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(54) Title: MEFLOQUINE, NELFINAVIR AND SAQUINAVIR AS NOVEL AGENTS FOR NEURODEGENERATIVE AND (NEURO-) INFLAMMATORY DISEASES

(57) Abstract: The present invention generally relates to the neuroprotective, anti-apoptotic and anti-inflammatory activity of mefloquine, nelfinavir and saquinavir and derivatives thereof based on recently discovered interactions with prohibitin and estrogen receptors and the inhibition of mitochondrial voltage- dependent anion channel 1. Thus, mefloquine, nelfinavir and saquinavir and derivatives thereof may be used as medicaments for the prevention and/or treatment of neurodegenerative and inflammatory, particularly neuroinflammatory diseases.

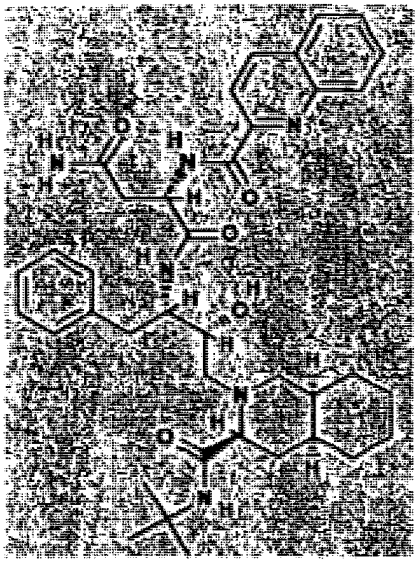
Mefloquine, Nelfinavir and Saquinavir as novel agents for neurodegenerative and (neuro-) inflammatory diseases

Description

The present invention generally relates to the neuroprotective, anti-apoptotic and anti-inflammatory activity of mefloquine, nelfinavir and saquinavir and derivatives thereof based on recently discovered interactions with prohibitin and estrogen receptors and the inhibition of mitochondrial voltage-dependent anion channel 1. Thus, mefloquine, nelfinavir and saquinavir and derivatives thereof may be used as medicaments for the prevention and/or treatment of neurodegenerative and inflammatory, particularly neuroinflammatory diseases.

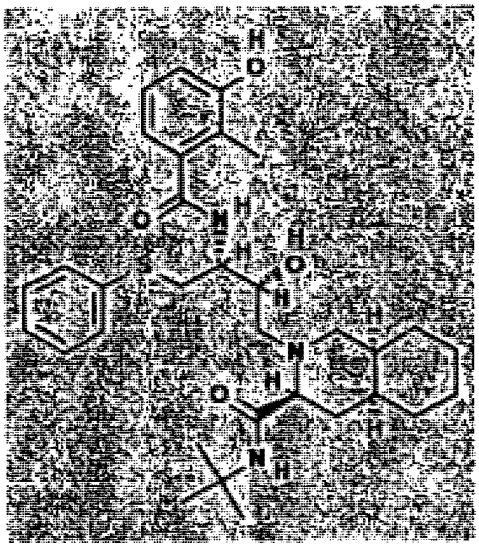
Nelfinavir (Viracept®) and saquinavir (Invirase® or Fortovase®) are known as anti-HIV drugs called HIV protease inhibitors. Further HIV protease inhibitors of the same class of compounds are amprenavir (Agenerase®), indinavir (Crixivan®), lopinavir (Kaletra®), ritonavir (Norvir®) and atazanavir (Reyataz®). These compounds are used for treatment of HIV.

Nelfinavir is usually administered in the form of (3S-(2(2S*,3S*), 3α,4aβ,8aβ))-N-(1,1-dimethylethyl)decahydro-2-(2-hydroxy-3-((3-hydroxy-2-methylbenzoyl)amino)-4-(phenylthio)butyl)-3-isoquinolinecarboxamide; The compound, its manufacture, its mechanism of action and its clinical efficacy have been described in the state of the art.



Nelfinavir

Saquinavir is usually administered in the form of Saquinavir mesylate (S)-N-((αS)-α-((1R)-2-((3S,4aS,8aS)-3-(tert-butylcarbamoyl)octahydro-2(1H)-isoquinolyl)-1-hydroxyethyl) phenethyl)-2-quinaldamidosuccinamide monomethanesulfonate (salt); DRG-0164; Fortovase®; Invirase®; Ro 31-8959/003; Saquinavir monomethanesulfonate salt; butanediamide, N(sup 1)-(3-(3-(((1,1-dimethylethyl)amino) carbonyl)octahydro-2(1H)-isoquinolinyl)-2-hydroxy-1- (phenylmethyl)propyl)-2-((2-quinolinylcarbonyl)amino)-, (3S-(2 (1R*(R*),2S*),3α,4aβ,8aβ))-, monomethanesulfonate (salt); N-[1-benzyl-2-hydroxy-3-[[3-(tert-butylcarbamoyl)-1,2,3,4,4a,5, 6,7,8,8a-decahydroisoquinol-2-yl]]propyl]-2-(2- quinolylcarbonylamino)succinamide; methanesulfonic acid. The compound, its manufacture, its mechanism of action and its clinical efficacy have been described in the state of the art.



