V1a antagonists to treat phase shift sleep disorders

Summary

This ~~invention~~ disclosure relates to a new medical use for certain chemical compounds and pharmaceutical compositions containing them. The ~~invention~~ disclosure relates to compounds which are V1a antagonists to treat phase shift sleep disorders, in particular jetlag. ~~In another aspect~~Further, the ~~invention~~ disclosure relates to a pharmaceutical composition for use in the treatment of phase shift sleep disorders comprising a compound according to the ~~invention~~ disclosure and a pharmaceutically acceptable carrier.

Background Art

The suprachiasmatic nucleus (SCN) is the endogenous clock of the body regulating circadian rhythmicity and is known to be rich in vasopressin neurons (Kalsbeek et al. 2010)[1], producing and releasing vasopressin with a 24h circadian rhythm (Schwartz et al. 1983)[2]. A major regulatory effect of vasopressin on circadian rhythm could not be demonstrated by the prior art. The Brattleboro rat, a rat strain naturally lacking vasopressin due to a point mutation, has no obvious defect in its circadian rhythm (Groblewski et al. 1981)[3]. Injection of vasopressin directly in the hamster SCN had no effect on circadian phase shift (Albers et al. 1984)[4]. In contrast, vasopressin may modulate the circadian clock in a more subtle way. Vasopressin deficient Brattleboro rats do not respond to a 6h phase advance of the light-dark period, but remain synchronized to the food presentation (Murphy et al. 1998)[5], in contrast to normal rats, which respond both to the new light dark rhythm and to food presentation.

More specifically, the vasopressin V1a receptor was shown to have a modulatory role on circadian behavior by studying V1a knock-out (KO) mice. V1a KO mice behave normally under a normal 12h-12h light-dark cycle, but in absence of light (dark-dark conditions) these mice show a gradual loss of circadian rhythm characterized by an expansion of the active period. Nevertheless they still respond normally to phase-shifts induced by brief light exposure during the dark phase (Li et al. 2009)[6].

We surprisingly found that administration of a single dose of a small molecule V1a antagonist to normal mice before a 6h phase shift (6h advance of light phase) induces a significantly faster re-entrainment to the new light-dark cycle than vehicle treated mice. More specifically, a selective V1a antagonist.

This finding is contrary to the prior art teaching, where treatment with melatonin to accelerate re-entrainment after a phase-shift, is only effective after daily administration for 3 days after the phase advance (Dubocovich et al. 2005)[7].

Poor sleep can lead to numerous health disturbances including anxiety, depression, irritability, impaired social interactions and psychomotor coordination and the like.

WO 2013/176220 [8] describes circadian rhythm-regulating agents which comprises an inhibitor capable of inhibiting vasopressin receptors V1a and V1b.

V1a antagonists have been described in the prior art, e.g. in EP 0382185, EP 0526348, WO 94/01113, WO 94/18975, WO 95/06035, WO 96/22292, WO 96/22293, WO 97/49707, WO 97/49708, WO 98/24430, WO 99/37637, WO 99/44613, WO 99/55340, WO 99/65525, WO 00/029405, WO 00/066117, WO 01/058880, WO 01/066109, WO 02/002531, WO 02/044179, WO 02/055514, WO 03/031407, WO 03/037901, WO 03/042181, WO 04/074291, WO 04/108138, WO 2005/039565, WO 2005/063754, WO 2006/020491, WO 2006/021213, WO 2006/051851, WO 2006/058705, WO 2006/102283, WO 2006/102308, WO 2007/006688, WO 2007/009906, WO 2007/014851, WO 2007/039438, WO 2007/077122, WO 2007/109615, WO 2008/068159, WO 2008/068183, WO 2008/068184, WO 2008/068185, WO 2008/077810, WO 2008/077811, WO 2008/080842, WO 2008/080844, WO 2008/084005, WO 2010/057795, WO 2010/060836, WO 2011/120877, WO 2011/128265, WO 2011/131596, WO 2011/134877, WO 2011/141396, WO 2012/003436, WO 2012/042534, WO 2013/045373, WO 2013/050334[9], etc.

