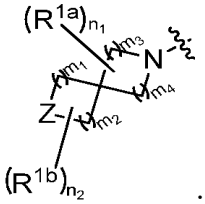


(I)

wherein

R_1 is selected from  ;

m1, m2, m3 and m4 are each independently selected from 0, 1, 2, 3 or 4; m1 and m2 are not both 0; m3 and m4 are not both 0;

n1 and n2 are each independently selected from 0, 1, 2, 3 or 4;

Z is selected from $CR^{z1}R^{z2}$ or NR^{z3};

R^{z1} and R^{z2} are each independently selected from H, F, Cl, Br, I, OH, CF_3, nitro, C_{1-6} alkyl, C_{1-6} alkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, -C(=O)-C_{1-6} alkyl, -$(CH_2)_q$-C(=O)O-C_{1-6} alkyl, -$(CH_2)_q$-$NR^{1e}R^{1f}$, -$(CH_2)_q$-COOH, -$(CH_2)_q$-$CONH_2$, C_{3-8} carbocyclyl or 3- to 8-membered heterocyclyl, wherein the alkyl, the alkoxy, the alkenyl, the alkynyl, the carbocyclyl or the heterocyclyl is optionally further substituted with 0-5 substituents selected from F, Cl, Br, I, OH, CF_3, =O, carboxyl, nitro, cyano, amino, C_{1-6} alkyl, C_{1-6} alkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} carbocyclyl or 3- to 8-membered heterocyclyl, the heterocyclyl contains 1 to 3 heteroatoms optionally selected from N, O or S, and when the heteroatom is selected from S, the heterocyclyl is optionally further S, S=O or $S(=O)_2$;

R^{1e} and R^{1f} are each independently selected from H, C_{1-6} alkyl, C(=O)O-C_{1-6} alkyl, -C(=O)O-$(CH_2)_q$-C_{3-8} carbocyclyl or -C(=O)O-$(CH_2)_q$-3- to 8-membered heterocyclyl, wherein the alkyl, the carbocyclyl or the heterocyclyl is optionally further substituted with 0-5 substituents selected from F, Cl, Br, I, OH, CF_3, cyano, nitro, C_{1-6} alkyl, C_{1-6} alkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} carbocyclyl or 3- to 8-membered heterocyclyl, and the heterocyclyl contains 1 to 3 heteroatoms selected from N, O or S;

or R^{z1} and R^{z2}, together with the carbon atom to which they are attached, form a 3- to 10-membered nitrogen-containing heterocyclic ring, wherein the ring is optionally further substituted with a substituent selected from F, Cl, Br, I, OH, CF_3, cyano, nitro, =O, C_{1-6} alkyl, C_{1-6} alkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} carbocyclyl or 3- to 8-membered heterocyclyl;

R^{1a} and R^{1b} are each independently selected from F, CF_3, NH_2, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl or 3- to 8-membered heterocyclyl, wherein the alkyl, the alkenyl, the alkynyl or the heterocyclyl is optionally further substituted with 0-5 substituents selected from F, Cl, Br, I, OH, CF_3, nitro, cyano, C_{1-6} alkyl, C_{1-6} alkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} carbocyclyl or 3- to 8-membered heterocyclyl, and the heterocyclyl contains 1 to 3 heteroatoms optionally selected from N, O or S;

R^{z3} is independently selected from H, -C(=O)-C_{1-6} alkyl, -C(=O)O-C_{1-6} alkyl, -C(=O)-C_{3-8} carbocyclyl, -C(=O)O-C_{3-8} carbocyclyl, -C(=O)O-(3- to 8-membered heterocyclyl), -$S(=O)_p$-C_{1-6} alkyl, -$S(=O)_p$-C_{3-8} carbocyclyl, -$S(=O)_p$-(3- to 8-membered heterocyclyl), -C(=O)$NR^{1g}R^{1h}$, -S(=O)p-$NR^{1i}R^{1j}$ or 3- to 8-membered heterocyclyl, wherein the alkyl, the carbocyclyl or the heterocyclyl is optionally further substituted with 0-5 substituents selected from F, Cl, Br, I, OH, CF_3, nitro, cyano, amino, C_{1-6} alkyl, C_{1-6} alkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} carbocyclyl or 3- to 8-membered heterocyclyl, and the heterocyclyl contains 1 to 3 heteroatoms optionally selected from N, O or S;

