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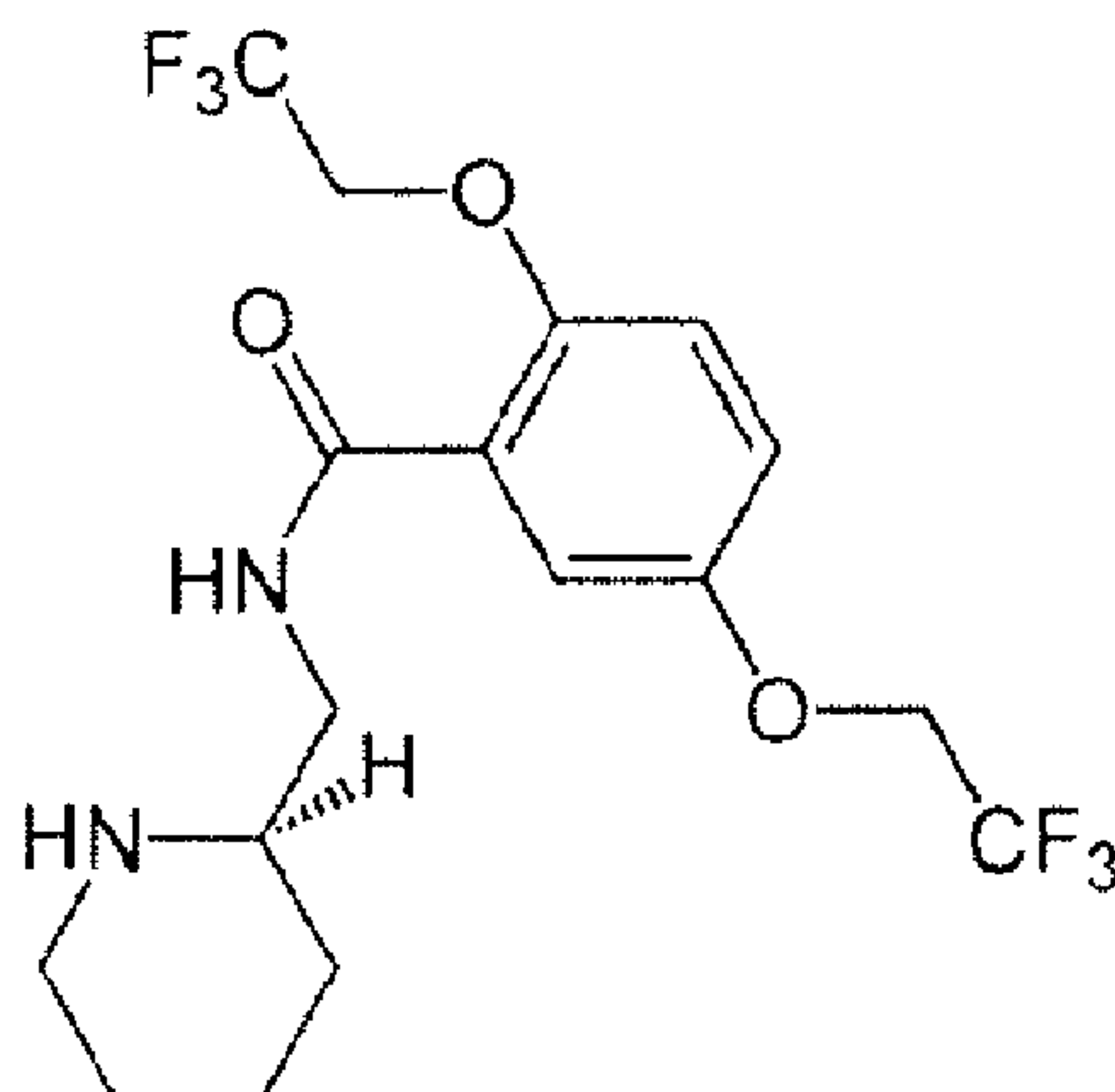
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(54) Titre : UTILISATION DE LA FLECAINIDE EN TANT QU'AGENT ANTI-CONNEXINE ET PROCEDE DE
POTENTIALISATION DES EFFETS D'UN MEDICAMENT PSYCHOTROPE

(54) Title: USE OF FLECAINIDE AS AN ANTI-CONNEXIN AGENT AND METHOD FOR POTENTIATING THE EFFECTS
OF A PSYCHOTROPIC DRUG



(57) **Abrégé/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 effect of various psychotropic drugs. More specifically, the invention provides a combination product containing flecainide and modafinil.

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 effect of 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

This is a division of Canadian patent application no. 2,919,140 filed July 24, 2014.

5 **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.

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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),
15 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.

20 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
25 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 cytoplasm of the two cells in contact, over the
5 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
10 following conditions:

- cancers (WO2006/134494 and WO2006/049157),
- some cardiovascular diseases (WO2006/134494),
- wounds (WO2006/134494 and WO2009/097077),
- pain (WO2009/148613),
- 15 - 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),
- 20 - drug-induced liver injury (Patel et al, 2012)
- infectious diseases (WO2011/067607),
- cytotoxicity induced by chemotherapeutic agents (Tong X. et al, 2013)
- and
- 25 - 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
30 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
5 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,
10 flecainide had been shown not to influence junctional resistance of cardiac myocyte cell pairs (Daleau et al, 1998).

Detailed description of the invention

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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
20 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
25 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
30 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).

5 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
10 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.
15 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 ± 3.7 mg) 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
20 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
25 (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.

5 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 (-)-
10 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
15 alkalized 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
20 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
25 signals that pass through the heart muscle. These electrical signals cause the two pairs of heart chambers (left and right atria 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.
30 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
5 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
10 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
15 significant difference in the effect caused by the enantiomers separately [Lic 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].

20 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
25 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).

5 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
10 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
15 (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
20 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
25 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).

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; remifentanyl;
		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; dipyrrocetyl; benorilate; diflunisal; potassium salicylate; guacetisal; carbasalate calcium; imidazole salicylate
		39. Pyrazolones	40. phenazone; metamizole sodium; aminophenazone ; propyphenazone; nifhenazone;
		41. Anilides	42. paracetamol; phenacetin; buccetin; 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; barbexalone; 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
	89. Antipsychotics	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; trifluoperidol; 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; ascenapine; 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;

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

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

system drugs	homimetics	terases	distigmine; ambenonium;
		<i>168.</i> Choline esters	<i>169.</i> carbachol; bethanechol
		<i>170.</i> Other parasympathomimetics	<i>171.</i> pilocarpine; choline alfoscerate; cevimeline
	<i>172.</i> Drugs used in addictive disorders	<i>173.</i> Drugs used in nicotine dependence	<i>174.</i> nicotine; varenicline
		<i>175.</i> Drugs used in alcohol dependence	<i>176.</i> disulfiram; calcium carbimide; acamprosate; naltrexone; baclofene
		<i>177.</i> Drugs used in opioid dependence	<i>178.</i> buprenorphine; levacetylmethadol ; lofexidine;
	<i>179.</i> Antivertigo preparations	<i>180.</i> Antivertigo preparations	<i>181.</i> betahistine; cinnarizine; flunarizine; acetylleucine
	<i>182.</i> Other nervous system drugs	<i>183.</i> Other nervous system drugs	<i>184.</i> 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, serotonergic, opioidergic, adenosinergic, ionotropic, histaminergic, IMAO, Catechol-O-methyl transferase, DOPA
5 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
10 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
15 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, serotonin, glutamate, GABA, orexine and histamine receptors (Ishizuka et al, 2012; Minzenberg et al, 2008). Therefore, modafinil acts as a GABAergic, dopaminergic, norepinephrinergic, serotonergic, 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 psychotropic drug associated with flecainide is therefore preferably selected in the group consisting of: GABAergic, dopaminergic, norepinephrinergic, serotonergic, 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, pregabalin, gabapentine, phenobarbital, felbamate and vigabatrin.

