J. Japan Pediatric Soc., Vol. 116, No. 11, 2012, pp. 1728-1732.

Non-Patent Document 5: Nollet, M., *et al.*, Neurogenesis-Independent Antidepresssant-Like Effects on Behavior and Stress Axis Response of a Dual Orexin Receptor Antagonist in a Rodent Model of Depression. Neuropsychopharmacology, Vol. 37, pp. 2210-2221, 2012.

Non-Patent Document 6: Pich, E.M. and Melotto, S., Orexin 1 receptor antagonists in compulsive behavior and anxiety: possible therapeutic use. Front. Neurosci., Vol. 8, pp. 1-6, 2014.

Non-Patent Document 7: Johnson, P.L., *et al.*, Orexin 1 receptors are a novel target to modulate panic responses and the panic brain network, Physiol. Behav., Vol. 105, pp. 733-742, 2012.

Non-Patent Document 8: Saito, T., *et al.*, Affinity of Nalfurafine for its new receptor, 1P-11, Conference Proceedings of the 32th Medicinal Chemistry Symposium, 2014, Division of Medicinal Chemistry, The Pharmaceutical Society of Japan (eds.), p. 74.

Summary of the Invention

Problem to be Solved by the Invention

[0012]

However, in previously published Patent Documents 1 to 7 and Non-Patents Documents 1 to 8, there is no disclosure or no suggestion of morphinan derivatives having a particular structure and exhibiting excellent selectivity for and antagonism against orexin receptors.

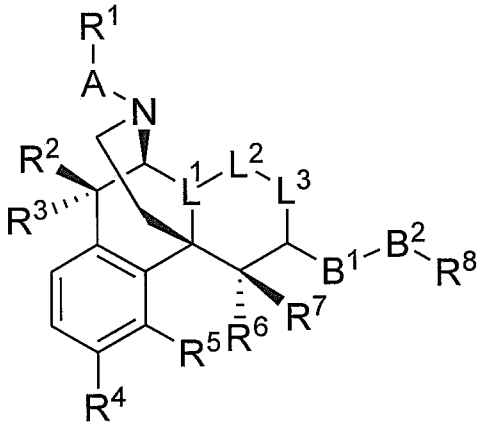
[0013]

Thus, an object of the present invention is to provide a novel compound having the morphinan skeleton which is useful for the treatment or prevention of various diseases or symptoms related to orexin receptors.

Summary

[0013a] In one aspect, there is provided a morphinan derivative represented by the

general formula (I) below or a pharmaceutically acceptable acid addition salt thereof



(I)

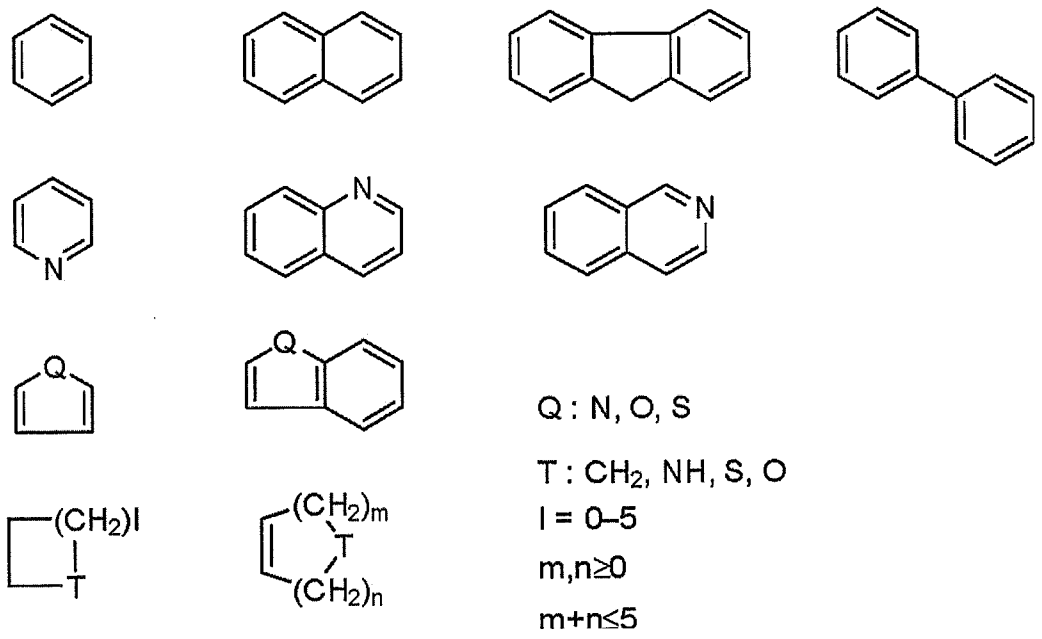
[wherein L^1-L^2-L^3 represents $C(R^9)$-CH_2-CH_2, $C(R^9)$-CH=CH, or C=CH-CH_2, wherein R^9 represents a hydrogen atom, hydroxy, nitro, C_1-C_5 alkanoyloxy, C_1-C_5 alkoxy, C_1-C_5 alkyl, amino, monoalkylamino (the alkyl moiety has one to five carbon atoms), dialkylamino (the alkyl moiety has one to five carbon atoms), C_1-C_5 alkanamide, benzamide, or C_7-C_{14} aryl-alkanamide;