R^{1g}, R^{1h}, $R^{1i'}$ and R^{1j} are each independently selected from H or C_{1-6} alkyl;

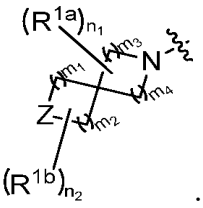
or R^{1g} and R^{1h}, together with the nitrogen atoms to which they are attached, form a 3- to 10-membered heterocyclic ring, wherein the ring is optionally further substituted with a substituent selected from F, Cl, Br, I, OH, CF_3, cyano, nitro, amino, C_{1-6} alkyl, C_{1-6} alkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl or -$S(=O)_p$-C_{1-6} alkyl, and the heterocyclyl contains 1 to 3 heteroatoms selected from N, O or S;

q is selected from 0, 1, 2, 3 or 4;

p is selected from 0, 1 or 2;

a is selected from 0, 1, 2 or 3;

R^4 is independently selected from H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl or -$(CH_2)_q$-C_{3-8} carbocyclyl, wherein the alkyl, the alkenyl, the alkynyl or the carbocyclyl is optionally further substituted with 0-5 substituents selected from F,

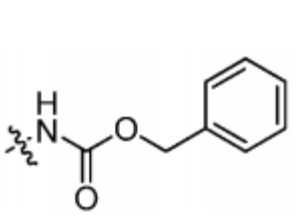
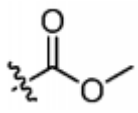
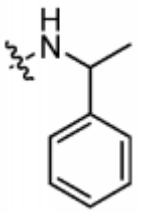
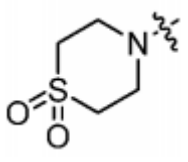
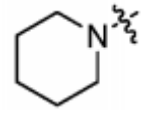
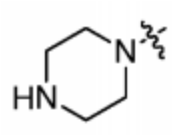
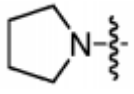
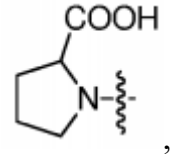
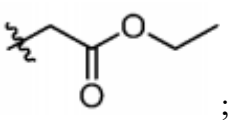
R_1 is selected from  ;

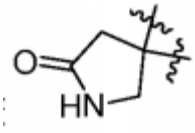
m1, m2, m3 and m4 are each independently selected from 0, 1 or 2; m1 and m2 are not both 0; m3 and m4 are not both 0;

n1 and n2 are each independently selected from 0 or 2;

Z is selected from $CR^{z1}R^{z2}$ or NR^{z3};

R^{1a}、R^{1b} are independently selected from F or NH_2;

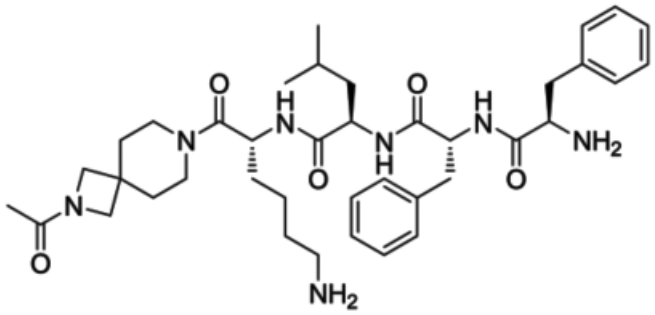
R^{z1} and R^{z2} are each independently selected from H, carboxyl, , , , , , , , , amino, $-CH_2NH_2$ or  ;

or R^{z1} and R^{z2} can, together with the carbon atom to which they are attached, form a lactam  ;

R^{z3} is independently selected from H, -C(=O)-C_{1-4} alkyl, -C(=O)O-C_{1-4} alkyl, -C(=O)-C_{3-6} carbocyclyl, -C(=O)O-C_{3-6} carbocyclyl, -$S(=O)_p$-C_{1-4} alkyl, -$S(=O)_p$-C_{3-6} carbocyclyl, $-C(=O)NR^{1g}R^{1h}$, $-S(=O)_p-NR^{1i}R^{1j}$ or 3- to 6-membered heterocyclyl, wherein the alkyl, the carbocyclyl or the heterocyclyl is optionally further substituted with 0-5 substituents selected from F, Cl, Br, I, OH, CF_3, nitro, cyano, amino, methyl, ethyl, methoxy, ethoxy, cyclopropyl or phenyl, and the heterocyclyl contains 1 to 3 heteroatoms optionally selected from N, O or S;

R^{1g}, R^{1h}, $R^{1i'}$ and R^{1j} are each independently selected from H or C_{1-4} alkyl;

or R^{1g} and R^{1h}, together with the nitrogen atom to which they are attached, form a 4- to 6-membered heterocyclic ring, wherein the ring is optionally further



Compound 1.

