile Tyr His
    210                 215                 220

Leu Gly Trp Lys Lys Leu Lys Gln Gly Val Thr Ser Arg Leu Gly Pro
225                 230                 235                 240

Asp Ala Ser Glu Ala Pro Leu Gly Thr Ala Asp Pro Pro Pro Leu Pro
                245                 250                 255

Pro Ser Ser Arg Pro Pro Ala Val Ala Ile Gly Phe Pro Pro Tyr Tyr
            260                 265                 270

Ala His Thr Ala Ala Pro Leu Gly Gln Ala Arg Ala Val Gly Tyr Pro
        275                 280                 285

Gly Ala Pro Pro Pro Ala Ala Asp Phe Lys Leu Leu Ala Leu Thr Glu
    290                 295                 300
```

```
Ala Arg Gly Lys Gly Gln Ser Ala Lys Leu Tyr Asn Gly His His His
305                 310                 315                 320

Leu Leu Met Thr Glu Gln Asn Trp Ala Asn Gln Ala Ala Glu Arg Gln
                325                 330                 335

Pro Pro Ala Leu Lys Ala Tyr Pro Ala Ala Ser Thr Pro Ala Ala Pro
            340                 345                 350

Ser Pro Val Gly Ser Ser Ser Pro Pro Leu Ala His Glu Ala Glu Ala
        355                 360                 365

Gly Ala Ala Pro Leu Leu Leu Asp Gly Ser Gly Ser Ser Leu Glu Gly
    370                 375                 380

Ser Ala Leu Ala Gly Thr Pro Glu Glu Glu Glu Gln Ala Val Thr Thr
385                 390                 395                 400

Ala Ala Gln Met His Gln Pro Pro Leu Pro Leu Gly Asp Pro Gly Arg
                405                 410                 415

Ala Ser Lys Ala Ser Arg Ala Ser Ser Gly Arg Ala Arg Pro Glu Asp
            420                 425                 430

Leu Ala Ile
        435
```

<210> 18
<211> 439
<212> PRT
<213> homo sapiens

<220>
<221> MISC_FEATURE
<223> Cx47 (NP_065168.2)

<400> 18

```
Met Thr Asn Met Ser Trp Ser Phe Leu Thr Arg Leu Leu Glu Glu Ile
1               5                   10                  15

His Asn His Ser Thr Phe Val Gly Lys Val Trp Leu Thr Val Leu Val
            20                  25                  30

Val Phe Arg Ile Val Leu Thr Ala Val Gly Gly Glu Ala Ile Tyr Ser
        35                  40                  45

Asp Glu Gln Ala Lys Phe Thr Cys Asn Thr Arg Gln Pro Gly Cys Asp
    50                  55                  60
```

```
Asn Val Cys Tyr Asp Ala Phe Ala Pro Leu Ser His Val Arg Phe Trp
65                  70                  75                  80

Val Phe Gln Ile Val Val Ile Ser Thr Pro Ser Val Met Tyr Leu Gly
                85                  90                  95

Tyr Ala Val His Arg Leu Ala Arg Ala Ser Glu Gln Glu Arg Arg Arg
            100                 105                 110

Ala Leu Arg Arg Arg Pro Gly Pro Arg Arg Ala Pro Arg Ala His Leu
        115                 120                 125

Pro Pro Pro His Ala Gly Trp Pro Glu Pro Ala Asp Leu Gly Glu Glu
    130                 135                 140

Glu Pro Met Leu Gly Leu Gly Glu Glu Glu Glu Glu Glu Glu Thr Gly
145                 150                 155                 160

Ala Ala Glu Gly Ala Gly Glu Glu Ala Glu Glu Ala Gly Ala Glu Glu
                165                 170                 175

Ala Cys Thr Lys Ala Val Gly Ala Asp Gly Lys Ala Ala Gly Thr Pro
            180                 185                 190

Gly Pro Thr Gly Gln His Asp Gly Arg Arg Arg Ile Gln Arg Glu Gly
        195                 200                 205