Detailed description of the invention

In one aspect, there is provided the use of a V1a antagonist for the manufacture of a medicament for the treatment and/or prevention of phase shift sleep disorders.

In another aspect, there is provided a pharmaceutical composition comprising a V1a antagonist in a pharmaceutically acceptable form.

In another aspect, there is provided a pharmaceutical composition comprising a V1a antagonist as described herein in a pharmaceutically acceptable form.

In another aspect, there is provided a pharmaceutical composition comprising a V1a antagonist in a pharmaceutically acceptable form for use in the treatment and/or prevention of phase shift sleep disorders.

In another aspect, there is provided a pharmaceutical composition comprising a V1a antagonist as described herein in a pharmaceutically acceptable form for use in the treatment and/or prevention of phase shift sleep disorders.

In another aspect, there is provided a V1a antagonist for use in the treatment and/or prevention of phase shift sleep disorders.

In another aspect, there is provided a V1a antagonist as described herein for use in the treatment and/or prevention of phase shift sleep disorders.

In another aspect, there is provided a selective V1a antagonist as described herein for use in the treatment and/or prevention of phase shift sleep disorders, wherein the V1a antagonist is selected from the group consisting of

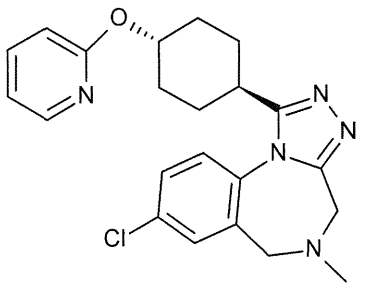
trans-8-Chloro-1-(4-phenoxy-cyclohexyl)-4H,6H-2,3,5,10b-tetraaza-benzoazulene-5-carboxylic acid tert-butyl ester,
trans-8-Chloro-1-(4-phenoxy-cyclohexyl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzoazulene hydrochloride,
trans-8-Chloro-5-methyl-1-(4-phenoxy-cyclohexyl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene,
trans-1-[8-Chloro-1-(4-phenoxy-cyclohexyl)-4H,6H-2,3,5,10b-tetraaza-benzoazulen-5-yl]-ethanone,
trans-8-Chloro-5-methanesulfonyl-1-(4-phenoxy-cyclohexyl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzoazulene,
trans-2-[8-Chloro-1-(4-phenoxy-cyclohexyl)-4H,6H-2,3,5,10b-tetraaza-benzoazulen-5-yl]-ethanol,
trans-8-Chloro-5-isopropyl-1-(4-phenoxy-cyclohexyl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzoazulene,
trans-8-Chloro-1-(4-phenoxy-cyclohexyl)-4H,6H-2,3,5,10b-tetraaza-benzoazulene-5-sulfonic acid dimethylamide,
trans-8-Chloro-1-(4-phenoxy-cyclohexyl)-5-pyridin-2-ylmethyl-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzoazulene,
trans-1-[8-Chloro-1-(4-phenoxy-cyclohexyl)-4H,6H-2,3,5,10b-tetraaza-benzoazulen-5-yl]-2-dimethylamino-ethanone,
trans-8-Fluoro-1-(4-phenoxy-cyclohexyl)-4H,6H-2,3,5,10b-tetraaza-benzo[e]azulene-5-carboxylic acid tert-butyl ester,
trans-8-Fluoro-5-methyl-1-(4-phenoxy-cyclohexyl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzoazulene,
cis-8-Chloro-1-(4-phenoxy-cyclohexyl)-4H,6H-2,3,5,10b-tetraaza-benzoazulene-5-carboxylic acid tert-butyl ester,
cis-8-Chloro-5-methyl-1-(4-phenoxy-cyclohexyl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzoazulene,
trans-8-Chloro-1-[4-(4-fluoro-phenoxy)-cyclohexyl]-4H,6H-2,3,5,10b-tetraaza-benzoazulene-5-carboxylic acid tert-butyl ester,
trans-8-Chloro-1-[4-(4-fluoro-phenoxy)-cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene hydrochloride,
trans-8-Chloro-1-[4-(4-fluoro-phenoxy)-cyclohexyl]-5-methyl-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzoazulene,

