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(54) Title: BUPRENORPHINE DERIVATIVES AND PHARMACEUTICALLY ACCEPTABLE SALTS THEREOF

(57) Abstract: The present invention relates to a buprenorphine derivative or a pharmaceutically acceptable salt thereof which is an effective analgesic having a much reduced level of addictiveness and an analgesic composition comprising same as an active ingredient.



WO 2006/025710 A1

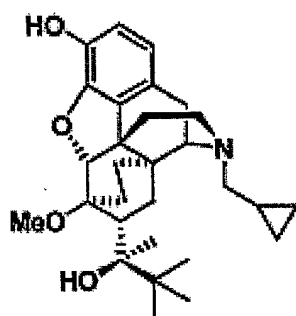
BUPRENORPHINE DERIVATIVES AND PHARMACEUTICALLY ACCEPTABLE SALTS THEREOF

Field of the Invention

The present invention relates to a buprenorphine derivative or a pharmaceutically acceptable salt thereof which is an effective analgesic having a much reduced addictiveness.

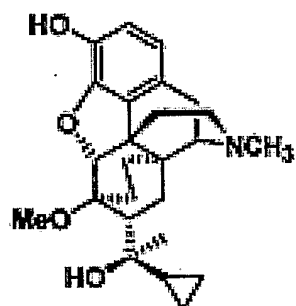
Background of the Invention

United States Patent No. 3,433,791 discloses buprenorphine of formula (Ia) as a semisynthetic analgesic derived from thebaine.

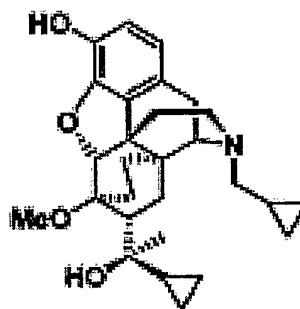


(Ia)

Buprenorphine acts as an excellent partial agonist of opioid receptor and has fewer side effects than that of existing analgesics, but still has the problem of addictiveness when administered for a long period of time. Although various derivatives of buprenorphine have been developed to improve the analgesic effect of buprenorphine, the problem of addiction remained unresolved. For example, the buprenorphine derivatives of formula (Ib) and (Ic), disclosed in United States Patent No. 5,849,915, had a dosage-dependent analgesic effect similar to that of buprenorphine, but the addictiveness was not reduced.



(Ib)



(Ic)

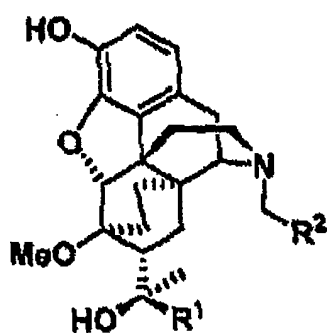
Therefore, there has been a need to develop a new analgesic to overcome the addictiveness of buprenorphine.

Summary of the Invention

Accordingly, it is an object of the present invention to provide a buprenorphine derivative useful as an analgesic which has a reduced level of addictiveness.

It is another object of the present invention to provide an analgesic composition comprising the buprenorphine derivative or a pharmaceutically acceptable salt thereof as an active ingredient.

In accordance with one aspect of the present invention, there is provided a buprenorphine derivative of formula (I) and a pharmaceutically acceptable salt thereof:



(I)

wherein,

R^1 is cyclobutyl; and

R^2 is cyclopropyl or cyclobutyl.

In accordance with another aspect of the present invention, there is provided an analgesic composition comprising the buprenorphine derivative or a pharmaceutically acceptable salt thereof as an active ingredient together with a pharmaceutically acceptable carrier.

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Detailed Description of the Invention

The most preferred derivative of buprenorphine of the present invention is the compound wherein R^2 is cyclopropyl.

