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(54) **ANORECTIC**

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(57) **ABSTRACT**

The present invention relates to an anorectic containing a compound having a DGAT inhibitory activity (DGAT1 inhibitory activity) or a prodrug thereof or a pharmaceutically acceptable salt thereof as an active ingredient. The present invention provides an anti-obesity drug which is an anorectic that does not directly act on the central nervous system and is satisfactory in terms of activity, and a therapeutic strategy for preventing or treating obesity.

ANORECTIC

TECHNICAL FIELD

[0001] The present invention relates to an anorectic action of a compound having a DGAT (diacylglycerol acyltransferase) inhibitory activity (e.g., DGAT1 inhibitory activity). Moreover, the present invention relates to a combined use of such DGAT inhibitors (e.g., DGAT1 inhibitor) and various drugs.

BACKGROUND ART

[0002] It is known that various intracerebral neural activities and neurotransmitters are involved in the control of appetite in human and animals. These neural activities are affected by biochemical, neurological or endocrine signals that occur in the process of nutritive digestion, absorption, metabolism and storage.

[0003] Sugars and lipids themselves as nutrients, or metabolites in fat, muscule and liver cause biochemical signals that act promotively or suppressively on cerebral nerve activities involved in appetite.

[0004] It is also known that endocrine signals (e.g., CCK, GLP1, Enterostatin, ApoAIV etc.) or neural signals via chemical receptors of the gastrointestinal tract or from enteric plexus, during the process of digestion and absorption of sugars and lipids, affect gastrointestinal functions and cerebral nerve activities.

[0005] Moreover, it is known that fat tissue, which is a fat storage organ, produces endocrine or biochemical signals, such as leptin, adiponectin and free fatty acid, along with storage and consumption of fat. These signals alone or cooperative combinations of signals are considered to affect the central nervous system which controls appetite.

[0006] The DGAT1 inhibitor is expected to inhibit absorption of fat by suppressing re-synthesis of triglyceride in the gastrointestinal tract, and changes the above-mentioned signals that affect function of the gastrointestinal tract or brain.

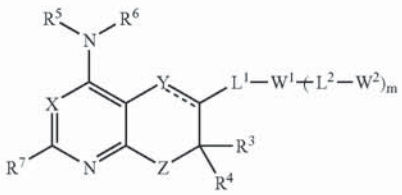
[0007] In addition, the DGAT1 inhibitor is expected to change biochemical or endocrine signals from fat tissue by suppressing re-synthesis of triglyceride in the fat tissue.

[0008] Furthermore, it has been reported that DGAT1 deficient mice show an accelerated sensitivity of brain function to leptin which is an anti-obese factor derived from fat tissue. Therefore, a similar effect is expected by the administration of a DGAT1 inhibitor.

[0009] In the meantime, as a compound having a DGAT inhibitory activity, the following compounds are known.

[0010] The following compound has been disclosed to have a DGAT inhibitory activity (e.g., WO2004/47755

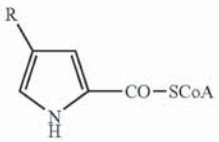
(1)



[0011] This reference discloses inhibition of DGAT. However, disclosure of anorectic action resulting from the inhibition of DGAT as in the present application is not contained at all.

[0012] For example, the following compound has been disclosed to have a DGAT inhibitory activity (e.g., JP-A-H5-213985).

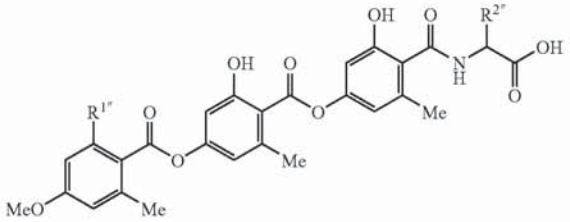
(3)



[0013] This reference discloses inhibition of ACAT and DGAT. However, disclosure of anorectic action resulting from the inhibition of DGAT as in the present application is not contained at all.