trans-8-Chloro-1-[4-(4-cyano-phenoxy)-cyclohexyl]-4H,6H-2,3,5,10b-tetraaza-benzo[e]azulene-5-carboxylic acid tert-butyl ester,
trans-4-[4-(8-Chloro-5-methyl-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulen-1-yl)-cyclohexyloxy]-benzonitrile,
trans-8-Chloro-1-[4-(4-trifluoromethyl-phenoxy)-cyclohexyl]-4H,6H-2,3,5,10b-tetraaza-benzo[e]azulene-5-carboxylic acid tert-butyl ester,
trans-8-Chloro-1-[4-(3-chloro-phenoxy)-cyclohexyl]-4H,6H-2,3,5,10b-tetraaza-benzoazulene-5-carboxylic acid tert-butyl ester,
trans-8-Chloro-1-[4-(3-chloro-phenoxy)-cyclohexyl]-5-methyl-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzoazulene,
trans-8-Chloro-1-[4-(3-methoxy-phenoxy)-cyclohexyl]-4H,6H-2,3,5,10b-tetraaza-benzoazulene-5-carboxylic acid tert-butyl ester,
trans-8-Chloro-1-[4-(3-methoxy-phenoxy)-cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene hydrochloride,
trans-8-Chloro-1-[4-(3-methoxy-phenoxy)-cyclohexyl]-5-methyl-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzoazulene,
trans-3-[4-(8-Chloro-5-methyl-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzoazulen-1-yl)-cyclohexyloxy]-benzonitrile,
trans-8-Chloro-1-(4-m-tolyloxy-cyclohexyl)-4H,6H-2,3,5,10b-tetraaza-benzo[e]azulene-5-carboxylic acid tert-butyl ester,
trans-8-Chloro-1-(4-m-tolyloxy-cyclohexyl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene hydrochloride,
trans-8-Chloro-5-methyl-1-(4-m-tolyloxy-cyclohexyl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene,
trans-1-[4-(3-tert-Butyl-phenoxy)-cyclohexyl]-8-chloro-4H,6H-2,3,5,10b-tetraaza-benzo[e]azulene-5-carboxylic acid tert-butyl ester,
trans-8-Chloro-1-[4-(2-fluoro-phenoxy)-cyclohexyl]-4H,6H-2,3,5,10b-tetraaza-benzo[e]azulene-5-carboxylic acid tert-butyl ester,
trans-8-Chloro-1-[4-(2-fluoro-phenoxy)-cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene hydrochloride,
trans-8-Chloro-1-[4-(2-fluoro-phenoxy)-cyclohexyl]-5-methyl-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene,
trans-8-Chloro-1-[4-(2-cyano-phenoxy)-cyclohexyl]-4H,6H-2,3,5,10b-tetraaza-benzoazulene-5-carboxylic acid tert-butyl ester,
trans-2-[4-(8-Chloro-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulen-1-yl)-cyclohexyloxy]-benzonitrile hydrochloride,
trans-2-[4-(8-Chloro-5-methyl-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzoazulen-1-yl)-cyclohexyloxy]-benzonitrile,
trans-8-Chloro-1-(4-o-tolyloxy-cyclohexyl)-4H,6H-2,3,5,10b-tetraaza-benzoazulene-5-carboxylic acid tert-butyl ester,