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The buprenorphine derivative of the present invention may be prepared by the procedure shown in Reaction Scheme (I):

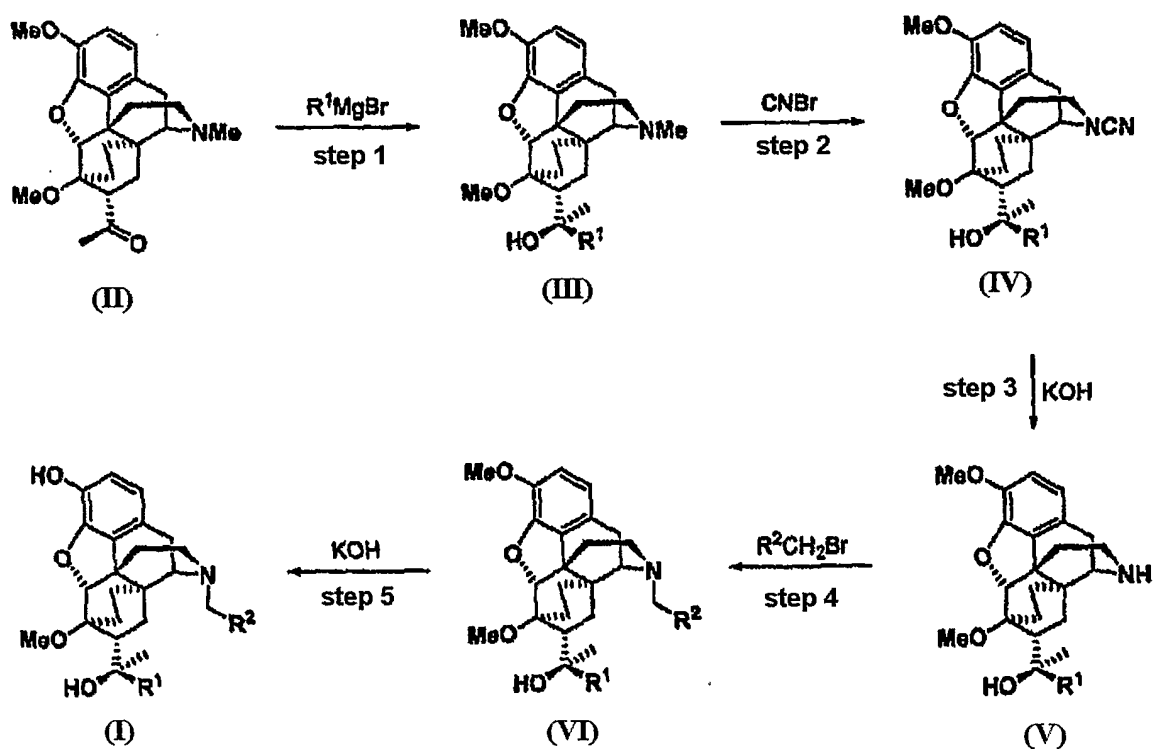
Reaction Scheme (I)

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25

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wherein,

R^1 and R^2 have same meanings as defined for formula (I).

As shown in Reaction Scheme (I), the inventive compound of formula (I) may be prepared by a process comprising the following steps.

Step 1: A compound of formula (II) is reacted with a Grignard reagent (R^1MgBr) to obtain a compound of formula (III). The compound of formula (II) can be synthesized from thebaine in accordance with a conventional method (*see*: Knipmeyer, L. L. and Rapoport, H., *J. Med. Chem.*, 28, 461-466, 1985). The Grignard reagent may be employed in an amount of 2 to 5 equivalents based on the compound of formula (II), and the reaction can be carried out in a solvent such as THF, benzene, diethyl ether under a reflux condition for 0.5 to 2 hours.

Step 2: The compound of formula (III) is converted to a compound of formula (IV) via a reaction with $CNBr$. $CNBr$ may be employed in an amount ranging from 1 to 3 equivalents based on the compound of formula (III), and the reaction can be carried out in a solvent such as $CHCl_3$, CH_2Cl_2 and THF at room temperature for 3 to 12 hours.