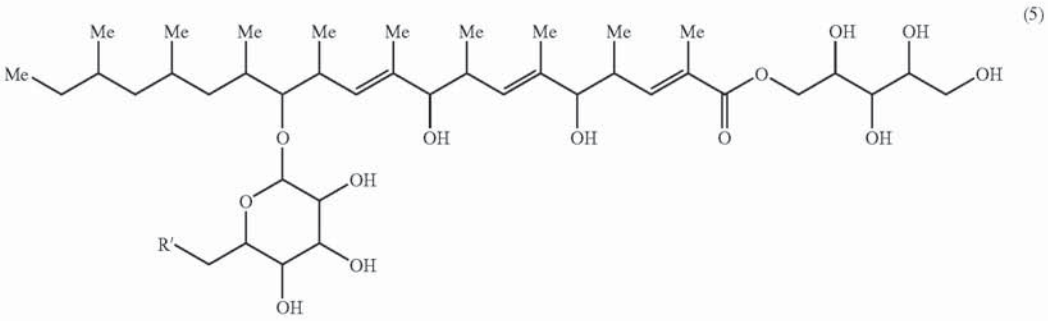
[0014] Similarly, the following compound has been disclosed to have a DGAT inhibitory activity (e.g., JP-A-H8-182496).

(4)



[0015] This reference discloses inhibition of DGAT. However, disclosure of anorectic action resulting from the inhibition of DGAT as in the present application is not contained at all.

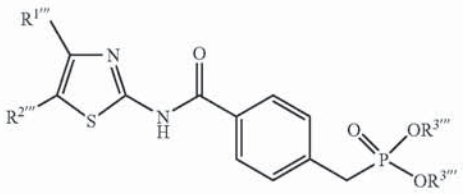
[0016] Moreover, the following compound has been dis-



(5)

[0017] This reference discloses inhibition of DGAT. However, disclosure of anorectic action resulting from the inhibition of DGAT as in the present application is not contained at all.

[0018] Moreover, the following compound has been disclosed to have a DGAT inhibitory activity (e.g., JP-A-2004-67635).



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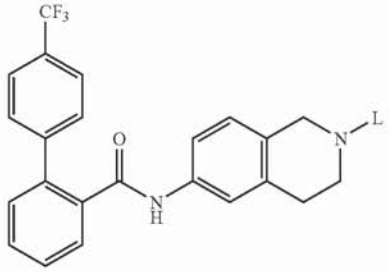
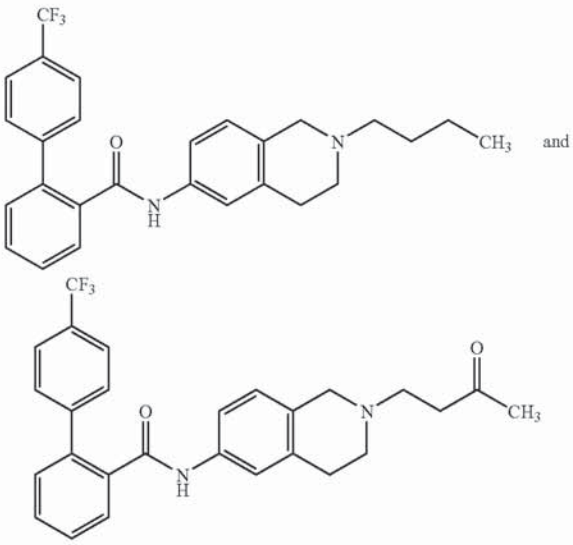
[0019] This reference discloses inhibition of DGAT. However, disclosure of anorectic action resulting from the inhibition of DGAT as in the present application is not contained at all.

[0020] As a compound having an anorectic action, ApoB secretion/MTP (Microsomal Triglyceride Transfer Protein) inhibitors have been disclosed (e.g., JP-A-2001-181209). As such compound, for example, the following formula has been disclosed.



Specifically, the following compounds have been disclosed.



and

[0021] However, this reference does not disclose that these compounds have a DGAT inhibitory activity.

[0022] In addition, the reference discloses that similar compounds have been disclosed to have a suppressive action on fat absorption from small intestine, but does not disclose that these compounds have a DGAT inhibitory activity (e.g., JP-A-2001-172180).