According to another specific embodiment, the said psychotropic drug is a serotonergic 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, caripramine, 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,
5 astemizole, azatadine, azelastine, brompheniramine, buclizine, carbinoxamine, carebastine, cetirizine, chlorcyclizine, chlorpheniramine, cinnarizine, clemastine, clemizole, clocinazine, clonidine, cyclizine, cyproheptadine, descarboethoxyloratidine, dexchlorpheniramine, dimenhydrinate, dimethindene, dimethothiazine, diphenhydramine, diphenylpyraline, doxylamine, ebastine, efletirizine, epinastine, fexofenadine, hydroxyzine,
10 ketotifen, levocabastine, loratidine, meclizine, mequitazine, methdilazine, mianserin, mizolastine, niaprazine, noberastine, norastemizole, oxatomide, oxomemazine, phenbenzamine, pheniramine, picumast, promethazine, pyrilamine, temelastine, terfenadine, trimeprazine, tripeleminamine, triprolidine, ranitidine, cimetidine, famotidine, nizatidine, tiotidine, zolantidine, ciproxifan, pitolisant and ritanserin.

15 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
20 norepinephrinergic effector selected in the group consisting of: (R)-3-nitrobiphenylene, 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,
25 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,
30 levosalbutamol, lofexidine, mabuterol, medetomidine, metaraminol, methoxamine, methoxyphenamine, methyl dopa, 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, tolونidine, 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 administering same to a patient, either before, at the same time, or 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, 5 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 10 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 15 (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 20 (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 Limb Movement Disorders (PLMD), neurological conditions commonly associated with sleepiness (such as Parkinson disease, multiple sclerosis, stroke, neuromuscular 25 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
5 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
10 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
15 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,
20 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
25 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.

5 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
10 “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
15 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*
20 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
25 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
30 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,
5 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
10 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
15 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
20 Limb 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
25 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
30 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.

5 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.).

10 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
15 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
20 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
25 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.

5 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.

10 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.

15 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.

20 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,
25 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.

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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 (280 μ M), mefloquine (10 μ M) and MFA (100 μ M) 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 Corosso 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 Dil, 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 μ M, mefloquine 10 μ M or meclofenamic acid (MFA) 100 μ M. 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 subtracted 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 μ l 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 literature, meclofenamic acid (MFA) (Dhein, 2004) (100 μ M) and mefloquine (Cruikshank et al, 2004) (10 μ M). 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

5 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
10 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
15 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,
20 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
25 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
30 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.

5 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
10 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
15 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
20 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
25 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).

5 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,
10 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
15 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
20 (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

25 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.

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

5.1. Material and methods

10 *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 than 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 neuropeptides 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.

- 5 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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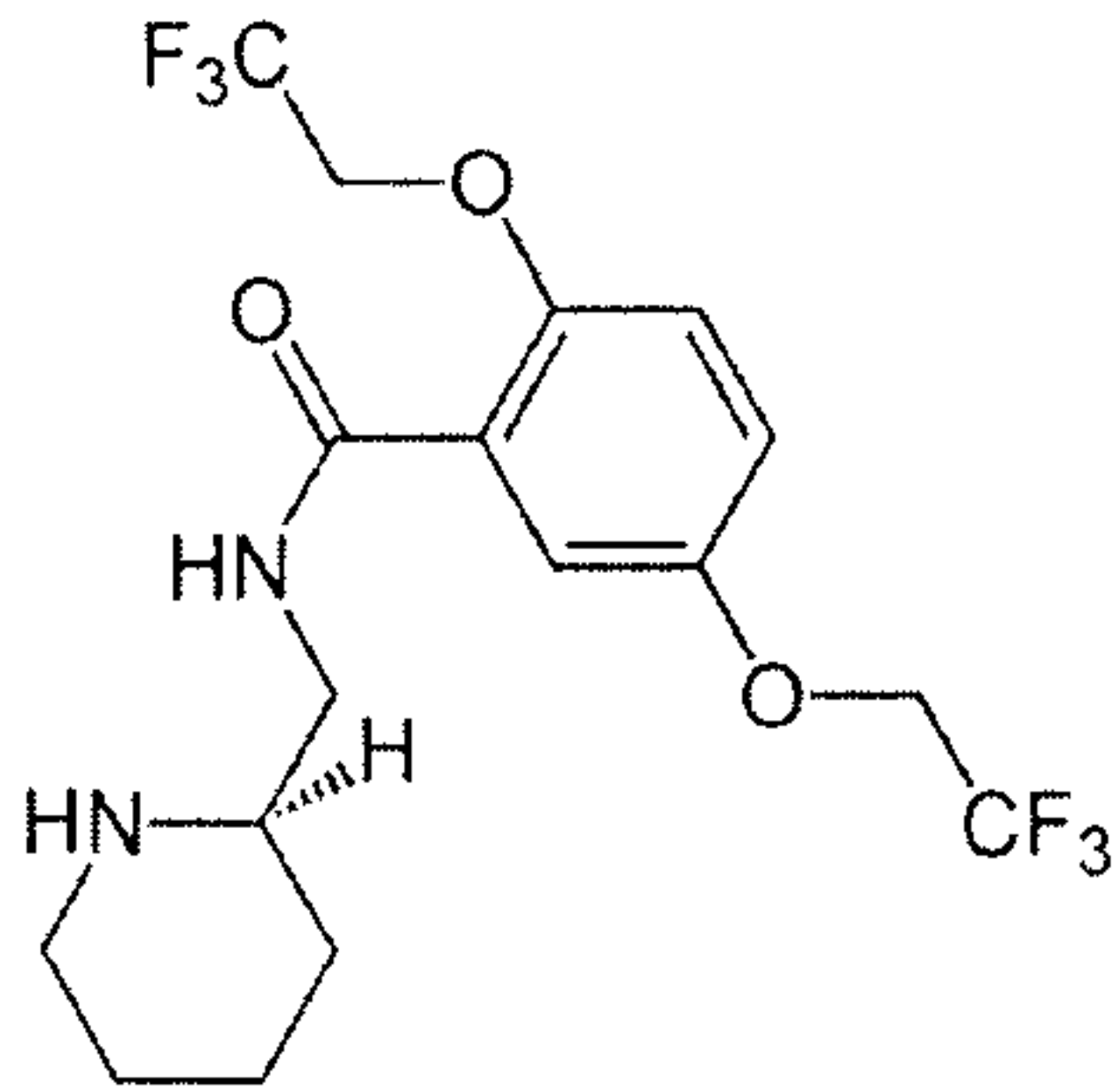
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CLAIMS

1. *In vitro* use of flecainide as an anti-connexin agent.
2. *In vitro* use of claim 1, wherein said flecainide is the R enantiomer of formula:



3. *In vitro* use according to claim 1 or 2, for blocking one or more connexin molecule selected from the group consisting of: Connexin 23, Connexin 25, Connexin 26, Connexin 30, Connexin 30.2, Connexin 30.3, Connexin 31, Connexin 31.1, Connexin 31.9, Connexin 32, Connexin 36, Connexin 37, Connexin 40, Connexin 40.1, Connexin 43, Connexin 45, Connexin 46, Connexin 47, Connexin 50, Connexin 59, and Connexin 62.
4. *In vitro* use according to claim 1 or 2, for blocking one or more connexin molecule selected from the group consisting of: connexin 26, connexin 30, connexin 30.2, connexin 32, connexin 36, connexin 37, connexin 40, connexin 43, connexin 45, connexin 46 and connexin 47.
5. *In vitro* use according to claim 1 or 2, for blocking one or more connexin molecule selected from the group consisting of: connexin Cx40, connexin Cx26, connexin 30, connexin 32, and connexin 43.
6. A therapeutic composition comprising flecainide and at least one psychotropic drug, wherein said psychotropic drug is an adrenergic, an acetylcholinergic, an opioidergic, an adenosinergic, an ionotropic, an IMAO, a Catechol-O-methyl transferase, a DOPA carboxylase, or a noradrenergic effector.

7. The therapeutic composition according to claim 6, wherein said adrenergic effector is chosen in the group consisting of: droperidol, etomidate, dihydroergotamine, ergotamine, lisuride, adrafinil, mirtazapine, clonidine, bromocriptine, pergolide, lamotrigine, ropinirole, pramipexole, cabergoline, apomorphine, acepromazine, chlorpromazine, levomepromazine, promazine, trifluoperazine, thioproperazine, periciazine, thioridazine, ziprasidone, sertindole, zuclopenthixol, asenapine, quetiapine, clozapine, olanzapine, loxapine, tiapride, risperidone, paliperidone, aripiprazole, dexmedetomidine, propiomazine, desipramine, trimipramine, nortriptyline, amoxapine, imipramine, doxepin, citalopram, etoperidone, escitalopram, trazodone, nefazodone, mianserin, amphetamine, dexamphetamine, methamphetamine, atomoxetine, lisdexamfetamine, lofexidine, flupentixol, dosulepin, maprotiline, amitriptyline, mirtazapine, and oxetorone.