In one embodiment of the present invention, an effective dose of the compound is selected from 1 ng-30 mg, 0.01 μg-10 mg, 0.1 μg-1 mg, 1 μg-1000 μg, 10 μg-800 μg, 10 μg-600 μg, 10 μg-400 μg and 10 μg-200 μg, and effective doses of the hydrate, metabolite, solvate, pharmaceutically acceptable salt or eutectic of the compound of the formula, and the composition thereof are converted based on the effective dose of the compound.

In one embodiment of the present invention, the administration form is one or more of single administration, multiple administrations, continuous administration, and target-controlled infusion.

In one embodiment of the present invention, the administration is performed via a route selected from: intravenous injection, intraarterial injection, intramuscular injection, transdermal absorption, buccal absorption, parenteral administration, rectal administration, transbuccal administration, intranasal administration, inhalation, topical delivery, subcutaneous administration, intraadipose administration, intraarticular administration, intraperitoneal administration, or intrathecal administration

In one embodiment of the present invention, the administration is performed via intravenous injection or intranasal administration.

In one embodiment of the present invention, an effective dose for intravenous injection is 40 μg-400 μg or 60 μg-180 μg.

In some embodiments of the present invention, the compound of formula (I) or the stereoisomer, hydrate, metabolite, solvate, pharmaceutically acceptable salt or eutectic thereof, and the composition thereof are administered before the end of surgery.

Within 24 h after the end of surgery, if the subject experienced ≥ 1 episode of vomiting, retching, or nausea and complained of requiring antiemetic treatment, the subject received rescue antiemetic agents specified in the protocol after assessment by the investigator (tropisetron was the preferred rescue antiemetic agent; it was recommended that an initial intravenous dose of 2.5 mg be administered, followed by additional doses as needed, not to exceed 10 mg within 24 h). If tropisetron was insufficiently effective, other agents were used by the investigator in accordance with routine clinical practice.

Within 30 min after the end of surgery, a PCA pump containing morphine hydrochloride injection was initiated. Subjects self-administered analgesia by pressing the PCA pump when experiencing pain. PCA parameter settings: Concentration: 1 mg/ml; continuous infusion: 0 ml/h; PCA bolus of 2 ml per press, with a lockout interval of 10 min. If the patient still complained of pain, an additional dose of morphine hydrochloride injection was administered (a single intravenous dose of 3 mg) after assessment by the investigator.

The occurrence of vomiting and the occurrence and severity of any nausea in the subjects were monitored and recorded within 24 h after the end of surgery. Within 24 h after the end of surgery, any spontaneous nausea, retching, or vomiting symptoms were recorded by the subject, and the severity of nausea was assessed using a visual analogue scale (VAS scale, 0 cm = no nausea, 10 cm = the most severe unbearable nausea). The investigators inquired about and recorded the occurrence of nausea, retching, or vomiting in subjects in the preceding 12 h at 12 ± 1 h and 24 ± 1 h after surgery.

Subject and investigator satisfaction scores for PONV were assessed at 24 ± 1 h after the administration.

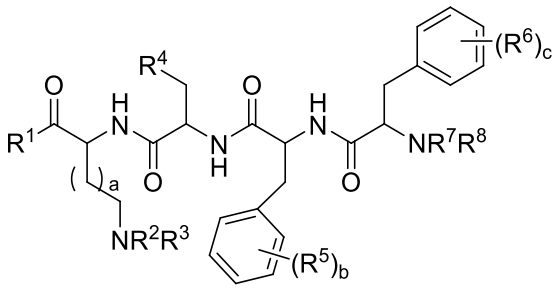
The dosage of rescue antiemetic agents and the cumulative dosage of analgesic agents administered to each subject within 24 h after surgery were recorded.