Leu Met Arg Val Tyr Val Ala Gln Leu Val Ala Arg Ala Ala Phe Glu
    210                 215                 220

Val Ala Phe Leu Val Gly Gln Tyr Leu Leu Tyr Gly Phe Glu Val Arg
225                 230                 235                 240

Pro Phe Phe Pro Cys Ser Arg Gln Pro Cys Pro His Val Val Asp Cys
                245                 250                 255

Phe Val Ser Arg Pro Thr Glu Lys Thr Val Phe Leu Leu Val Met Tyr
            260                 265                 270

Val Val Ser Cys Leu Cys Leu Leu Leu Asn Leu Cys Glu Met Ala His
        275                 280                 285

Leu Gly Leu Gly Ser Ala Gln Asp Ala Val Arg Gly Arg Arg Gly Pro
    290                 295                 300

Pro Ala Ser Ala Pro Ala Pro Ala Pro Arg Pro Pro Pro Cys Ala Phe
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305 310 315 320

Pro Ala Ala Ala Ala Gly Leu Ala Cys Pro Pro Asp Tyr Ser Leu Val
325 330 335

Val Arg Ala Ala Glu Arg Ala Arg Ala His Asp Gln Asn Leu Ala Asn
340 345 350

Leu Ala Leu Gln Ala Leu Arg Asp Gly Ala Ala Ala Gly Asp Arg Asp
355 360 365

Arg Asp Ser Ser Pro Cys Val Gly Leu Pro Ala Ala Ser Arg Gly Pro
370 375 380

Pro Arg Ala Gly Ala Pro Ala Ser Arg Thr Gly Ser Ala Thr Ser Ala
385 390 395 400

Gly Thr Val Gly Glu Gln Gly Arg Pro Gly Thr His Glu Arg Pro Gly
405 410 415

Ala Lys Pro Arg Ala Gly Ser Glu Lys Gly Ser Ala Ser Ser Arg Asp
420 425 430

Gly Lys Thr Thr Val Trp Ile
435

<210> 19
<211> 433
<212> PRT
<213> homo sapiens

<220>
<221> MISC_FEATURE
<223> Cx50 (NP_005258.2)