A represents -C(=O)- or -SO_2-;

R^1 represents C_1-C_7 linear or branched alkyl, C_3-C_6 cycloalkyl, C_4-C_7 cycloalkylalkyl, C_4-C_6 cycloalkenyl, C_5-C_7 cycloalkenylalkyl, C_7-C_{13} aralkyl, C_4-C_7 alkenyl, allyl, or an organic group containing any of basic skeletons (II) below, wherein, in the basic skeletons (II), Q represents N, O, or S; T represents CH_2, NH, S, or O; l represents an integer of 0 to 5; m and n each independently represent an integer of 0 to 5, provided that the sum of m and n is not more than 5; said organic group represented by R^1 is optionally substituted by at least one substituent selected from the group consisting of C_1-C_5 alkyl, C_1-C_5 alkoxy, C_1-C_5 alkanoyloxy, hydroxy, fluorine, chlorine, bromine, iodine, amino, monoalkylamino (the alkyl moiety has one to five carbon atoms), dialkylamino (the alkyl moiety has one to five carbon atoms), nitro, cyano, carboxy, carbamoyl, N,N-dialkylcarbamoyl (the alkyl moiety has one to five carbon atoms), amidino, guanidino, isothiocyanate, trifluoromethyl,

phenyl, trifluoromethoxy, and methylenedioxy;

(basic skeletons II)



both R^2 and R^3 represent a hydrogen atom, or one of R^2 and R^3 represents a hydrogen atom and the other represents hydroxy, or R^2 and R^3 together represent oxo;

R^4 represents a hydrogen atom, hydroxy, C_1-C_5 alkoxy, C_3-C_7 alkenyloxy, C_7-C_{13} aralkyloxy, or C_1-C_5 alkanoyloxy;

R^5 and R^6 together represent -O-, -S-, or $-CH_2-$, or R^6 represents a hydrogen atom and R^5 represents a hydrogen atom, hydroxy, C_1-C_5 alkoxy, or C_1-C_5 alkanoyloxy;

R^7 represents a hydrogen atom, C_1-C_5 alkyl, C_2-C_5 alkenyl, or C_7-C_{13} aralkyl;

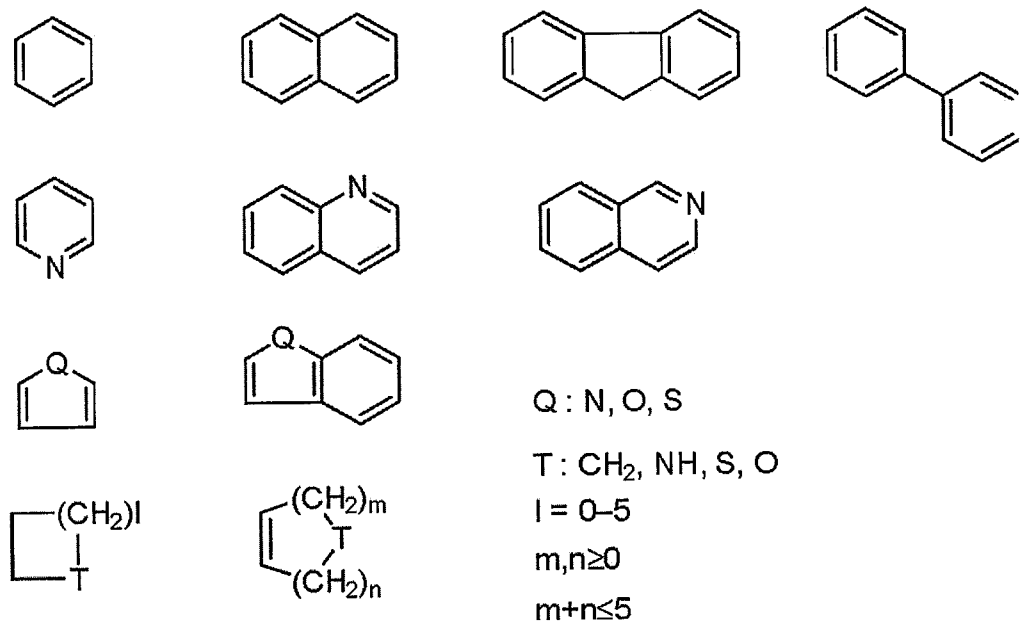
B^1 represents $-N(R^{10})C(=O)-$ or $-NR^{10}-$, wherein R^{10} represents a hydrogen atom, C_1-C_5 linear or branched alkyl;