8. The therapeutic composition according to claim 6, wherein said acetylcholinergic effector is chosen in the group consisting of: hexobarbital, propanidid, ketamine, procaine, chlorprocaine, cocaine, pethidine, tramadol, methylphenobarbital, phenobarbital, primidone, metharbital, carbamazepine, trihexyphenidyl, biperiden, metixene, procyclidine, profenamine, dexetimide, phenglutarimide, mazaticol, bornaprine, tropatepine, etanautine, orphenadrine, lamotrigine, benztropine, etybenztropine, triflupromazine, molindone, chlorprothixene, flupentixol, pentobarbital, amobarbital, butobarbital, aprobarbital, barbital, secobarbital, heptabarbital, thiopental, allobarbital, scopolamine, dimetacrine, dosulepin, maprotiline, paroxetine, minaprine, bupropion, tacrine, donepezil, rivastigmine, galantamine, memantine, neostigmine, pyridostigmine, distigmine, ambenonium, carbachol, bethanechol, pilocarpine, choline alfoscerate, cevimeline, nicotine, varenicline, chlorpromazine, levomepromazine, promazine, ziprasidone, quetiapine, clozapine, olanzapine, loxapine, aripiprazole, propiomazine, desipramine, trimipramine, nortriptyline, amoxapine, imipramine, doxepin, citalopram, etoperidone, escitalopram, levacetylmethadol, and cinnarizine.

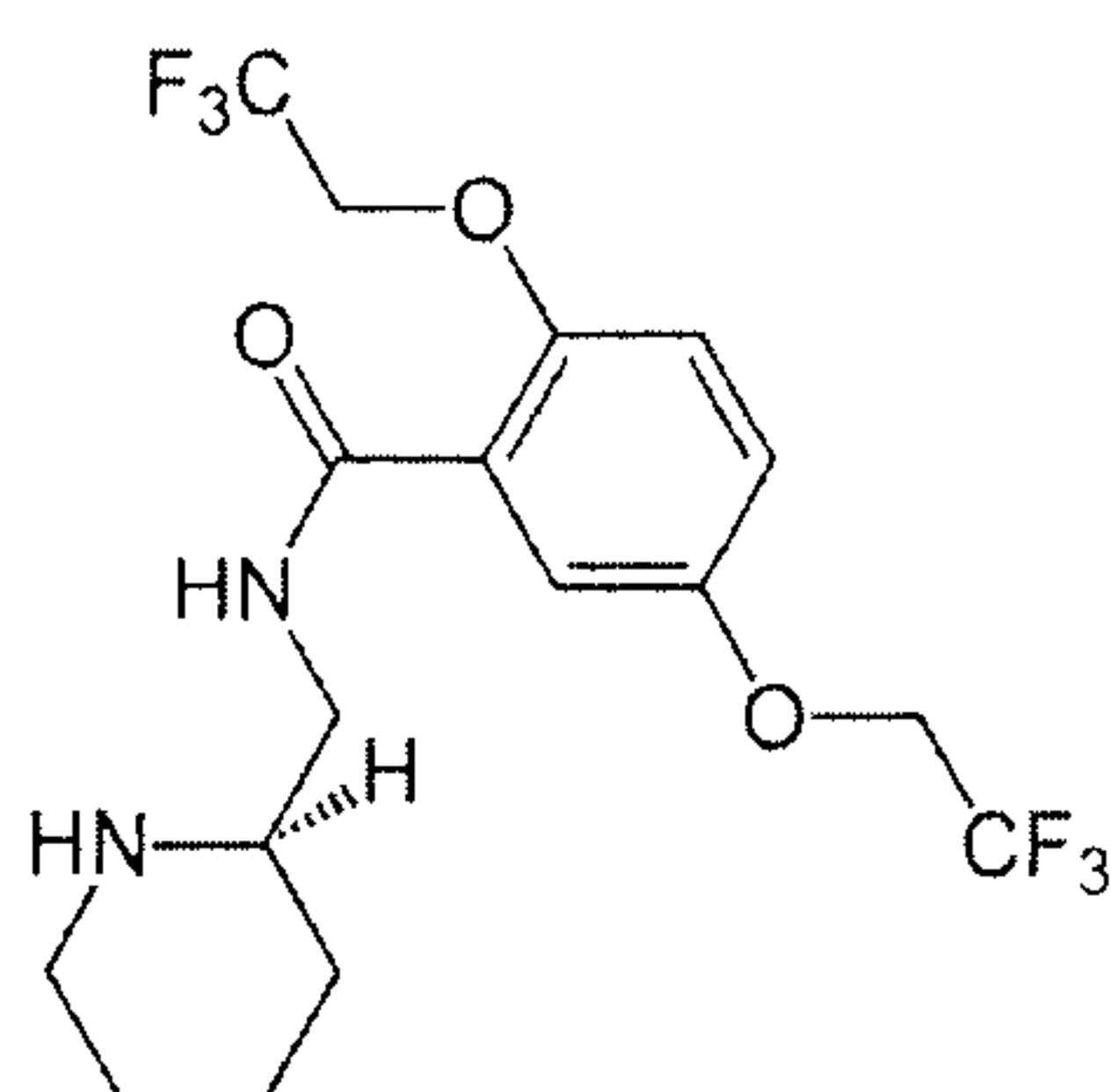
9. The therapeutic composition according to claim 6, wherein said opioidergic effector is chosen in the group consisting of: fentanyl, alfentanil, sufentanil, phenoperidine, anileridine, remifentanil, opium, hydromorphone, nicomorphine, propanidid, ketamine, oxycodone, dihydrocodeine, diamorphine, papaveretum, morphine, cocaine, codeine, ketobemidone, dextromoramide, piritramide, dextropropoxyphene, pethidine, tramadol, bezitramide, methadone, pentazocine, phenazocine, butorphanol, nalbuphine, tilidine, dezocine, meptazinol,

tapentadol, amitryptiline, mirtazapine, naltrexone, buprenorphine, mianserin, and levacetlmethadol.

10. The therapeutic composition according to claim 6, wherein said ionotropic effector is chosen in the group consisting of: halothane, enflurane, isoflurane, desflurane, sevoflurane, Propofol, tetracaine, benzocaine, bupivacaine, lidocaine, mepivacaine, prilocaine, lidocaine, mepivacaine, prilocaine, cinchocaine, ropivacaine, levobupivacaine, dyclonine, capsaicin, procaine, cocaine, chloroprocaine, paracetamol, ziconotide, methoxyflurane, ethotoin, thioridazine, sertindole, loxapine, phenythoin, mephenytoin, fosphenytoin, paramethadione, trimethadione, ethosuximide, mesuximide, oxcarbazepine, rufinamide, carbamazepine, valproic acid, phenacemide, topiramate, levetiracetam, orphenadrine, zonisamide, pregabalin, lacosamide, retigabine, gabaptenin, lamotrigine, carbamazepine, fluspirilene, pimozide, nitrazepam, fluoxetine, fluvoxamine, vinpocetine, flunarizine, riluzole, ketamine, imipramine, doxepin, amitryptiline, nefazodone, cinnarizine and fampridine.

11. The therapeutic composition according to claims 6-10, 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); medication-induced somnolence (due to benzodiazepines, barbiturates, sleeping pills, antidepressants, anti-psychotics...); somnolence or sleepiness associated with Parkinson disease, multiple sclerosis, stroke, neuromuscular disorders, structural brain disorders, respiratory disorders, chronic renal failure, liver failure, or rheumatologic disorders; and fatigue, notably due to cancer, neurodegenerative disorders, menopause, traumatic brain injuries, viral infection or post-myelitis, or to fibromyalgia.

12. The therapeutic composition of any one of claims 6 to 11, wherein said flecainide is the R enantiomer of formula:



13. A combination product comprising flecainide and an adrenergic effector, for simultaneous, separated or staggered use 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, antipsychotics...), 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.

14. A combination product comprising flecainide and an acetylcholinergic effector, for simultaneous, separated or staggered use 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, antipsychotics...), 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.

15. A combination product comprising flecainide and an opioidergic effector, for simultaneous, separated or staggered use 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 Limb 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, antipsychotics...), 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.

16. A combination product comprising flecainide and an ionotropic effector, for simultaneous, separated or staggered use 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, antipsychotics...), 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.