Step 3: The compound of formula (IV) is hydrolyzed in the presence of KOH to obtain a compound of formula (V). KOH may be employed in an amount ranging from 4 to 8 equivalents based on the compound (IV), and the reaction can be carried out in a solvent such as diethylene glycol, ethylene glycol and triethylene glycol at a temperature ranging from 175 to 185°C for 2 to 5 hours.

Step 4: The compound of formula (V) is subjected to alkylation to obtain an N-alkylated compound of formula (VI). The alkylating reagent used in this step is bromomethylcyclopropane or bromomethylcyclobutane, and the reagent may be employed in an amount ranging from 1 to 2 equivalents based on the compound of formula (V). This reaction can be carried out in the presence of a base such as K_2CO_3 , and the base may be employed in an amount ranging from 2 to 3 equivalent based on the compound (V). Further, the reaction can be carried out in a solvent such as dimethyl formamide, acetonitrile and THF at a temperature ranging from 120 to 140°C for 2 to 4 hours.

Step 5: The compound of formula (VI) is treated with KOH to obtain the buprenorphine derivative of formula (I) as a pure diastereomeric free base. KOH may be employed in an amount ranging from 25 to 35 equivalents based on the compound of formula (VI), and the reaction can be carried out in a solvent such as diethylene glycol at a temperature ranging from 210 to 230 °C for 2 to 4 hours.

The buprenorphine derivative of formula (I) of the present invention can also be used in the form of a pharmaceutically acceptable salt formed with an inorganic or organic acid, such as hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid, acetic acid, glycolic acid, lactic acid, pyruvic acid, malonic acid, succinic acid, glutaric acid, fumaric acid, malic acid, mandelic acid, tartaric acid, citric acid, ascorbic acid, palmitic acid, maleic acid, hydroxymaleic acid, benzoic acid, hydroxybenzoic acid, phenylacetic acid, cinnamic acid, salicylic acid, methanesulfonic acid, benzenesulfonic acid and toluenesulfonic acid.

The inventive buprenorphine derivative or a pharmaceutically acceptable salt thereof having an excellent analgesic effect and reduced addictiveness is useful for relieving pain over a long-period.

The inventive buprenorphine derivative or a pharmaceutically acceptable salt thereof may be formulated in the form of a pharmaceutical composition together with a pharmaceutically acceptable carrier.

The pharmaceutical compositions of the invention may be formulated for oral and parenteral administration, including intravenous, intraperitoneal, subcutaneous, rectal and topical routes of administration in accordance with conventional methods. The composition for administration may take various forms such as tablets, powder, soft and hard gelatin capsules, aqueous solutions, suspensions, emulsions, syrups, granules, aerosol elixirs, sterilized aqueous solution, sterilized powder, non-aqueous solution and lyophilized agent, and additionally includes conventional additives such as a diluent, lubricant, filler, extender, wetting agent, absorbent, colorant, flavor, sweetener, preservative, emulsifier and the like.

The inventive pharmaceutical composition for oral administration may be prepared by mixing the active ingredient with a carrier, diluent or excipient.

Examples of the carrier, excipient and diluent are a disintegrator (e.g., starch, sugar and mannitol); a filler and extender (e.g., calcium phosphate and silicate derivatives); a binder (e.g., carboxymethyl cellulose and a derivative thereof, gelatin, and polyvinyl pyrrolidone); and a lubricant (e.g., talc, calcium stearate and magnesium stearate, and polyethylene glycol(s)).

Examples of the carrier employed in the injectable composition of the present invention is a water, saline solution, glucose solution, alcohol, glycol, ether (e.g., polyethylene glycol 400), oil, fatty acid, fatty acid ester, glyceride, surfactant, suspension or emulsifier.

The compound of formula (I) or a pharmaceutically acceptable salt thereof may be administered orally or parenterally as an active ingredient in an effective amount ranging from about 0.001 to 0.5 mg/kg body weight per day in case of mammals including human in a single dose or in divided doses. However, the foregoing dosage should be monitored, and change in consideration of idiosyncrasy and weight of the patient, kind and seriousness of illnesses, characteristics of the drug and interval and duration of drug.