[0023] While the development of anti-obesity drugs is currently ongoing, they are not satisfactory in terms of activity. The development of anorectic agents to prevent or treat obesity is also ongoing. However, since most of these anorectic agents directly act on the central nervous system and side effects are worried, the development of anorectic agents that do not directly act on the center has been strongly desired.

[0024] The problem to be solved by the present invention is provision of an anti-obesity drug which is an anorectic agent that does not directly act on the central nervous system

DISCLOSURE OF THE INVENTION

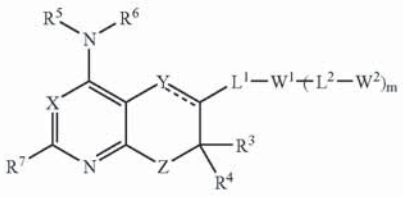
[0025] In view of the above-mentioned problem, the present inventors have intensively studied in an attempt to search a useful anorectic and surprisingly found that a compound having a DGAT inhibitory activity (e.g., DGAT1 inhibitory activity) has a remarkable anorectic activity, which resulted in the completion of the present invention.

[0026] More particularly, the invention provides the following [1]-[33].

[1] An anorectic comprising, as an active ingredient, a compound having a DGAT (diacylglycerol acyltransferase) inhibitory activity or a prodrug thereof or a pharmaceutically acceptable salt thereof.

[0027] [2] The anorectic of the above-mentioned [1], wherein the compound having a DGAT inhibitory activity is a compound represented by the following formula (1):

(1)



wherein

[0028] X is $C(R^1)$ or N,

[0029] wherein R^1 is a hydrogen atom, a C_{1-8} alkyl group, a C_{2-8} alkenyl group, a C_{2-8} alkynyl group, a C_{1-8} fluoroalkyl group, an aryl group, an aryl C_{1-4} alkyl group, $C(O)R^a$, CO_2R^a or $C(O)NR^aR^b$, wherein R^a and R^b are the same or different and each is a hydrogen atom, a C_{1-8} alkyl group, a C_{2-8} alkenyl group, a C_{2-8} alkynyl group, a C_{1-8} fluoroalkyl group, an aryl group or an aryl C_{1-4} alkyl group;

[0030] Y is $C(R^1)$, $C(R^2)(R^2)$, N or $N(R^2)$,

[0031] wherein R^1 is as defined above and each R^2 is independently a hydrogen atom, a C_{1-8} alkyl group, a C_{2-8} alkenyl group, a C_{2-8} alkynyl group, a C_{1-8} fluoroalkyl group, $C(O)R^a$, CO_2R^a, $C(O)NR^aR^b$, an aryl group or an aryl C_{1-4} alkyl group, wherein R^a and R^b are as defined above;

[0032] Z is O or S;

[0033] W^1 is an optionally substituted C_{3-8} cycloalkylene group, an optionally substituted C_{3-8} heterocycloalkylene group, an optionally substituted arylene group or an optionally substituted heteroarylene group;

[0034] W^2 is an optionally substituted C_{3-8} cycloalkyl group, an optionally substituted C_{3-8} heterocycloalkyl group, an optionally substituted aryl group or an optionally substituted heteroaryl group;

[0035] L^1 is a single bond, a C_{1-4} alkylene group, a C_{2-4} alkenylene group, O, $C(O)N(R^a)$ or $N(R^a)C(O)$, wherein R^a is as defined above;

[0036] L^2 is a single bond, O, a C_{1-4} alkylene group, a C_{2-4} alkenylene group, a C... heteroalkylene group,

[0037] m is 0 or 1;

[0038] when m is 1 and L^2 is a single bond, a substituent of W^2 may form, together with a substituent of W^1, a 5 to 7-membered ring that is condensed with W^1 and forms a fused ring or Spiro ring with W^2;

[0039] R^3 and R^4

[0040] are the same or different and each is a hydrogen atom, a C_{1-8} alkyl group, a C_{2-8} alkenyl group, a C_{2-8} alkynyl group, $C(O)R^a$, CO_2R^a, $C(O)NR^aR^b$ or a C_{1-4} alkylene-OR^a group, wherein R^a and R^b are as defined above, or R^3 and R^4 may form a 3 to 6-membered ring together with the carbon atom binding thereto; or