17. The combination product of any one of claims 13 to 16, wherein said flecainide is the R enantiomer of formula:

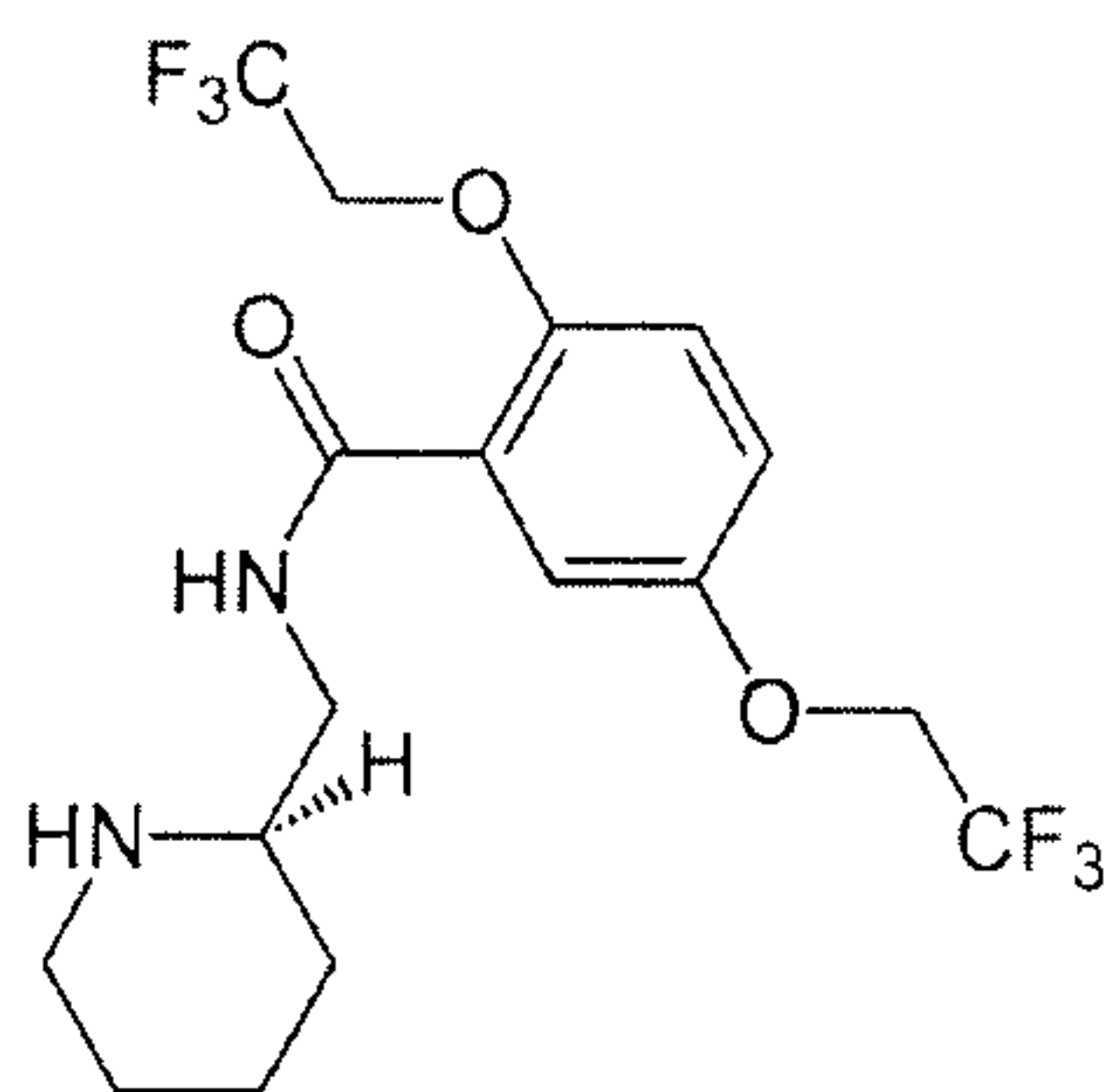