The following Examples are intended to further illustrate the present invention without limiting its scope.

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Example 1: Preparation of 7 α -acetyl-6,14-endo-ethanotetrahydrothebaine (compound (II))

1 g (2.6 mmol) of 7 α -acetyl-6,14-endo-ethanotetrahydrothebaine synthesized from thebaine was dissolved in 40 ml of ethanol, and hydrogenated in the presence of 0.2 g of 5% palladium catalyst at room temperature under a hydrogen pressure of 60 psi for 30 hours. The catalyst was removed filtration, filtered reaction mixture was concentrated, and recrystallized from ethanol to obtain the title compound (80%; m.p: 141-143 °C).

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Example 2: Preparation of 6,14-endoethano-7-(2-hydroxy-2-cyclobutyl-2-ethyl)-tetrahydrothebaine (compound (III))

A round-bottomed flask was purged with nitrogen, and 13.7 mmol of cyclobutyl magnesium bromide was placed therein together with 10 ml of benzene. The mixture was brought to a reflux condition, 1.05 g (2.74 mmol) of the compound of formula (II) obtained in Example 1 dissolved in 15 ml of benzene was added dropwise thereto, and the resulting mixture was refluxed for 1.5 hours. The reaction mixture was then cooled to room temperature and 30 ml of saturated ammonium chloride was added thereto. The organic layer was separated, the solvent was removed under a reduced pressure, and the residue was subjected to flash column chromatography (column: silica gel; eluent: diethyl ether) to obtain the title compound (7.22 mg, 60%).

Example 3: Preparation of N-cyano-6,14-endoethano-7-(2-hydroxy-2-cyclobutyl-2-ethyl)-tetrahydrothebaine (compound (IV))

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2.1 g (4.8 mmol) of the compound of formula (III) obtained in Example 2 was dissolved in 20 ml of chloroform, and 1.6 g (15 mmol) of CNBr was added thereto. After stirring the mixture for 4 hours, the solvent was removed, and the resulting solid was recrystallized from ethanol to obtain the title compound (88%).

20

Example 4: Preparation of 6,14-endoethano-7-(2-hydroxy-2-cyclobutyl-2-ethyl)-tetrahydronorthebaine (compound (V))

25

1.8 g (4 mmol) of the compound of formula (IV) obtained in Example 3 and 2.2 g (40 mmol) of KOH were allowed to react in 40 ml of diethylene glycol by stirring at 180°C for 4 hours. The reaction mixture was cooled to about 0°C, and 60 ml of distilled water was added thereto. Ammonium chloride was added to the resulting solution to a saturation point. The solid remaining therein was filtered, washed and dried to obtain the title compound (1.5 g, 88%).

30

Example 5: Preparation of N-cyclobutylmethyl-6,14-endoethano-7-(2-hydroxy-2-cyclobutyl-2-ethyl)-tetrahydronorthebaine (compound (VI); R¹ and R²= cyclobutyl)

5 596 mg (4 mmol) of bromomethyl cyclobutane, 1 g (7.2 mmol) of potassium carbonate and 1 g (2.5 mmol) of the compound of formula (V) obtained in Example 4 were added slowly to 10 ml of dimethylformamide. The resulting mixture was heated to 135 °C and stirred for 3 hours. The excess potassium carbonate was removed by filtration, and the solvent was removed by
10 vacuum distillation. The remaining solid was filtered and vacuum dried to obtain the title compound (0.94 g, 81%).

Example 6: Preparation of N-cyclopropylmethyl-6,14-endoethano-7-(2-hydroxy-2-cyclobutyl-2-ethyl)-tetrahydronorthebaine (compound (VI); R¹= cyclobutyl and R²= cyclopropyl)

 The procedure of Example 5 was repeated except for using 540 mg (4 mmol) of bromomethyl cyclopropane instead of bromomethyl cyclobutane to
20 obtain the title compound (0.902 g, 80%).