trans-8-Chloro-5-methyl-1-(4-o-tolyloxy-cyclohexyl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzoazulene,
trans-8-Chloro-1-[4-(3,5-difluoro-phenoxy)-cyclohexyl]-4H,6H-2,3,5,10b-tetraaza-benzoazulene-5-carboxylic acid tert-butyl ester,
trans-8-Chloro-1-[4-(3,5-difluoro-phenoxy)-cyclohexyl]-5-methyl-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzoazulene,
trans-8-Chloro-1-[4-(naphthalen-2-yloxy)-cyclohexyl]-4H,6H-2,3,5,10b-tetraaza-benzoazulene-5-carboxylic acid tert-butyl ester,
trans-8-Chloro-5-methyl-1-[4-(naphthalen-2-yloxy)-cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzoazulene,
trans-8-Chloro-1-[4-(pyridin-3-yloxy)-cyclohexyl]-4H,6H-2,3,5,10b-tetraaza-benzoazulene-5-carboxylic acid tert-butyl ester,
trans-8-Chloro-5-methyl-1-[4-(pyridin-3-yloxy)-cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzoazulene,
trans-8-Chloro-1-[4-(5-chloro-pyridin-3-yloxy)-cyclohexyl]-4H,6H-2,3,5,10b-tetraaza-benzoazulene-5-carboxylic acid tert-butyl ester,
trans-8-Chloro-1-[4-(5-chloro-pyridin-3-yloxy)-cyclohexyl]-5-methyl-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzoazulene,
trans-8-Chloro-1-[4-(pyridin-2-yloxy)-cyclohexyl]-4H,6H-2,3,5,10b-tetraaza-benzoazulene-5-carboxylic acid tert-butyl ester,
trans-8-Chloro-1-[4-(pyridin-2-yloxy)-cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzoazulene hydrochloride,
trans-8-Chloro-5-methyl-1-[4-(pyridin-2-yloxy)-cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzoazulene,
trans-8-Chloro-1-[4-(6-chloro-pyridin-2-yloxy)-cyclohexyl]-4H,6H-2,3,5,10b-tetraaza-benzo[e]azulene-5-carboxylic acid tert-butyl ester,
trans-8-Chloro-1-[4-(6-chloro-pyridin-2-yloxy)-cyclohexyl]-5-methyl-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene,
trans-8-Chloro-1-[4-(5-chloro-pyridin-2-yloxy)-cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene hydrochloride,
trans-8-Chloro-1-[4-(5-chloro-pyridin-2-yloxy)-cyclohexyl]-5-methyl-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene,
trans-8-Chloro-1-[4-(pyrimidin-2-yloxy)-cyclohexyl]-4H,6H-2,3,5,10b-tetraaza-benzo[e]azulene-5-carboxylic acid tert-butyl ester,
cis-8-Chloro-1-[4-(pyrimidin-2-yloxy)-cyclohexyl]-4H,6H-2,3,5,10b-tetraaza-benzo[e]azulene-5-carboxylic acid tert-butyl ester,
trans-8-Chloro-5-methyl-1-[4-(pyrimidin-2-yloxy)-cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene,
trans-8-Chloro-1-[4-(pyrazin-2-yloxy)-cyclohexyl]-4H,6H-2,3,5,10b-tetraaza-benzo[e]azulene-5-carboxylic acid tert-butyl ester,