<400> 19

Met Gly Asp Trp Ser Phe Leu Gly Asn Ile Leu Glu Glu Val Asn Glu
1 5 10 15

His Ser Thr Val Ile Gly Arg Val Trp Leu Thr Val Leu Phe Ile Phe
20 25 30

Arg Ile Leu Ile Leu Gly Thr Ala Ala Glu Phe Val Trp Gly Asp Glu
35 40 45

Gln Ser Asp Phe Val Cys Asn Thr Gln Gln Pro Gly Cys Glu Asn Val
50 55 60

```
Cys Tyr Asp Glu Ala Phe Pro Ile Ser His Ile Arg Leu Trp Val Leu
65                  70                  75                  80

Gln Ile Ile Phe Val Ser Thr Pro Ser Leu Met Tyr Val Gly His Ala
                85                  90                  95

Val His Tyr Val Arg Met Glu Glu Lys Arg Lys Ser Arg Glu Ala Glu
            100                 105                 110

Glu Leu Gly Gln Gln Ala Gly Thr Asn Gly Gly Pro Asp Gln Gly Ser
        115                 120                 125

Val Lys Lys Ser Ser Gly Ser Lys Gly Thr Lys Lys Phe Arg Leu Glu
    130                 135                 140

Gly Thr Leu Leu Arg Thr Tyr Ile Cys His Ile Ile Phe Lys Thr Leu
145                 150                 155                 160

Phe Glu Val Gly Phe Ile Val Gly His Tyr Phe Leu Tyr Gly Phe Arg
                165                 170                 175

Ile Leu Pro Leu Tyr Arg Cys Ser Arg Trp Pro Cys Pro Asn Val Val
            180                 185                 190

Asp Cys Phe Val Ser Arg Pro Thr Glu Lys Thr Ile Phe Ile Leu Phe
        195                 200                 205

Met Leu Ser Val Ala Ser Val Ser Leu Phe Leu Asn Val Met Glu Leu
    210                 215                 220

Gly His Leu Gly Leu Lys Gly Ile Arg Ser Ala Leu Lys Arg Pro Val
225                 230                 235                 240

Glu Gln Pro Leu Gly Glu Ile Pro Glu Lys Ser Leu His Ser Ile Ala
                245                 250                 255

Val Ser Ser Ile Gln Lys Ala Lys Gly Tyr Gln Leu Leu Glu Glu Glu
            260                 265                 270

Lys Ile Val Ser His Tyr Phe Pro Leu Thr Glu Val Gly Met Val Glu
        275                 280                 285

Thr Ser Pro Leu Pro Ala Lys Pro Phe Asn Gln Phe Glu Glu Lys Ile
    290                 295                 300

Ser Thr Gly Pro Leu Gly Asp Leu Ser Arg Gly Tyr Gln Glu Thr Leu
305                 310                 315                 320
```

```
Pro Ser Tyr Ala Gln Val Gly Ala Gln Glu Val Glu Gly Glu Gly Pro
                325                 330                 335

Pro Ala Glu Glu Gly Ala Glu Pro Glu Val Gly Glu Lys Lys Glu Glu
            340                 345                 350

Ala Glu Arg Leu Thr Thr Glu Glu Gln Glu Lys Val Ala Val Pro Glu
        355                 360                 365

Gly Glu Lys Val Glu Thr Pro Gly Val Asp Lys Glu Gly Glu Lys Glu
    370                 375                 380

Glu Pro Gln Ser Glu Lys Val Ser Lys Gln Gly Leu Pro Ala Glu Lys
385                 390                 395                 400

Thr Pro Ser Leu Cys Pro Glu Leu Thr Thr Asp Asp Ala Arg Pro Leu
                405                 410                 415

Ser Arg Leu Ser Lys Ala Ser Ser Arg Ala Arg Ser Asp Asp Leu Thr
            420                 425                 430

Val
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<210> 20
<211> 515
<212> PRT
<213> homo sapiens

<220>
<221> MISC_FEATURE
<223> Cx59 (NP_110399.2)

<400> 20

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Met Gly Asp Trp Asn Leu Leu Gly Asp Thr Leu Glu Glu Val His Ile
1               5                   10                  15

His Ser Thr Met Ile Gly Lys Ile Trp Leu Thr Ile Leu Phe Ile Phe
            20                  25                  30

Arg Met Leu Val Leu Gly Val Ala Ala Glu Asp Val Trp Asn Asp Glu
        35                  40                  45

Gln Ser Gly Phe Ile Cys Asn Thr Glu Gln Pro Gly Cys Arg Asn Val
    50                  55                  60

Cys Tyr Asp Gln Ala Phe Pro Ile Ser Leu Ile Arg Tyr Trp Val Leu
65                  70                  75                  80
```

```
Gln Val Ile Phe Val Ser Ser Pro Ser Leu Val Tyr Met Gly His Ala
                85                  90                  95

Leu Tyr Arg Leu Arg Val Leu Glu Glu Glu Arg Gln Arg Met Lys Ala
            100                 105                 110

Gln Leu Arg Val Glu Leu Glu Glu Val Glu Phe Glu Met Pro Arg Asp
        115                 120                 125

Arg Arg Arg Leu Glu Gln Glu Leu Cys Gln Leu Glu Lys Arg Lys Leu
    130                 135                 140

Asn Lys Ala Pro Leu Arg Gly Thr Leu Leu Cys Thr Tyr Val Ile His
145                 150                 155                 160

Ile Phe Thr Arg Ser Val Val Glu Val Gly Phe Met Ile Gly Gln Tyr
                165                 170                 175

Leu Leu Tyr Gly Phe His Leu Glu Pro Leu Phe Lys Cys His Gly His
            180                 185                 190

Pro Cys Pro Asn Ile Ile Asp Cys Phe Val Ser Arg Pro Thr Glu Lys
        195                 200                 205

Thr Ile Phe Leu Leu Phe Met Gln Ser Ile Ala Thr Ile Ser Leu Phe
    210                 215                 220

Leu Asn Ile Leu Glu Ile Phe His Leu Gly Phe Lys Lys Ile Lys Arg
225                 230                 235                 240

Gly Leu Trp Gly Lys Tyr Lys Leu Lys Lys Glu His Asn Glu Phe His
                245                 250                 255

Ala Asn Lys Ala Lys Gln Asn Val Ala Lys Tyr Gln Ser Thr Ser Ala
            260                 265                 270

Asn Ser Leu Lys Arg Leu Pro Ser Ala Pro Asp Tyr Asn Leu Leu Val
        275                 280                 285

Glu Lys Gln Thr His Thr Ala Val Tyr Pro Ser Leu Asn Ser Ser Ser
    290                 295                 300

Val Phe Gln Pro Asn Pro Asp Asn His Ser Val Asn Asp Glu Lys Cys
305                 310                 315                 320

Ile Leu Asp Glu Gln Glu Thr Val Leu Ser Asn Glu Ile Ser Thr Leu
```