Example 7: Preparation of N-cyclobutylmethyl-6,14-endoethano-7-(2-hydroxy-2-cyclobutyl-2-ethyl)-tetrahydronoripavine (compound (I); R¹ and R²= cyclobutyl)

 494 mg (1 mmol) of the compound of formula (VI) obtained in Example 5 was added to 1.6 g (29 mmol) of KOH dissolved in 5 ml of diethylene glycol at 220 °C under a nitrogen atmosphere. The mixture was stirred for 2 hours
30 and 50 ml of ice-water was added thereto. The solution was saturated with ammonium chloride, and the solid remaining therein was collected, washed with water and recrystallized from ethanol to obtain the title compound (325 mg, 68%).

Example 8: Preparation of N-cyclopropylmethyl-6,14-endoethano-7-(2-hydroxy-2-cyclobutyl-2-ethyl)-tetrahydronororipavine (compound (I); R¹=cyclobutyl and R²=cyclopropyl)

5 The procedure of Example 7 was repeated except for using 480 mg (1 mmol) of the compound obtained in Example 6 instead of the compound obtained in Example 5 to obtain the title compound (316 mg, 68%).

10 **Example 9: Preparation of N-cyclobutylmethyl-6,14-endoethano-7-(2-hydroxy-2-cyclobutyl-2-ethyl)-tetrahydronororipavine hydrochloride**

15 1 ml of 1 M hydrogen chloride in ether was added to 335 mg (0.7 mmol) of the compound of formula (I) obtained in Example 7 dissolved in a mixture of 10 ml of dichloromethane and 5 ml of methanol, and then 14 ml of ether was added thereto to induce precipitation. The precipitate was collected, washed with 5 ml of ether and dried to obtain the title compound (324 mg, 90%).

20 **Example 10: Preparation of N-cyclopropylmethyl-6,14-endoethano-7-(2-hydroxy-2-cyclobutyl-2-ethyl)-tetrahydronororipavine hydrochloride**

25 1 ml of 1 M hydrogen chloride in ether was added to 325 mg (0.7 mmol) of the compound of formula (I) obtained Example 8 dissolved in a mixture of 15 ml of dichloromethane and 5 ml of methanol, and then 14 ml of ether was added thereto to induce precipitation. The precipitate was collected, washed with 10 ml of ether and dried to obtain the title compound (323 mg, 92%).

30 **Test Example 1: Analgesic effect test**

 To measure the analgesic effect of the buprenorphine derivative of the present invention, writhing test based on chemical irritation produced by

intraperitoneal injection of 0.5 ml of 1% aqueous acetic acid into mice was carried out. The number of writhing was recorded for 10 min after the injection. The test compound was injected into the tail vein of each mouse just before the injection in an amount of 5 $\mu\text{g}/10\text{ g}$ body weight. The analgesic effect was evaluated by the concentration at which the number of mice writhing in the test group injected with the test compound is reduced by 50% as compared with that in the control group injected with saline solution, and it is represented in the form of ED_{50} . The results are listed in Table 1.

10

Table 1

Test compound	ED_{50} ($\mu\text{g}/\text{ml}$)
Example 9	22.4
Example 10	11.2
buprenorphine	22.3

As shown in Table 1, the analgesic effects of the compounds of the present invention are either similar to or higher than that of buprenorphine.

15

Test Example 2: Addiction test

The addictiveness of the inventive buprenorphine derivative was examined using test cages whose front wall had a hole of a 1 cm diameter and the opposite wall had a 5 mm-wide vertical opening. The hole was equipped with an infrared sensor interfaced to a computer that recorded nose-poke responses and controlled a two-syringe infusion pump. The vertical opening allowed the test animal extend its tail to the outside of the box.