trans- 8-Chloro-5-methyl-1-[4-(pyrazin-2-yloxy)-cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene,
trans-8-Chloro-1-[4-(pyrimidin-4-yloxy)-cyclohexyl]-4H,6H-2,3,5,10b-tetraaza-benzo[e]azulene-5-carboxylic acid tert-butyl ester,
trans-8-Chloro-5-methyl-1-[4-(pyrimidin-4-yloxy)-cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene,
trans-8-Chloro-1-[4-(pyridazin-3-yloxy)-cyclohexyl]-4H,6H-2,3,5,10b-tetraaza-benzo[e]azulene-5-carboxylic acid tert-butyl ester,
cis-8-Chloro-1-[4-(pyridazin-3-yloxy)-cyclohexyl]-4H,6H-2,3,5,10b-tetraaza-benzo[e]azulene-5-carboxylic acid tert-butyl ester,
trans-8-Chloro-5-methyl-1-[4-(pyridazin-3-yloxy)-cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene,
cis-8-Chloro-1-[4-(pyridin-2-yloxy)-cyclohexyl]-4H,6H-2,3,5,10b-tetraaza-benzo[e]azulene-5-carboxylic acid tert-butyl ester ,
cis-8-Chloro-1-[4-(pyridin-2-yloxy)-cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene ,
cis-8-Chloro-5-methyl-1-[4-(pyridin-2-yloxy)-cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene ,
trans-8-Chloro-1-[4-(3-fluoro-pyridin-2-yloxy)-cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene,
trans-8-Chloro-1-[4-(3-fluoro-pyridin-2-yloxy)-cyclohexyl]-5-methyl-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene,
trans-8-Chloro-1-[4-(5-fluoro-pyridin-2-yloxy)-cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene
trans-8-Chloro-1-[4-(5-fluoro-pyridin-2-yloxy)-cyclohexyl]-5-methyl-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene,
trans-8-Chloro-1-[4-(6-methyl-pyridin-2-yloxy)-cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene,
trans-8-Chloro-5-(2,2-difluoro-ethyl)-1-[4-(6-methyl-pyridin-2-yloxy)-cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene,
trans-8-Chloro-5-(2-fluoro-ethyl)-1-[4-(5-fluoro-pyridin-2-yloxy)-cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene,
trans-8-Chloro-5-ethyl-1-[4-(3-fluoro-pyridin-2-yloxy)-cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene,
trans-8-Chloro-5-ethyl-1-[4-(5-fluoro-pyridin-2-yloxy)-cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene,
trans-8-Chloro-5-ethyl-1-[4-(6-methyl-pyridin-2-yloxy)-cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene, and
trans-8-Chloro-5-methyl-1-[4-(6-methyl-pyridin-2-yloxy)-cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene.

In another aspect, there is provided a selective V1a antagonist for use in the treatment and/or prevention of phase shift sleep disorders, wherein the V1a antagonist is



example 1.

The following definitions of the general terms used in the present description apply irrespectively of whether the terms in question appear alone or in combination with other groups.

The term "phase shift sleep disorders" summarizes conditions classified as disturbances in the circadian rhythm, i.e. the approximately 24-hour cycles that are generated by an organism, e.g. a human being.

Phase shift sleep disorders include, but are not limited to transient disorders like jetlag or or a changed sleep schedule due to work, social responsibilities, or illness, as well as chronic disorders like delayed sleep-phase syndrome (DSPS), delayed sleep-phase type (DSPT), advanced sleep-phase syndrome (ASPS), and irregular sleep-wake cycle.

The term "V1a antagonist" refers to antagonists of the V1a vasopressin receptor subtype. Examples include OPC-21268, OPC-31260, OPC-41061, VPA-985, SR-49059, SR-121463, VP-343, FR-161282, CI-1025, SRX-251, SRX-246, JNJ-17158063, FE-202158, VT-913, LY307174, Org-52186, PF-184563, YM-218, 1-({(2*R*,3*S*)-5-chloro-3-(2-chlorophenyl)-1-[(3,4-dimethoxyphenyl)sulfonyl]-3-hydroxy-2,3-dihydro-1*H*-indol-2-yl}carbonyl)-L-prolinamide, [6-chloro-1-[2-(dimethylamino)ethyl]indol-3-yl]-spiro[1H-isobenzofuran-3,4'-piperidine]-1'-yl-methanone, 8-Chloro-5-methyl-1-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-yl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene, trans-8-chloro-5-methyl-1-(4-pyridin-2-yloxycyclohexyl)-4,6-dihydro-[1,2,4]triazolo[4,3-a][1,4]benzodiazepine and the like. The term "selective V1a

Claims

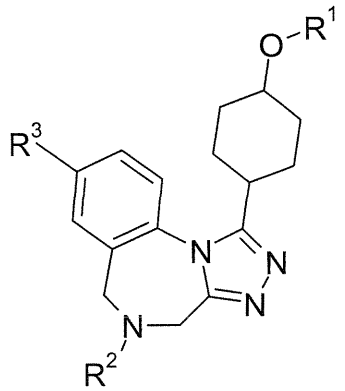
1. Use of a V1a antagonist for the manufacture of a medicament for the treatment and/or prevention of phase shift sleep disorders.