325 330 335

Ser Thr Ser Cys Ser His Phe Gln His Ile Ser Ser Asn Asn Asn Lys
340 345 350

Asp Thr His Lys Ile Phe Gly Lys Glu Leu Asn Gly Asn Gln Leu Met
355 360 365

Glu Lys Arg Glu Thr Glu Gly Lys Asp Ser Lys Arg Asn Tyr Tyr Ser
370 375 380

Arg Gly His Arg Ser Ile Pro Gly Val Ala Ile Asp Gly Glu Asn Asn
385 390 395 400

Met Arg Gln Ser Pro Gln Thr Val Phe Ser Leu Pro Ala Asn Cys Asp
405 410 415

Trp Lys Pro Arg Trp Leu Arg Ala Thr Trp Gly Ser Ser Thr Glu His
420 425 430

Glu Asn Arg Gly Ser Pro Pro Lys Gly Asn Leu Lys Gly Gln Phe Arg
435 440 445

Lys Gly Thr Val Arg Thr Leu Pro Pro Ser Gln Gly Asp Ser Gln Ser
450 455 460

Leu Asp Ile Pro Asn Thr Ala Asp Ser Leu Gly Gly Leu Ser Phe Glu
465 470 475 480

Pro Gly Leu Val Arg Thr Cys Asn Asn Pro Val Cys Pro Pro Asn His
485 490 495

Val Val Ser Leu Thr Asn Asn Leu Ile Gly Arg Arg Val Pro Thr Asp
500 505 510

Leu Gln Ile
515

<210> 21
<211> 543
<212> PRT
<213> homo sapiens

<220>
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<223> Cx62 (NP_115991.1)

<400> 21

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Met Gly Asp Trp Asn Leu Leu Gly Gly Ile Leu Glu Glu Val His Ser
1               5                  10                  15

His Ser Thr Ile Val Gly Lys Ile Trp Leu Thr Ile Leu Phe Ile Phe
            20                  25                  30

Arg Met Leu Val Leu Arg Val Ala Ala Glu Asp Val Trp Asp Asp Glu
        35                  40                  45

Gln Ser Ala Phe Ala Cys Asn Thr Arg Gln Pro Gly Cys Asn Asn Ile
    50                  55                  60

Cys Tyr Asp Asp Ala Phe Pro Ile Ser Leu Ile Arg Phe Trp Val Leu
65                  70                  75                  80

Gln Ile Ile Phe Val Ser Ser Pro Ser Leu Val Tyr Met Gly His Ala
                85                  90                  95