Figure 1

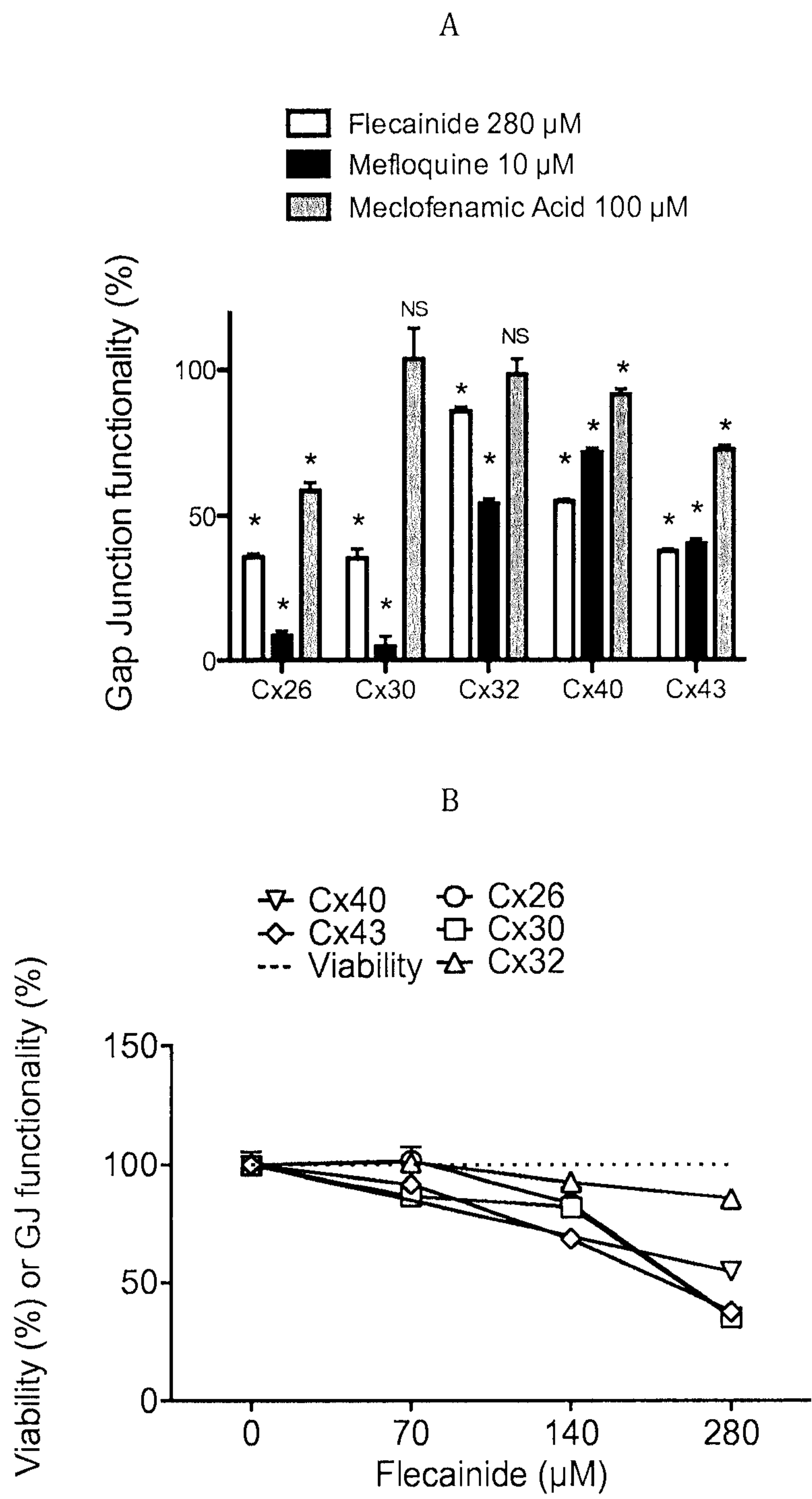


Figure 2

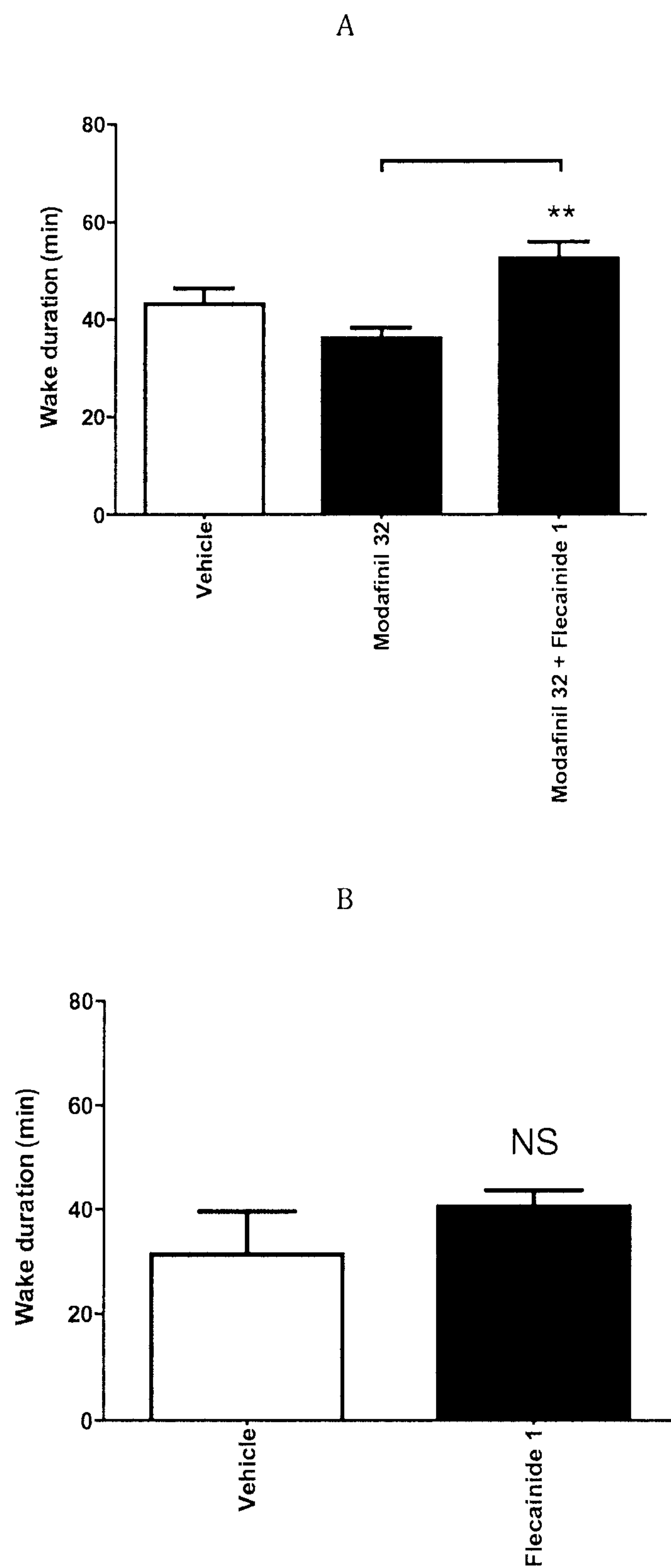
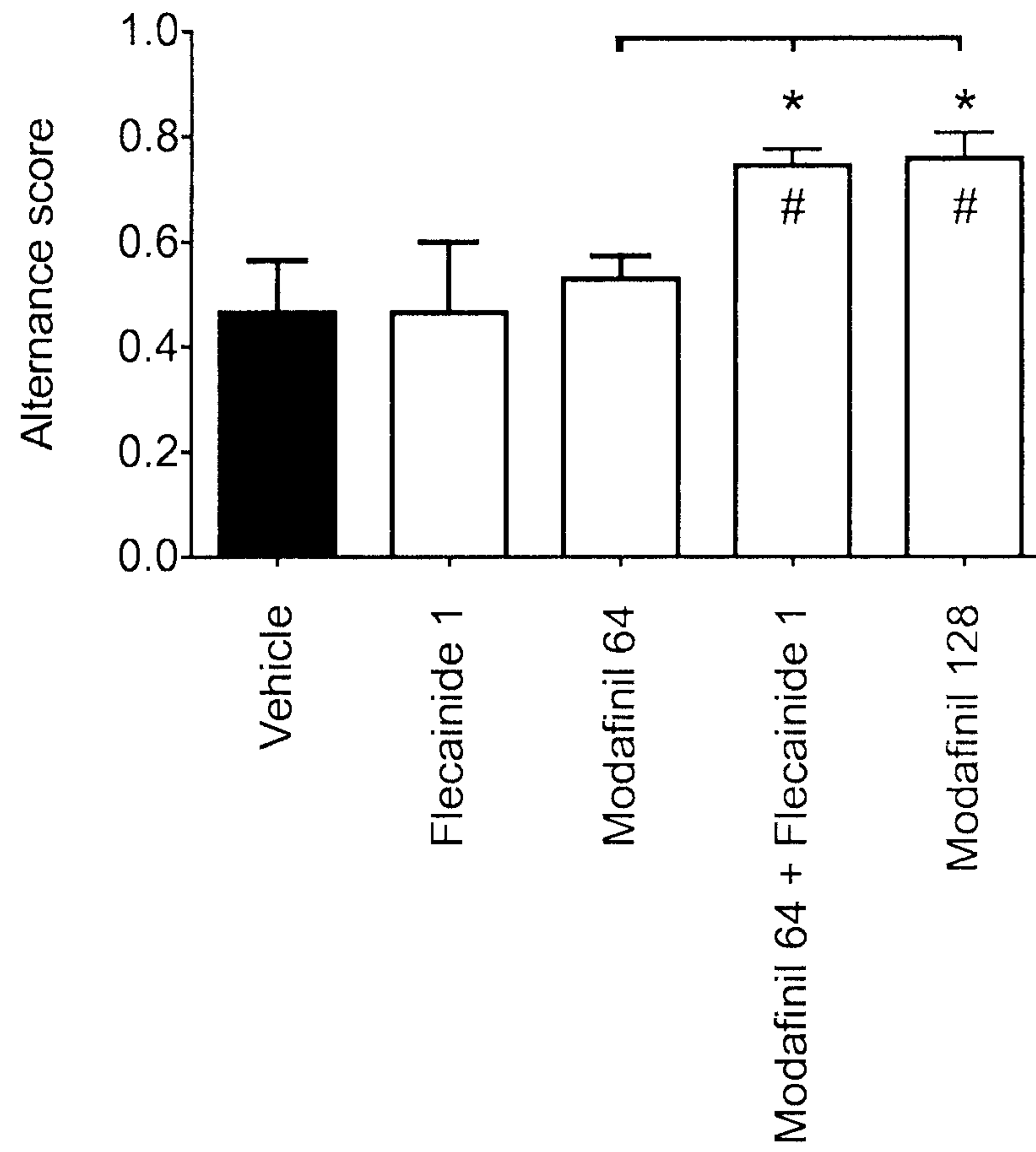