Saquinavir

The assumed antiapoptotic properties of this class of compounds have already been disclosed (Badley A. D. In vitro and in vivo effects of HIV protease inhibitors on apoptosis. Cell Death Differ. (2005) Mar 11; [Epub ahead of print]; Phenix B. N., Lum J.J., Nie Z., Sanchez-Dardon J., and Badley A. D., Antiapoptotic mechanism of HIV protease inhibitors: preventing mitochondrial transmembrane potential loss; Blood. 98, 1078-1085 (2001)).

Mefloquine (Lariam®) is known as an anti-malaria drug which has high efficacy in treating the widespread chloroquine-resistant *Plasmodium falciparum* strains. Mefloquine is used both for prophylaxis and treatment of malaria and is relatively well tolerated.

Mefloquine is usually administered in the form of mefloquine hydrochloride *(R*,S*)-(+-)-α-2- piperidinyl-2,8-bis (trifluoromethyl)-4-quinolinemethanol-monohydrochloride;* DL-erythro-α-2-piperidyl-2,8-bis(trifluoromethyl)-4-quinolinemethanol monohydrochloride; WR-142490; Ro-21-5998; Lariam®. $C_{17}H_{17}ClF_6N_2O$; mol wt 414.78. C 49.23%, H 4.13%, Cl 8.55%, F 27.48%, N 6.75%, O 3.86%. The compound, its manufacture, its mechanism of action and its clinical efficacy have been described extensively in C. J. Ohnmacht

et al. *J. Med. Chem.* 14, 926 (1971); DE patent 28 06 909, *CA.* 90, 22838q (1979); U.S. patent 4,507,482; J. T. Blackwell, *J. Med. Chem.* 17, 210 (1974); M. W. Davidson *et al, J. Med. Chem.* 20, 1117 (1977); R. E. Brown *et al., Life Sci.* 25, 1857 (1979); Photochemistry: G. A. Epling, U. C. Yoon, *Chem. Letters* 1982 (2), 211; Pharmacokinetics: D. E. Schwartz *et al., Chemotherapy (Basel)* 28, 70 (1982). HPLC determination: 1. M. Kapetanovic *et al, .1. Chromatog.* 277, 209 (1983); G. M. Trenholme *et al., Science* 190, 792 (1975); F. Tin *et al. Bull. WHO* 60, 913 (1982); J. M. Kofe Ekue *et al., ibid.* 61, 713 (1983); J.-M. de Souza *ibid.* 809, 815 and P. Lim in *Analytical Profiles of Drug Substances* vol. 14, K. Florey, Ed. (Academic Press, New York, 1985) pp 157-180 (all citations from Merck Index, 12th edition, 1996).

The relatively new antimalarial mefloquine (Lariam®) has become extremely popular due to its efficacy in treating the wide-spread chloroquine-resistant *Plasmodium falciparum* strains. Mefloquine is known both for severe neurologic and psychiatric adverse effects associated with its use.

There have also been reports about neurotoxic effects of mefloquine at higher dosages (Rendi-Wagner P. et al., Acta Trop. 81, 167-173 (2002). The mechanisms of these adverse effects are discussed controversially in the literature. Toxic encephalopathy appears to be one of the serious neurological manifestations which is slowly reversible depending on individual predisposition. Self-administration schemes can be therefore both most useful and dangerous due to expected benefits and potential risks. (Nicolas X. et al., Presse Med. 30, 1349-1350 (2001); Dow G. S. et al., Antimicrob. Agents Chemother. 48, 2624-2632 (2004). There are indications that disruption of neuronal calcium homeostasis can induce an ER stress response at physiologically relevant concentrations, thus contributing to the neurotoxicity of the drug in vitro (Dow G. S. et al., Malar. J. 2, 14 (2003). There are other indications, that mefloquine shows stereoselective brain uptake in humans and rats and is a substrate and an inhibitor of the efflux protein P-glycoprotein (Barraud de Lagerie S. et al., Br. J. Pharmacol. 141,

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