2. Use according to claim 1, for the treatment of phase shift sleep disorders.

3. Use according to claim 1, for the prevention of phase shift sleep disorders.

4. Use according to any one of claims 1-3, wherein the phase shift sleep disorder is jetlag.

5. Use according to any one of claims 1-4, wherein the V1a antagonist is a compound of formula I.



I

wherein

R^1 is aryl or heteroaryl, unsubstituted or substituted with one or more substituents independently selected from A,

R^2 is H,

C_{1-12}-alkyl, unsubstituted or substituted with one or more OH, halo, cyano or C_{1-12}-alkoxy,

$-(CH_2)_q-R^a$, wherein R^a is phenyl or 5- or 6-membered heteroaryl, each unsubstituted or substituted with one or more substituents independently selected from A,

$-(CH_2)_rNR^iR^{ii}$,

$-C(O)-C_{1-12}$-alkyl, wherein C_{1-12}-alkyl is unsubstituted or substituted with one or more OH, halo, cyano or C_{1-12}-alkoxy,

$-C(O)(CH_2)_qOC(O)-C_{1-12}$-alkyl,

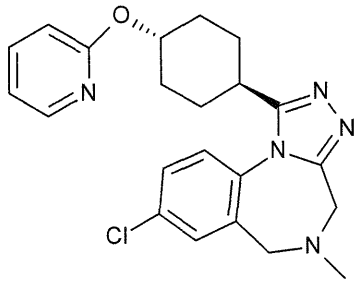
$-C(O)(CH_2)_qNR^iR^{ii}$,

$-C(O)O-C_{1-12}$-alkyl, wherein alkyl is unsubstituted or substituted with one or more OH, halo, cyano or C_{1-12}-alkoxy,

$-S(O)_2-C_{1-12}$-alkyl, or

trans-8-Chloro-5-(2-fluoro-ethyl)-1-[4-(5-fluoro-pyridin-2-yloxy)-cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene,
trans-8-Chloro-5-ethyl-1-[4-(3-fluoro-pyridin-2-yloxy)-cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene,
trans-8-Chloro-5-ethyl-1-[4-(5-fluoro-pyridin-2-yloxy)-cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene,
trans-8-Chloro-5-ethyl-1-[4-(6-methyl-pyridin-2-yloxy)-cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene, and
trans-8-Chloro-5-methyl-1-[4-(6-methyl-pyridin-2-yloxy)-cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene.

13. Use according to any one of claims 1-12, wherein the V1a antagonist is



example 1.

~~14. A method for the treatment and/or prevention of phase shift sleep disorders in a subject in need of such treatment, which comprises administering to said subject a therapeutically effective amount of a V1a antagonist.~~

~~15. A method for the treatment and/or prevention of phase shift sleep disorders in a subject in need of such treatment, which comprises administering to said subject a therapeutically effective amount of a V1a antagonist according to any one of claims 5-13.~~

~~16.~~14. A pharmaceutical composition comprising a V1a antagonist in a pharmaceutically acceptable form.

~~17.~~15. A pharmaceutical composition comprising a V1a antagonist according to any one of claims 5-13 in a pharmaceutically acceptable form.

~~18.~~16. A pharmaceutical composition comprising a V1a antagonist in a pharmaceutically acceptable form for use in the treatment and/or prevention of phase shift sleep disorders.

~~19.~~17. A pharmaceutical composition comprising a V1a antagonist according to any one of claims 5-13 in a pharmaceutically acceptable form for use in the treatment and/or prevention of phase shift sleep disorders.

~~20.~~18. A V1a antagonist for use in the treatment and/or prevention of phase shift sleep disorders.