Figure 3



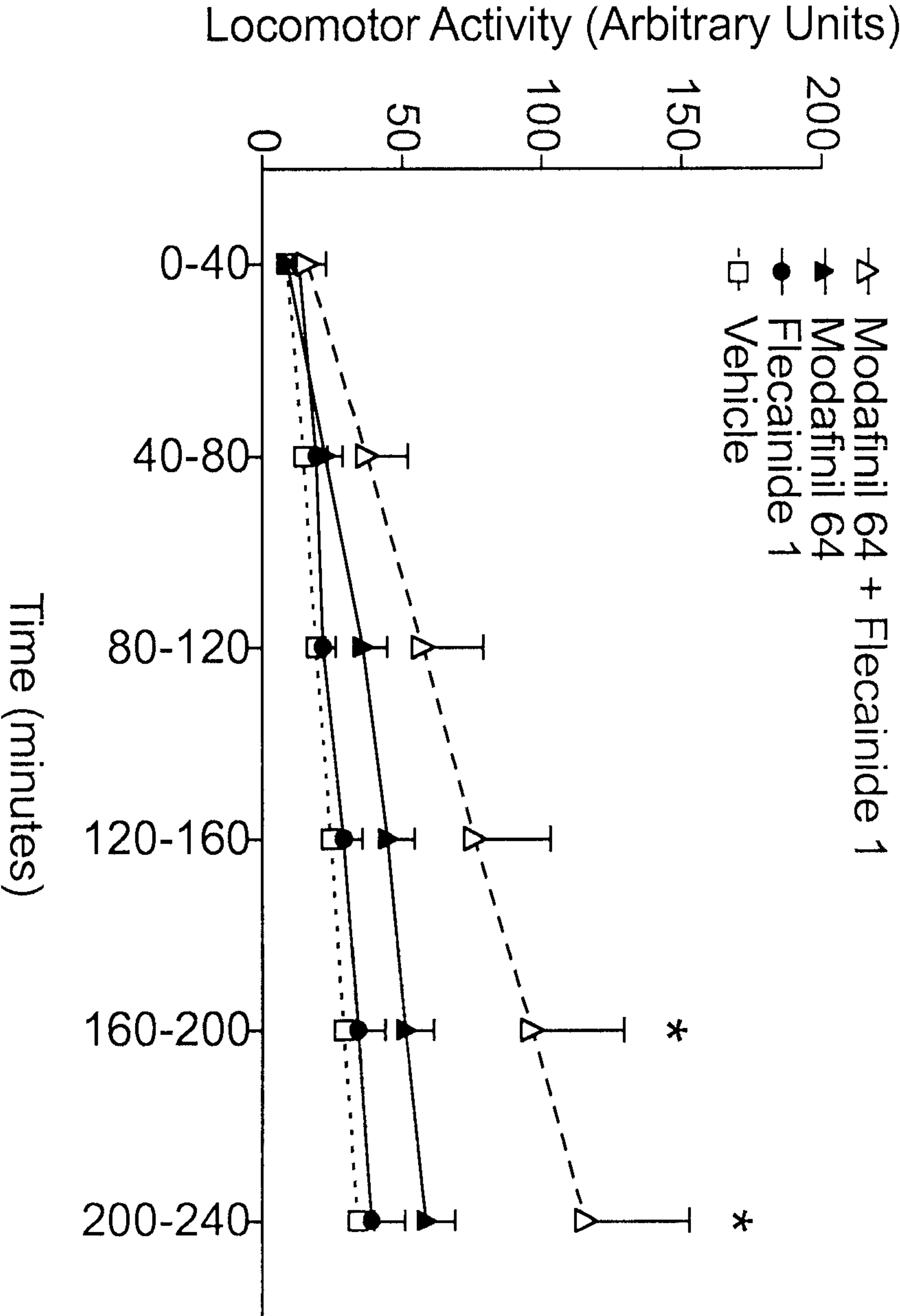
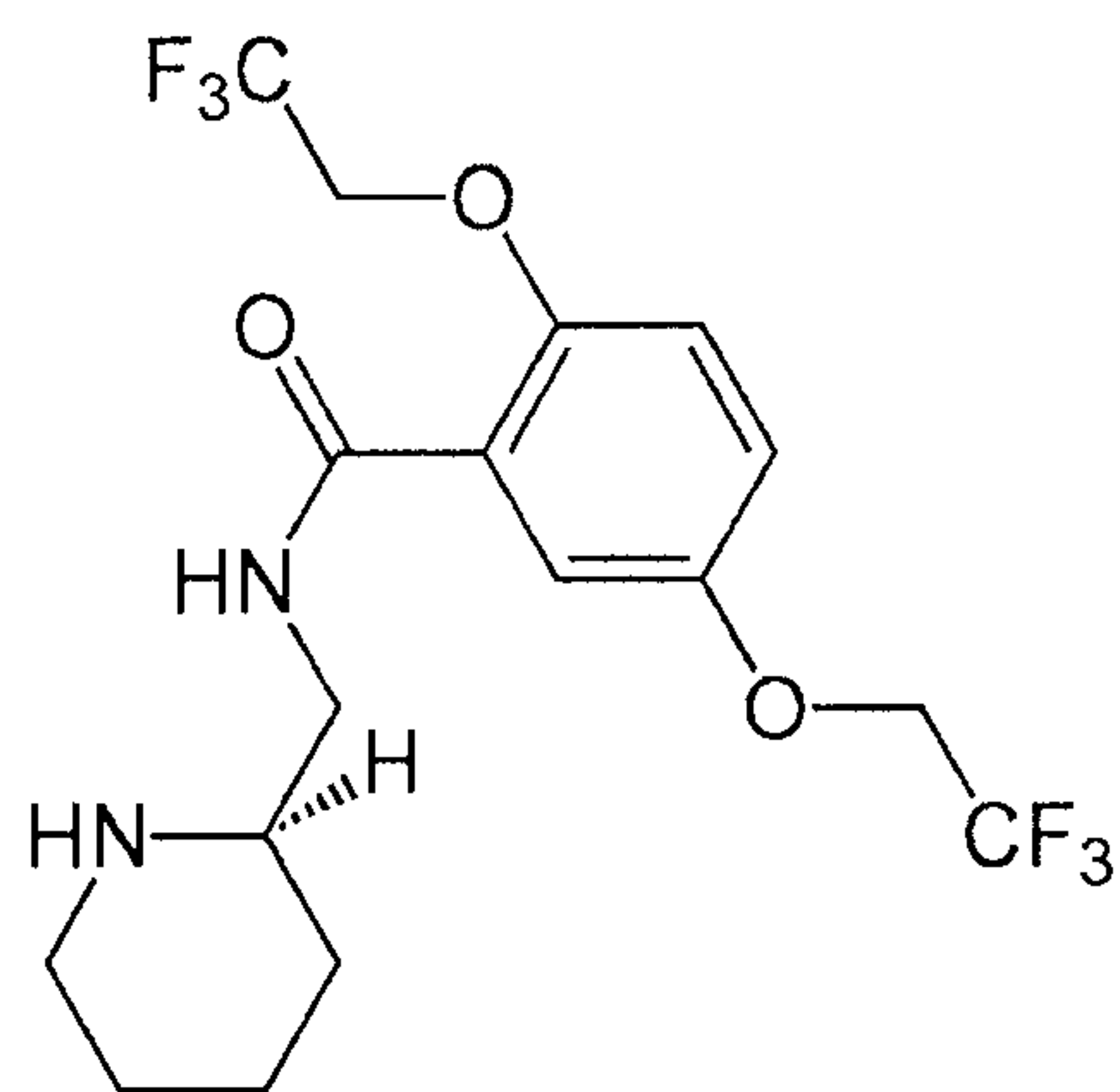
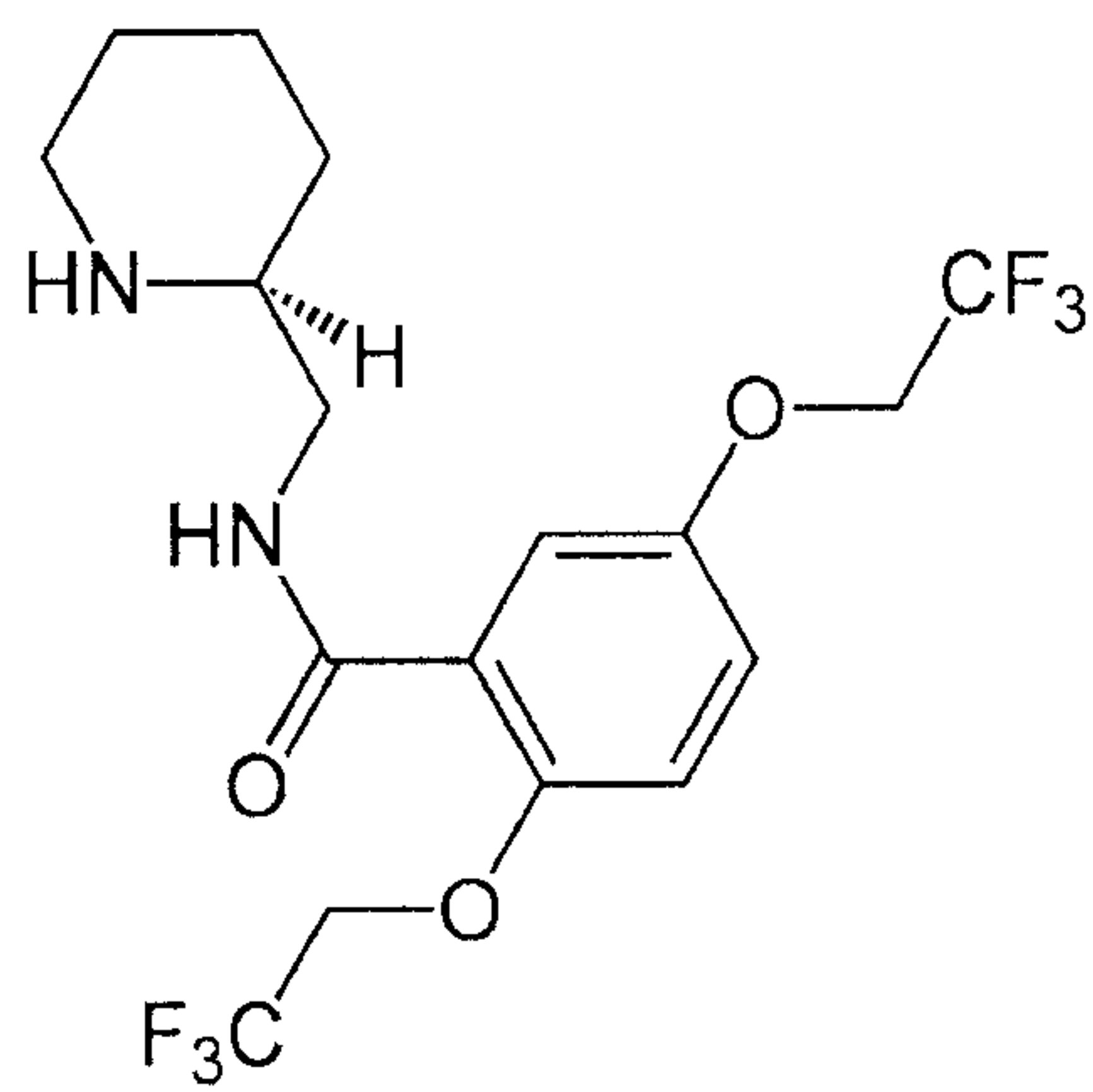