B^2 represents a valence bond, C_1-C_{14} linear or branched alkylene (provided that said alkylene is optionally substituted with at least one substituent selected from the group consisting of C_1-C_5 alkoxy, C_1-C_5 alkanoyloxy, hydroxy, fluorine, chlorine,

bromine, iodine, amino, monoalkylamino (the alkyl moiety has one to five carbon atoms), dialkylamino (the alkyl moiety has one to five carbon atoms), nitro, cyano, carboxy, carbamoyl, amidino, guanidino, trifluoromethyl, phenyl and phenoxy; and one to three methylene groups are optionally replaced with carbonyl groups), C_2-C_{14} linear or branched acyclic unsaturated divalent hydrocarbon group containing one to three double and/or triple bonds (provided that said hydrocarbon group is optionally substituted with at least one substituent selected from the group consisting of C_1-C_5 alkoxy, C_1-C_5 alkanoyloxy, hydroxy, fluorine, chlorine, bromine, iodine, amino, monoalkylamino (the alkyl moiety has one to five carbon atoms), dialkylamino (the alkyl moiety has one to five carbon atoms), nitro, cyano, carboxy, carbamoyl, amidino, guanidino, trifluoromethyl, trifluoromethoxy, phenyl, and phenoxy; and one to three methylene groups are optionally replaced with carbonyl groups), or C_1-C_{14} linear or branched saturated or unsaturated divalent hydrocarbon group containing one to five thioether bonds, ether bonds, and/or amino bonds (-N(H)-) (provided that the hetero atom comprised in said thioether bond, ether bond, or amino bond is not directly linked to B^1; and one to three methylene groups are optionally replaced with carbonyl or sulfonyl groups);

R^8 represents a hydrogen atom or an organic group containing any of basic skeletons (III) below, wherein, in the basic skeletons (III), Q represents N, O, or S; T represents CH_2, NH, S, or O; l represents an integer of 0 to 5; m and n each independently represent an integer of 0 to 5, provided that the sum of m and n is not more than 5; said organic group represented by R^8 is optionally substituted by at least one substituent selected from the group consisting of C_1-C_5 alkyl, C_1-C_5 alkoxy, C_1-C_5 alkanoyloxy, hydroxy, fluorine, chlorine, bromine, iodine, amino, monoalkylamino (the alkyl moiety has one to five carbon atoms), dialkylamino (the alkyl moiety has one to five carbon atoms), nitro, cyano, isothiocyanate, trifluoromethyl, phenyl, phenoxy, trifluoromethoxy, and methylenedioxy; and

(basic skeletons III)



said general formula (I) inclusively represents the (+)-form, the (-)-form, and the (±)-form of the molecule].

[0013b] In another aspect, there is provided a pharmaceutical drug comprising, as an active ingredient, the morphinan derivative or the pharmaceutically acceptable acid addition salt thereof as described herein.