Before starting the test, the operant level of nose-poking was recorded for each mouse for the whole set of experimental mice for 10 min while its tail was immobilized but no needle was inserted thereto. Based on these pre-test results, mice were grouped in pairs so that both mice of a pair exhibited approximately equal levels of the nose-poke activity. After 1 hour, these pairs

were placed again in the test cages equipped with an opaque partition in front of the hole to prevent nose-poking. One mouse of each pair was allowed to move freely ("active" mouse), and the other was yoked ("passive" mouse). A needle (OD 0.4 mm) was inserted into the lateral tail vein of each mouse of the pair, and the mice were allowed to habituate to the test situation for 5 min. After the habituation period, the opaque partition was removed, and in response to every nose-poke, the test compound or saline solution (for the control group) was administered. Each experiment lasted for 30 min, and afterwards, the mice were returned to their home cages. All mice were tested only once. The number of nose-poke responses (NPR) to the administration of the test compound during the 30 min test period was compared with that observed during the 10 min pre-test period.

The reinforcing effect (R-criterion) of the test compound for each pair of mice was calculated as follow:

$$R = \log (A_T/P_T) - \log (A_{BL}/P_{BL})$$

wherein, A_T and P_T are the total number of the nose-poke response (NPR) of the active mouse and the passive mouse during the 30-min test, respectively, and A_{BL} and P_{BL} are the total number of the nose poke responses of the active mouse and the passive mouse during the 10-min pre-test (baseline), respectively. Thus, the reinforcing effect of the test compound (R) was set by the difference between the log of the ratio between the cumulative number of the nose-poke responses (NPR) of the active and passive mice in a pair during a 30-min period and the log of the same ratio taken without using the test compound. Also, the difference in the NPR of the active and passive mice was calculated (Delta criterion), and the cumulative dose of the self-administered test compound was recorded.

As a quantitative measure of the reinforcing effect of the test compound (N-plus criterion), the percentage of pairs in the group with R higher than the upper confidence limit (95%) of the R-value of the group self-administered with saline was used. As a quantitative measure of the aversive effect of the test compound (N-minus criterion), the percentage of pairs in the group with R

lower than the lower confidence limit (95%) of the R-value of the group self-administered with saline was used. The value of R between the upper and lower confidence limits in a group with the saline self-administration was considered as a neutral reaction (N0).

5 The difference between the test compound and saline self-administration (R-criterion) was statistically analyzed with the nonparametric Kruskal-Wallis ANOVA test followed by Dunn's Multiple Comparisons test for all test compounds used. Nonparametric ANOVA was used because the difference among SDs in populations was very significant (some of the data was not
10 distributed normally). Mann-Whitney test for gradual data and exact Fisher's test for quantitative data (N+/N-/N0) were used wherever between-group pairwise comparisons were needed. Values of ED₅₀ for each test compound were calculated using Litchfield-Wilcoxon method.

15 In accordance with the above method, the addictiveness of the test compounds of Examples 9 and 10 was examined and the results are listed in Table 2.

Table 2

Test compound	Unit ED ₅₀ ^a (μ g/kg/injection)	Optimal unit dose ^b (μ g/kg/injection)	Cumulative dose of self-administration ^c (μ g/kg)
Buprenorphine	1.15	1.92	80
Example 9	3.6	4.29	180
Example 10	4.1	8.7	1,240
a: a unit dose supporting an initiation of self-administration in 50% of mice, calculated by the aid of N+ values. b: as a unit dose corresponding to the maximal values of reinforcing criteria (delta and R), a unit dose supporting an initiation of self-administration in maximal number of mice. c: a dose consumed during self-administration period at the concentration corresponding to the highest R value.			

As shown in Table 2, the compounds of Examples 9 and 10 of the present invention demonstrated higher ED₅₀ and optimal unit doses to initiate i.v. drug taking behavior than those of buprenorphine, and accordingly, the inventive compounds showed lower addictiveness than buprenorphine.

5 In addition, addictive safety index, i.e. the ratio of addictive activity (unit ED₅₀, optimal unit dose or cumulative dose of self-administration) to the analgesic effects of the compounds of Examples 9 and 10 of the present invention was compared with buprenorphine, and the results are listed in Table 3.