Leu Tyr Arg Leu Arg Ala Phe Glu Lys Asp Arg Gln Arg Lys Lys Ser
            100                 105                 110

His Leu Arg Ala Gln Met Glu Asn Pro Asp Leu Asp Leu Glu Glu Gln
        115                 120                 125

Gln Arg Ile Asp Arg Glu Leu Arg Arg Leu Glu Glu Gln Lys Arg Ile
    130                 135                 140

His Lys Val Pro Leu Lys Gly Cys Leu Leu Arg Thr Tyr Val Leu His
145                 150                 155                 160

Ile Leu Thr Arg Ser Val Leu Glu Val Gly Phe Met Ile Gly Gln Tyr
                165                 170                 175

Ile Leu Tyr Gly Phe Gln Met His Pro Leu Tyr Lys Cys Thr Gln Pro
            180                 185                 190

Pro Cys Pro Asn Ala Val Asp Cys Phe Val Ser Arg Pro Thr Glu Lys
        195                 200                 205

Thr Ile Phe Met Leu Phe Met His Ser Ile Ala Ala Ile Ser Leu Leu
    210                 215                 220

Leu Asn Ile Leu Glu Ile Phe His Leu Gly Ile Arg Lys Ile Met Arg
225                 230                 235                 240

Thr Leu Tyr Lys Lys Ser Ser Ser Glu Gly Ile Glu Asp Glu Thr Gly
                245                 250                 255
```

```
Pro Pro Phe His Leu Lys Lys Tyr Ser Val Ala Gln Gln Cys Met Ile
            260                 265                 270

Cys Ser Ser Leu Pro Glu Arg Ile Ser Pro Leu Gln Ala Asn Asn Gln
        275                 280                 285

Gln Gln Val Ile Arg Val Asn Val Pro Lys Ser Lys Thr Met Trp Gln
    290                 295                 300

Ile Pro Gln Pro Arg Gln Leu Glu Val Asp Pro Ser Asn Gly Lys Lys
305                 310                 315                 320

Asp Trp Ser Glu Lys Asp Gln His Ser Gly Gln Leu His Val His Ser
                325                 330                 335

Pro Cys Pro Trp Ala Gly Ser Ala Gly Asn Gln His Leu Gly Gln Gln
            340                 345                 350

Ser Asp His Ser Ser Phe Gly Leu Gln Asn Thr Met Ser Gln Ser Trp
        355                 360                 365

Leu Gly Thr Thr Thr Ala Pro Arg Asn Cys Pro Ser Phe Ala Val Gly
    370                 375                 380

Thr Trp Glu Gln Ser Gln Asp Pro Glu Pro Ser Gly Glu Pro Leu Thr
385                 390                 395                 400

Asp Leu His Ser His Cys Arg Asp Ser Glu Gly Ser Met Arg Glu Ser
                405                 410                 415

Gly Val Trp Ile Asp Arg Ser Arg Pro Gly Ser Arg Lys Ala Ser Phe
            420                 425                 430

Leu Ser Arg Leu Leu Ser Glu Lys Arg His Leu His Ser Asp Ser Gly
        435                 440                 445

Ser Ser Gly Ser Arg Asn Ser Ser Cys Leu Asp Phe Pro His Trp Glu
    450                 455                 460

Asn Ser Pro Ser Pro Leu Pro Ser Val Thr Gly His Arg Thr Ser Met
465                 470                 475                 480

Val Arg Gln Ala Ala Leu Pro Ile Met Glu Leu Ser Gln Glu Leu Phe
                485                 490                 495

His Ser Gly Cys Phe Leu Phe Pro Phe Phe Leu Pro Gly Val Cys Met
            500                 505                 510
```

```
Tyr Val Cys Val Asp Arg Glu Ala Asp Gly Gly Gly Asp Tyr Leu Trp
        515                 520                 525

Arg Asp Lys Ile Ile His Ser Ile His Ser Val Lys Phe Asn Ser
    530                 535                 540
```