Figure 4

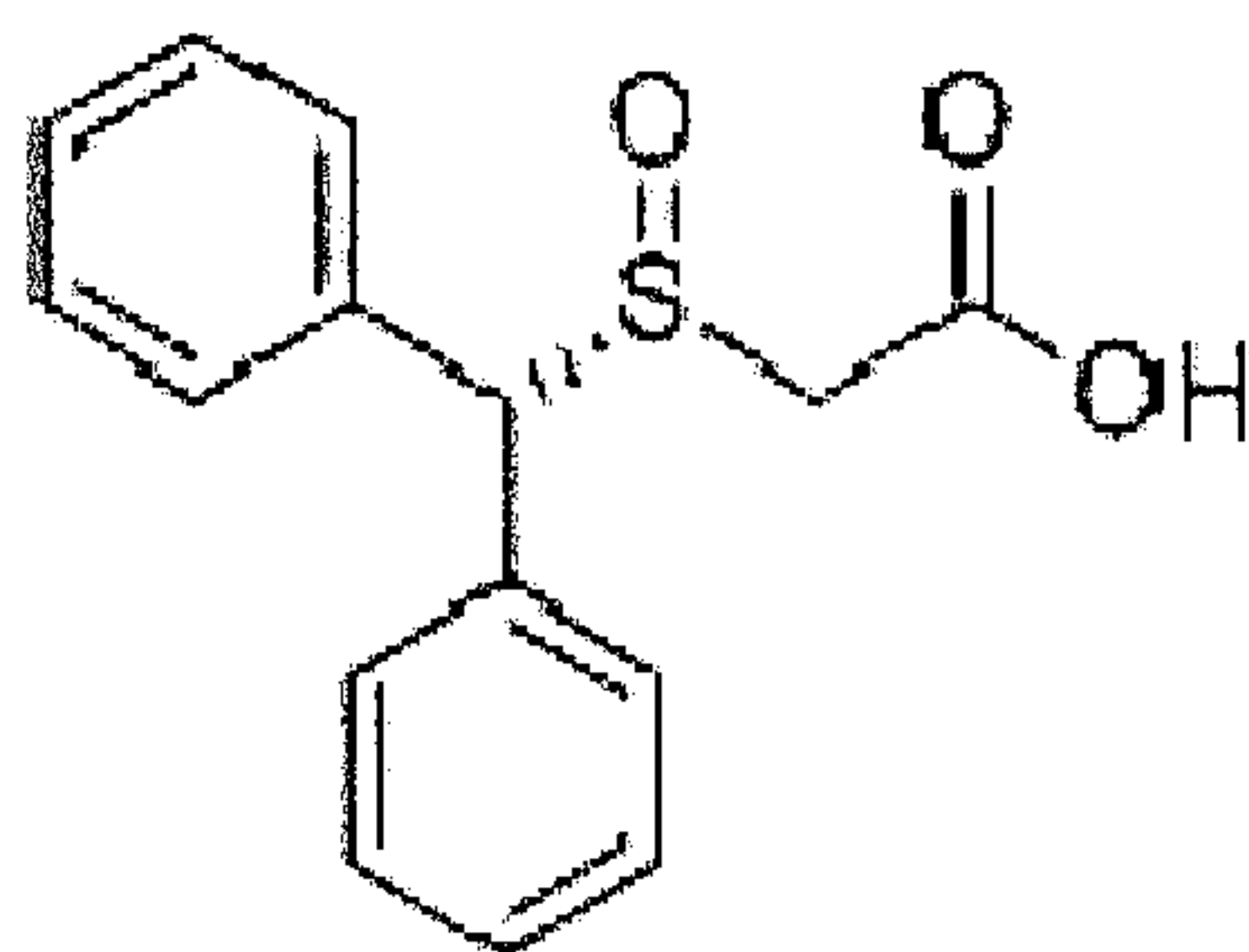
Figure 5



A



B



C

Figure 5 (continued)