10

Table 3

Test compound	ED ₅₀ of Writhing test (μ g/kg, i.v. injection)	Safety index for unit ED ₅₀ (ED ₅₀ of self-administration/ED ₅₀ of Writhing test)	Safety index for OUD (OUD of self-administration/ED ₅₀ of Writhing test)	Safety index for cumulative self-administered dose (cumulative self-administered dose/ED ₅₀ of Writhing test)
Buprenorphine	22.31	0.05	0.086	3.59
Example 9	22.4	0.16	0.19	8.04
Example 10	11.2	0.37	0.78	110.7
* OUD: optimal unit dose				

15 As shown in Table 3, the compounds of Examples 9 and 10 of the present invention are much safer toward addictiveness higher than that of buprenorphine.

Comparative Test Example

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The procedure of Test Example 2 was repeated except for using hydrochloride salts of compounds (Ia) and (Ib) of United States Patent No. 5,849,915 as controls (control 1 and control 2, respectively), the results are

compared with those of the inventive compounds and listed in Table 4.

Table 4

Test compound	Unit ED ₅₀ ^a (ED ₅₀ of buprenorphine /ED ₅₀ of test compound)	Optimal unit dose ^b (dose of self-administration /ED ₅₀ of Writhing test)	cumulative dose of self-administration ^c (cumulative dose of buprenorphine/ED ₅₀ of test compound)
Example 9	0.32	0.45	0.44
Example 10	0.28	0.11	0.06
Control 1	3.3	5.0	5.0
Control 2	1.5	2.4	2.0
a: a unit dose supporting an initiation of self-administration in 50% of mice, calculated by the aid of N+ values. b: as a unit dose corresponding to the maximal values of reinforcing criteria (delta and R), a unit dose supporting an initiation of self-administration in maximal number of mice. c: a dose consumed during self-administration period at the concentration corresponding to the highest R value.			

5

As shown in Table 4, the compounds of Examples 9 and 10 of the present invention exhibited much lower unit ED₅₀, optimal unit doses and cumulative dose of self-administration to buprenorphine than the comparative compounds of the prior art. Thus, the addictiveness of the inventive compounds is extremely low.

10

While the invention has been described with respect to the above specific embodiments, it should be recognized that various modifications and changes may be made and also fall within the scope of the invention as defined by the claims that follow.

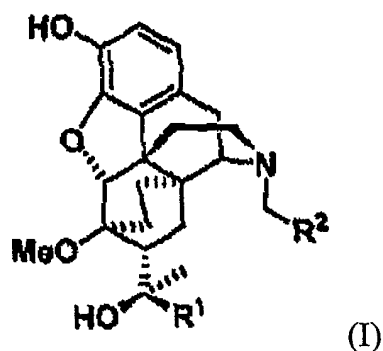
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What is claimed is:

1. A buprenorphine derivative of formula (I) or a pharmaceutically acceptable salt thereof:

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wherein,

R^1 is cyclobutyl; and

R^2 is cyclopropyl or cyclobutyl.

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2. The buprenorphine derivative or the pharmaceutically acceptable salt thereof according to claim 1, wherein R^2 is cyclopropyl.

20

3. An analgesic composition comprising the buprenorphine derivative or the pharmaceutically acceptable salt thereof according to claim 1 as an active ingredient together with a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR2005/002915

A. CLASSIFICATION OF SUBJECT MATTER**IPC7 C07D 489/04**

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7 C07D 489/04

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Korean Patents and applications for inventions since 1975.

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN(CASLINK)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5849915 (Dong Kook Pharmaceutical Company, Ltd..) 15 DEC. 1998, see entire document.	1 - 3



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

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Date of the actual completion of the international search

06 DECEMBER 2005 (06.12.2005)

Date of mailing of the international search report

07 DECEMBER 2005 (07.12.2005)

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/KR2005/002915

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5849915	15-12-1998	CN 1168377 A JP 2938405 B2	24-12-1997 23-08-1999