[0041] R^2, R^3 or R^4

[0042] may form, together with W^1, a 5 to 7-membered ring optionally having, in the ring, 1 to 3 heteroatoms selected from a nitrogen atom, an oxygen atom and a sulfur atom;

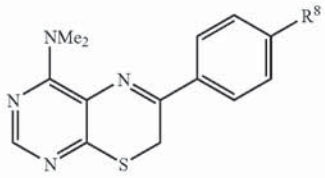
[0043] R^5 and R^6

[0044] are the same or different and each is a hydrogen atom, a C_{1-8} alkyl group, a C_{2-8} alkenyl group, a C_{2-8} alkynyl group, $C(O)R^a$ or CO_2R^a, wherein R^a is as defined above, R^5 and R^6 may form an N-containing 5 to 7-membered ring together with the nitrogen atom binding thereto, or, when X is $C(R^1)$, R^5 or R^6 may form, together with R^1, an N-containing 5 to 7-membered ring, wherein N may be substituted by R^5 or R^6;

[0045] R^7 is a hydrogen atom, a C_{1-8} alkyl group, a C_{1-4} haloalkyl group, a C_{2-8} alkenyl group, a C_{2-8} alkynyl group, $C(O)R^a$, OR^a or NR^aR^b, wherein R^a and R^b are as defined above, or, when X is $C(R^1)$, R^7 may form, together with R^1, a 5 to 7-membered ring; and

⋯⋯ is a single bond or a double bond;

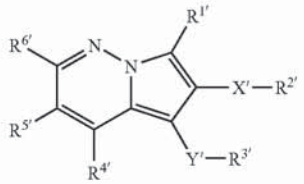
provided that the following compound is excluded:



wherein R^8 is a hydrogen atom, a nitro group, a chlorine atom, a methoxy group, a methyl group or a phenyl group.

[3] The anorectic of the above-mentioned [1], wherein the compound having a DGAT inhibitory activity is a compound represented by the following formula (2):

(2)



wherein

[0046] X' and Y'

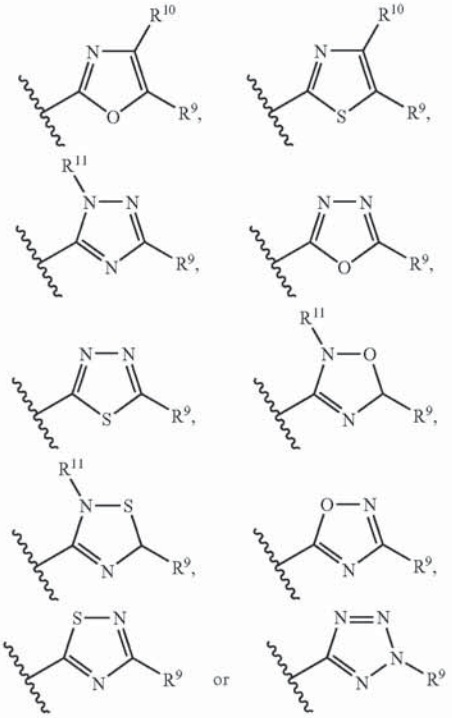
[0047] are the same or different and each is a single bond, a C_{1-4} alkylene group, a C_{2-4} heteroalkylene group, —O—, —CO_2—, —$S(O)_k$—,

[0048] —C(O)—, —$NR^{7'}$—, —$C(O)NR^{7'}$—, —$N(R^{8'})C(O)NR^{7'}$—, —$N(R^{7'})$ CO_2—, —$SO_2NR^{7'}$—, —$N(R^{8'})$ $SO_2NR^{7'}$—, —$NR^{7'}C(O)$—, —O—$C(O)N(R^{7'})$- or —$NR^{7'}$ SO_2—,

[0049] wherein $R^{7'}$ and $R^{8'}$ are the same or different and each is a hydrogen atom, a C_{1-8} alkyl group, an aryl group or an aryl C_{1-4} alkyl group and k is an integer of 0 or 1-2;