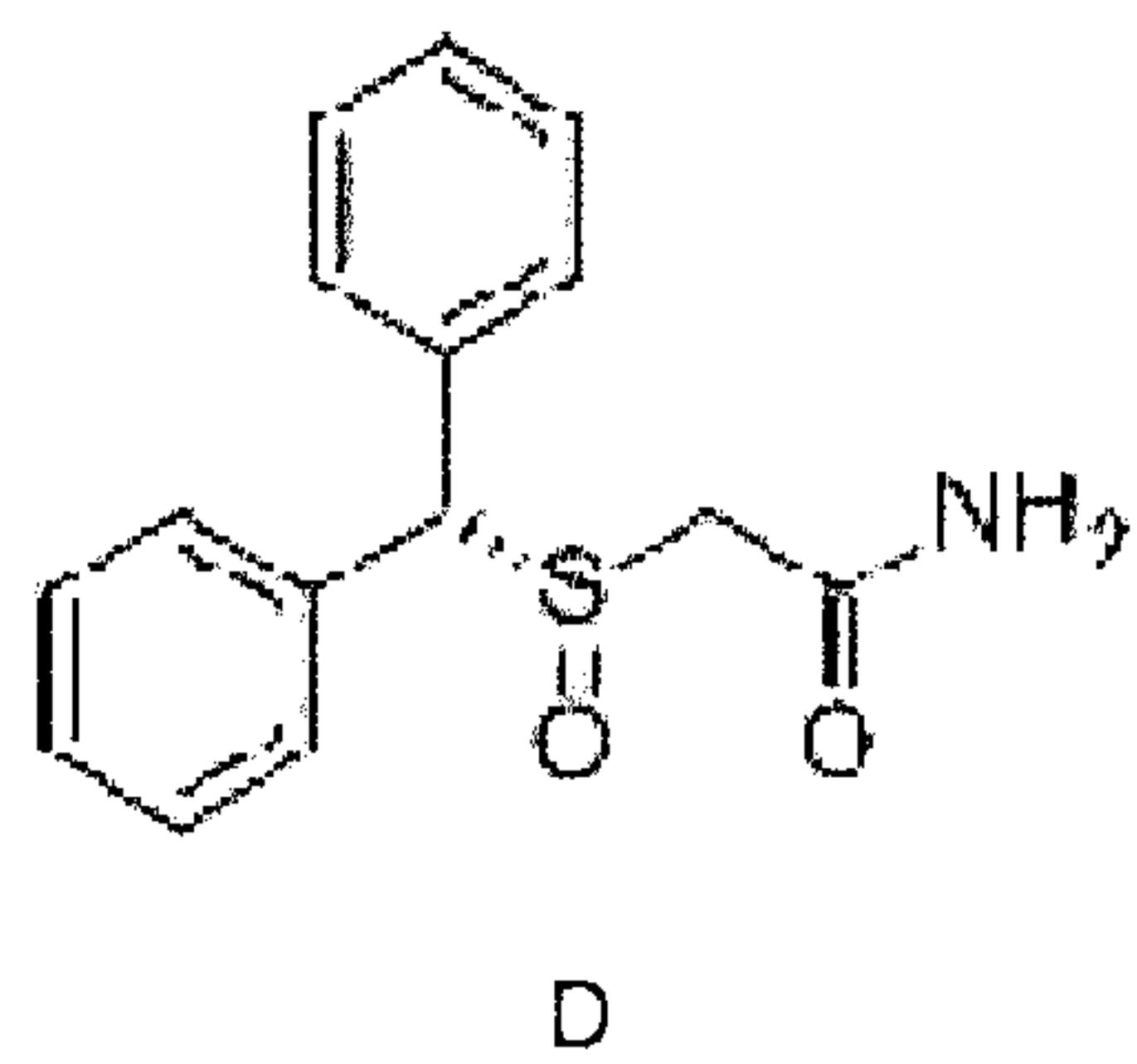


Figure 6

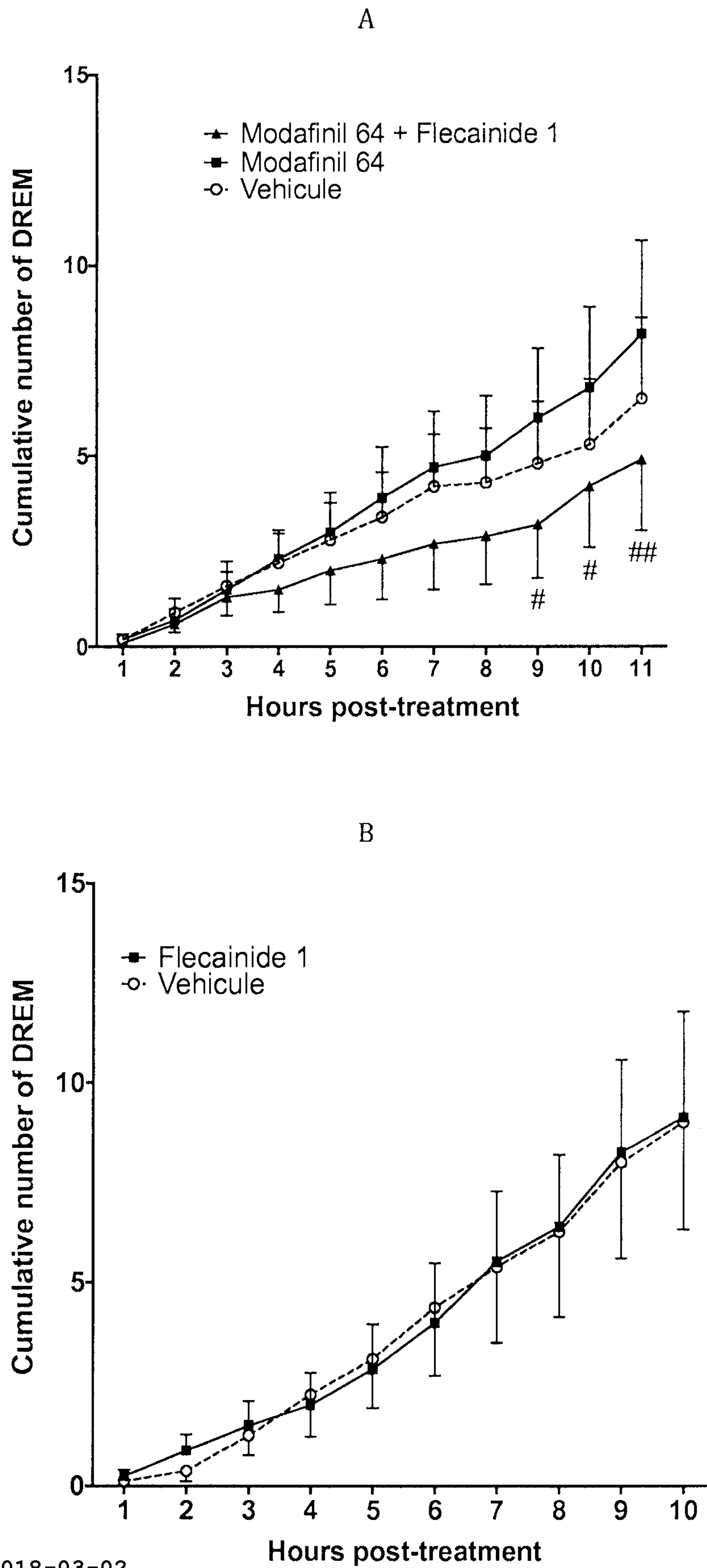
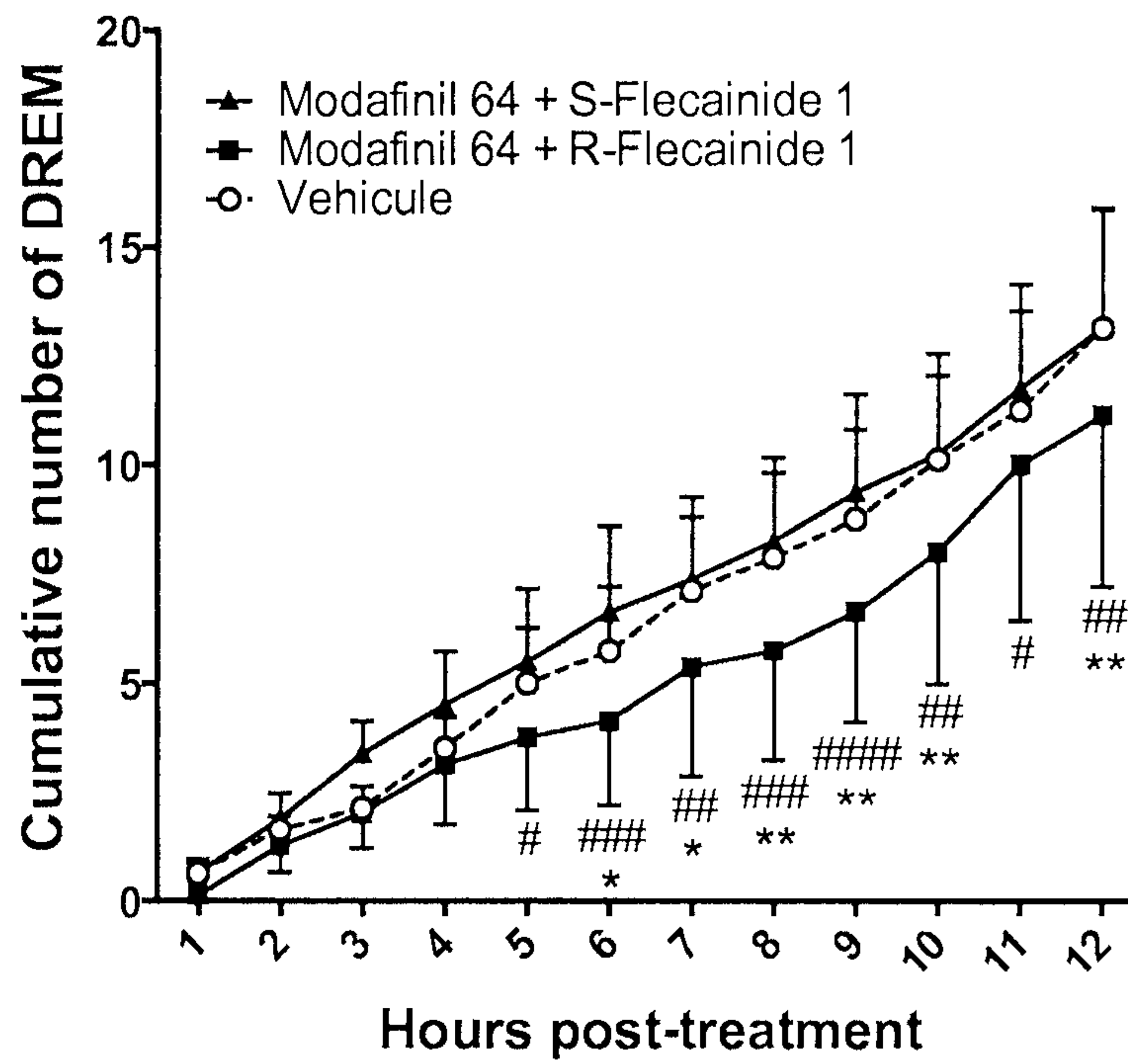


Figure 7



Two-way ANOVA, repeated measures by both factors

*p<0,05 vs Vehicle

#p<0,05 vs Modafinil 64