~~21.~~19. A V1a antagonist according to any one of claims 5-13 for use in the treatment and/or prevention of phase shift sleep disorders.

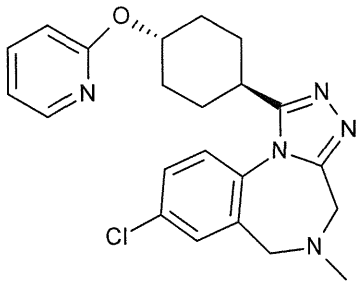
~~22. A V1a antagonist according to any one of claims 5-13 for the treatment and/or prevention of phase shift sleep disorders.~~

~~23.~~20. A selective V1a antagonist for use in the treatment and/or prevention of phase shift sleep disorders, wherein the V1a antagonist is selected from the group consisting of

trans-8-Chloro-1-(4-phenoxy-cyclohexyl)-4H,6H-2,3,5,10b-tetraaza-benzoazulene-5-carboxylic acid tert-butyl ester,
trans-8-Chloro-1-(4-phenoxy-cyclohexyl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzoazulene hydrochloride,
trans-8-Chloro-5-methyl-1-(4-phenoxy-cyclohexyl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene,
trans-1-[8-Chloro-1-(4-phenoxy-cyclohexyl)-4H,6H-2,3,5,10b-tetraaza-benzoazulen-5-yl]-ethanone,
trans-8-Chloro-5-methanesulfonyl-1-(4-phenoxy-cyclohexyl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzoazulene,
trans-2-[8-Chloro-1-(4-phenoxy-cyclohexyl)-4H,6H-2,3,5,10b-tetraaza-benzoazulen-5-yl]-ethanol,
trans-8-Chloro-5-isopropyl-1-(4-phenoxy-cyclohexyl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzoazulene,
trans-8-Chloro-1-(4-phenoxy-cyclohexyl)-4H,6H-2,3,5,10b-tetraaza-benzoazulene-5-sulfonic acid dimethylamide,
trans-8-Chloro-1-(4-phenoxy-cyclohexyl)-5-pyridin-2-ylmethyl-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzoazulene,
trans-1-[8-Chloro-1-(4-phenoxy-cyclohexyl)-4H,6H-2,3,5,10b-tetraaza-benzoazulen-5-yl]-2-dimethylamino-ethanone,
trans-8-Fluoro-1-(4-phenoxy-cyclohexyl)-4H,6H-2,3,5,10b-tetraaza-benzo[e]azulene-5-carboxylic acid tert-butyl ester,
trans-8-Fluoro-5-methyl-1-(4-phenoxy-cyclohexyl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzoazulene,
cis-8-Chloro-1-(4-phenoxy-cyclohexyl)-4H,6H-2,3,5,10b-tetraaza-benzoazulene-5-carboxylic acid tert-butyl ester,
cis-8-Chloro-5-methyl-1-(4-phenoxy-cyclohexyl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzoazulene,

trans-8-Chloro-5-ethyl-1-[4-(5-fluoro-pyridin-2-yloxy)-cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene,
trans-8-Chloro-5-ethyl-1-[4-(6-methyl-pyridin-2-yloxy)-cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene, and
trans-8-Chloro-5-methyl-1-[4-(6-methyl-pyridin-2-yloxy)-cyclohexyl]-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene.

~~24.~~21. A selective V1a antagonist for use in the treatment and/or prevention of phase shift sleep disorders, wherein the V1a antagonist is



example 1.

~~25. A V1a antagonist for the preparation of medicaments for the treatment and/or prevention of phase shift sleep disorders.~~

~~26. A V1a antagonist according to any one of claims 5-13 for the preparation of medicaments for the treatment and/or prevention of phase shift sleep disorders.~~

~~27. The use of a V1a antagonist for the preparation of medicaments for the treatment and/or prevention of phase shift sleep disorders.~~

~~28. The use of a V1a antagonist according to any one of claims 5-13 for the preparation of medicaments for the treatment and/or prevention of phase shift sleep disorders.~~