[0050] $R^{1'}$ is a hydrogen atom, a halogen atom, a C_{1-8} alkyl group, a C_{2-8} alkenyl group, a C_{2-8} alkynyl group, a C_{1-8} fluoroalkyl group, a C_{3-8} cycloalkyl group, a C_{2-8} heteroalkyl group, a C_{2-8} heteroalkenyl group; a C_{3-8} heterocycloalkyl group, an aryl group, an aryl C_{1-4} alkyl group, a heteroaryl group, $OR^{a'}$, $SR^{a'}$, $C(O)R^{a'}$, $CO_2R^{a'}$, $C(O)NR^{a'}R^{b'}$, $SO_2R^{a'}$, $SO_2NR^{a'}R^{b'}$ a nitro group or a cyano group, wherein $R^{a'}$ and $R^{b'}$ are the same or different and each is a hydrogen atom, a C_{1-8} alkyl group, a C_{3-8} cycloalkyl group, an aryl group or an aryl C_{1-4} alkyl group;

[0051] $R^{2'}$ is a C_{1-8} alkyl group, an aryl C_{1-4} alkyl group, $OR^{a'}$, a halogen atom, a nitro group, $NR^{a'}R^{b'}$, a cyano group or $W^{1'}$, wherein $W^{1'}$ is



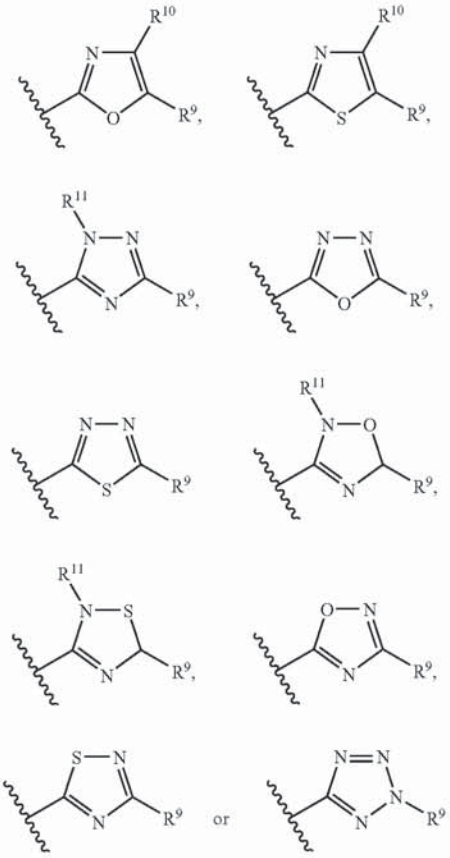
[0052] wherein R^9 and R^{10} are the same or different and each is a hydrogen atom, a C_{1-8} alkyl group, a C_{1-8} fluoroalkyl group, a C_{1-8} het-

group, an aryl group or an aryl C_{1-4} alkyl group, or R^9 and R^{10} may be linked to form a 5 to 7-membered ring optionally having, in the ring, 1 to 3 heteroatoms selected from a nitrogen atom, an oxygen atom and a sulfur atom, R^{11} is a hydrogen atom, a C_{1-8} alkyl group, an aryl group or an aryl C_{1-4} alkyl group, and $R^{a'}$ and $R^{b'}$ are as defined above; or

[0053] $R^{1'}$ and $R^{2'}$

[0054] may be linked to form a 5 to 7-membered ring optionally having, in the ring, one heteroatom selected from a nitrogen atom, an oxygen atom and a sulfur atom;

[0055] $R^{3'}$ is a hydrogen atom, a C_{1-8} alkyl group, an aryl C^{1-4} alkyl group, $OR^{a'}$, a halogen atom, a nitro group, $NR^{a'}R^{b'}$, a cyano group or $W^{2'}$, wherein $W^{2'}$ is



[0056] wherein R^9, R^{10} and R^{11} are as defined above, and $R^{a'}$ and $R^{b'}$ are as defined above; or

[0057] $R^{2'}$ and $R^{3'}$

[0058] may be linked to form a 5 to 7-membered ring optionally having, in the ring, one heteroatom selected from a nitrogen atom, an oxygen atom and a sulfur atom;

[0059] $R^{4'}$ is a C_{1-8} alkyl group, a C_{2-8} alkenyl group, a

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