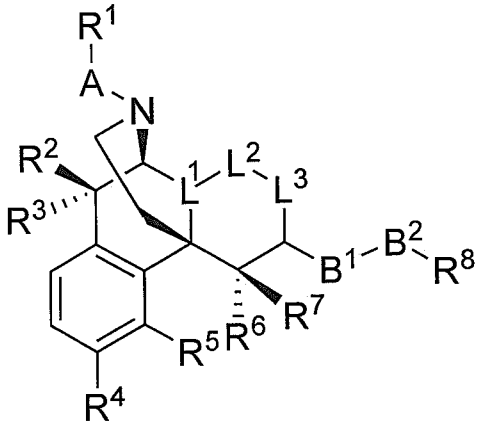
[0013c] In another aspect, there is provided a pharmaceutical composition comprising, as an active ingredient, the morphinan derivative or the pharmaceutically acceptable acid addition salt thereof as described herein.

[0013d] In another aspect, there is provided an orexin receptor antagonist comprising, as an active ingredient, the morphinan derivative or the pharmaceutically acceptable acid addition salt thereof as described herein.

[0013e] In another aspect, there is provided a therapeutic or prophylactic agent for drug dependence comprising, as an active ingredient, the morphinan derivative or the pharmaceutically acceptable acid addition salt thereof as described herein.

[0013f] In another aspect, there is provided use of the morphinan derivative or the pharmaceutically acceptable acid addition salt thereof as described herein in the manufacture of a medicament for treating or preventing drug dependence in a mammal in need thereof.

[0013g] In another aspect, there is provided a morphinan derivative represented by the general formula (I) below or a pharmaceutically acceptable acid addition salt thereof for use in treatment or prevention of drug dependence



(I)

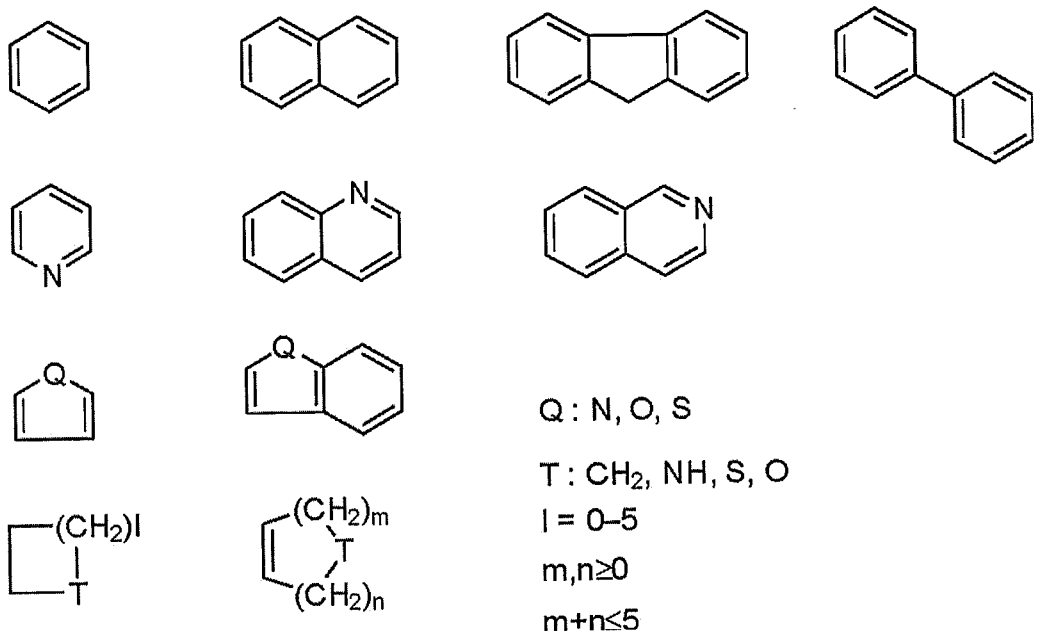
[wherein L^1-L^2-L^3 represents $C(R^9)$-CH_2-CH_2, $C(R^9)$-CH=CH, or C=CH-CH_2, wherein R^9 represents a hydrogen atom, hydroxy, nitro, C_1-C_5 alkanoyloxy, C_1-C_5 alkoxy, C_1-C_5 alkyl, amino, monoalkylamino (the alkyl moiety has one to five carbon atoms), dialkylamino (the alkyl moiety has one to five carbon atoms), C_1-C_5 alkanamide, benzamide, or C_7-C_{14} aryl-alkanamide;

A represents -C(=O)- or -SO_2-;

R^1 represents C_1-C_7 linear or branched alkyl, C_3-C_6 cycloalkyl, C_4-C_7 cycloalkylalkyl, C_4-C_6 cycloalkenyl, C_5-C_7 cycloalkenylalkyl, C_7-C_{13} aralkyl, C_4-C_7 alkenyl, allyl, or an organic group containing any of basic skeletons (II) below, wherein, in the basic skeletons (II), Q represents N, O, or S; T represents CH_2, NH, S, or O; l represents an integer of 0 to 5; m and n each independently represent an

integer of 0 to 5, provided that the sum of m and n is not more than 5; said organic group represented by R^1 is optionally substituted by at least one substituent selected from the group consisting of C_1-C_5 alkyl, C_1-C_5 alkoxy, C_1-C_5 alkanoyloxy, hydroxy, fluorine, chlorine, bromine, iodine, amino, monoalkylamino (the alkyl moiety has one to five carbon atoms), dialkylamino (the alkyl moiety has one to five carbon atoms), nitro, cyano, carboxy, carbamoyl, N,N-dialkylcarbamoyl (the alkyl moiety has one to five carbon atoms), amidino, guanidino, isothiocyanate, trifluoromethyl, phenyl, trifluoromethoxy, and methylenedioxy;

(basic skeletons II)



both R^2 and R^3 represent a hydrogen atom, or one of R^2 and R^3 represents a hydrogen atom and the other represents hydroxy, or R^2 and R^3 together represent oxo;

R^4 represents a hydrogen atom, hydroxy, C_1-C_5 alkoxy, C_3-C_7 alkenyloxy, C_7-C_{13} aralkyloxy, or C_1-C_5 alkanoyloxy;

R^5 and R^6 together represent -O-, -S-, or $-CH_2-$, or R^6 represents a hydrogen atom and R^5 represents a hydrogen atom, hydroxy, C_1-C_5 alkoxy, or C_1-C_5

alkanoyloxy;

R^7 represents a hydrogen atom, C_1-C_5 alkyl, C_2-C_5 alkenyl, or C_7-C_{13} aralkyl;

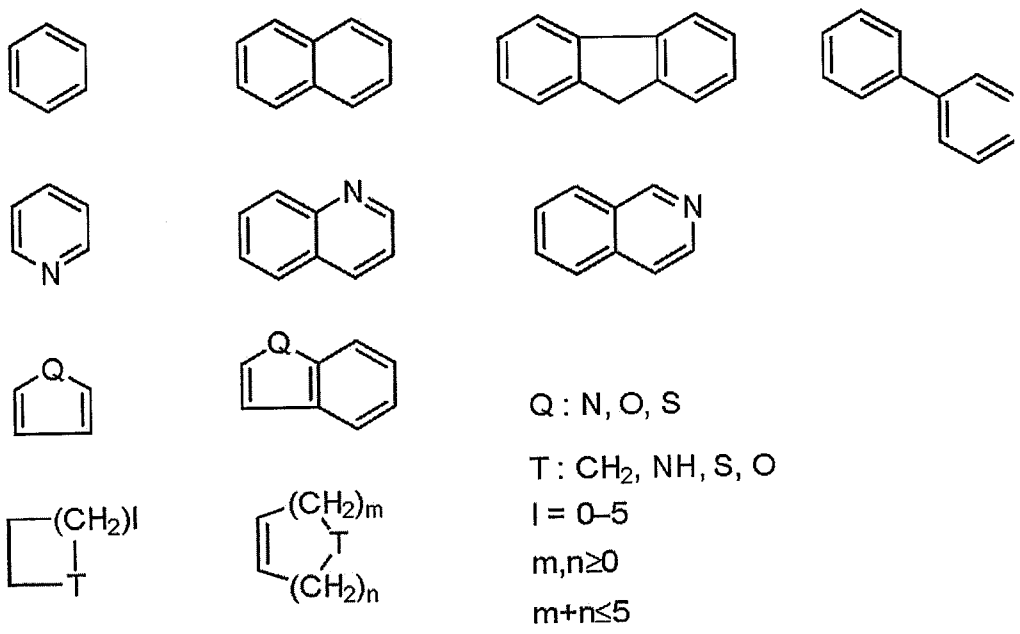
B^1 represents -N(R^{10})C(=O)- or -NR^{10}-, wherein R^{10} represents a hydrogen atom, C_1-C_5 linear or branched alkyl;

B^2 represents a valence bond, C_1-C_{14} linear or branched alkylene (provided that said alkylene is optionally substituted with at least one substituent selected from the group consisting of C_1-C_5 alkoxy, C_1-C_5 alkanoyloxy, hydroxy, fluorine, chlorine, bromine, iodine, amino, monoalkylamino (the alkyl moiety has one to five carbon atoms), dialkylamino (the alkyl moiety has one to five carbon atoms), nitro, cyano, carboxy, carbamoyl, amidino, guanidino, trifluoromethyl, phenyl and phenoxy; and one to three methylene groups are optionally replaced with carbonyl groups), C_2-C_{14} linear or branched acyclic unsaturated divalent hydrocarbon group containing one to three double and/or triple bonds (provided that said hydrocarbon group is optionally substituted with at least one substituent selected from the group consisting of C_1-C_5 alkoxy, C_1-C_5 alkanoyloxy, hydroxy, fluorine, chlorine, bromine, iodine, amino, monoalkylamino (the alkyl moiety has one to five carbon atoms), dialkylamino (the alkyl moiety has one to five carbon atoms), nitro, cyano, carboxy, carbamoyl, amidino, guanidino, trifluoromethyl, trifluoromethoxy, phenyl, and phenoxy; and one to three methylene groups are optionally replaced with carbonyl groups), or C_1-C_{14} linear or branched saturated or unsaturated divalent hydrocarbon group containing one to five thioether bonds, ether bonds, and/or amino bonds (-N(H)-) (provided that the hetero atom comprised in said thioether bond, ether bond, or amino bond is not directly linked to B^1; and one to three methylene groups are optionally replaced with carbonyl or sulfonyl groups);

R^8 represents a hydrogen atom or an organic group containing any of basic skeletons (III) below, wherein, in the basic skeletons (III), Q represents N, O, or S; T represents CH_2, NH, S, or O; l represents an integer of 0 to 5; m and n each

independently represent an integer of 0 to 5, provided that the sum of m and n is not more than 5; said organic group represented by R^8 is optionally substituted by at least one substituent selected from the group consisting of C_1-C_5 alkyl, C_1-C_5 alkoxy, C_1-C_5 alkanoyloxy, hydroxy, fluorine, chlorine, bromine, iodine, amino, monoalkylamino (the alkyl moiety has one to five carbon atoms), dialkylamino (the alkyl moiety has one to five carbon atoms), nitro, cyano, isothiocyanate, trifluoromethyl, phenyl, phenoxy, trifluoromethoxy, and methylenedioxy; and

(basic skeletons III)

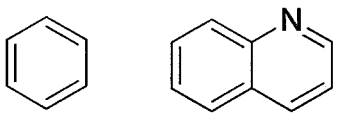


said general formula (I) inclusively represents the (+)-form, the (-)-form, and the (±)-form of the molecule].

Means for Solving the Problem

[0014]

salt thereof according to any one of claims 1 to 3, wherein R^1 represents an organic group containing any of basic skeletons below.



5. The morphinan derivative or the pharmaceutically acceptable acid addition salt thereof according to any one of claims 1 to 4, wherein R^4 represents a C_1-C_5 alkoxy or C_7-C_{13} aralkyloxy group.

6. A pharmaceutical drug comprising, as an active ingredient, the morphinan derivative or the pharmaceutically acceptable acid addition salt thereof according to any one of claims 1 to 5.

7. A pharmaceutical composition comprising, as an active ingredient, the morphinan derivative or the pharmaceutically acceptable acid addition salt thereof according to any one of claims 1 to 5.

8. An orexin receptor antagonist comprising, as an active ingredient, the morphinan derivative or the pharmaceutically acceptable acid addition salt thereof according to any one of claims 1 to 5.

9. A therapeutic or prophylactic agent for drug dependence comprising, as an active ingredient, the morphinan derivative or the pharmaceutically acceptable acid addition salt thereof according to any one of claims 1 to 5.

10. Use of the morphinan derivative or the pharmaceutically acceptable acid addition salt thereof according to any one of claims 1 to 5 in the manufacture of a medicament for treating or preventing drug dependence in a mammal in need thereof.

11. A morphinan derivative represented by the general formula (I) below or a pharmaceutically acceptable acid addition salt thereof for use in treatment or prevention of drug dependence