Follow-up period: From 24 h after the end of surgery to 48 h after the end of surgery

Vital signs, physical examination, 12-lead ECG, laboratory examinations, adverse events, and concomitant medications were collected from subjects. For

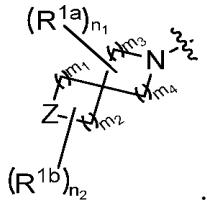
CLAIMS

1. Use of a compound of formula (I) or a stereoisomer, hydrate, metabolite, solvate, pharmaceutically acceptable salt or eutectic thereof, and a composition thereof in the preparation of a drug for preventing postoperation nausea and vomiting or chemotherapy-induced nausea and vomiting:



(I)

characterized in that

R_1 is selected from  ;

m1, m2, m3 and m4 are each independently selected from 0, 1, 2, 3 or 4; m1 and m2 are not both 0; m3 and m4 are not both 0;

n1 and n2 are each independently selected from 0, 1, 2, 3 or 4;

Z is selected from $CR^{z1}R^{z2}$ or NR^{z3};

R^{z1} and R^{z2} are each independently selected from H, F, Cl, Br, I, OH, CF_3, nitro, C_{1-6} alkyl, C_{1-6} alkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, -C(=O)-C_{1-6} alkyl, -$(CH_2)_q$-C(=O)O-C_{1-6} alkyl, -$(CH_2)_q$-$NR^{1e}R^{1f}$, -$(CH_2)_q$-COOH, -$(CH_2)_q$-$CONH_2$, C_{3-8} carbocyclyl or 3- to 8-membered heterocyclyl, wherein the alkyl, the alkoxy, the alkenyl, the alkynyl, the carbocyclyl or the heterocyclyl is optionally further substituted with 0-5 substituents selected from F, Cl, Br, I, OH, CF_3, =O, carboxyl, nitro, cyano, amino, C_{1-6} alkyl, C_{1-6} alkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} carbocyclyl or 3- to 8-membered heterocyclyl, the heterocyclyl contains 1 to 3 heteroatoms optionally selected from N, O or S, and when the heteroatom is selected from S, the heterocyclyl is optionally further S, S=O or $S(=O)_2$;

R^{1e} and R^{1f} are each independently selected from H, C_{1-6} alkyl, $C(=O)O-C_{1-6}$ alkyl, $-C(=O)O-(CH_2)q-C_{3-8}$ carbocyclyl or $-C(=O)O-(CH_2)_q$-3- to 8-membered heterocyclyl, wherein the alkyl, the carbocyclyl or the heterocyclyl is optionally further substituted with 0-5 substituents selected from F, Cl, Br, I, OH, CF_3, cyano, nitro, C_{1-6} alkyl, C_{1-6} alkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} carbocyclyl or 3- to 8-membered heterocyclyl, and the heterocyclyl contains 1 to 3 heteroatoms selected from N, O or S;

or R^{z1} and R^{z2}, together with the carbon atom to which they are attached, form a 3- to 10-membered nitrogen-containing heterocyclic ring, wherein the ring is optionally further substituted with a substituent selected from F, Cl, Br, I, OH, CF_3, cyano, nitro, =O, C_{1-6} alkyl, C_{1-6} alkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} carbocyclyl or 3- to 8-membered heterocyclyl;

R^{1a} and R^{1b} are each independently selected from F, CF_3, NH_2, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl or 3- to 8-membered heterocyclyl, wherein the alkyl, the alkenyl, the alkynyl or the heterocyclyl is optionally further substituted with 0-5 substituents selected from F, Cl, Br, I, OH, CF_3, nitro, cyano, C_{1-6} alkyl, C_{1-6} alkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} carbocyclyl or 3- to 8-membered heterocyclyl, and the heterocyclyl contains 1 to 3 heteroatoms optionally selected from N, O or S;

R^{z3} is independently selected from H, $-C(=O)-C_{1-6}$ alkyl, $-C(=O)O-C_{1-6}$ alkyl, $-C(=O)-C_{3-8}$ carbocyclyl, $-C(=O)O-C_{3-8}$ carbocyclyl, -C(=O)O-(3- to 8-membered heterocyclyl), $-S(=O)_p-C_{1-6}$ alkyl, $-S(=O)_p-C_{3-8}$ carbocyclyl, $-S(=O)_p$-(3- to 8-membered heterocyclyl), $-C(=O)NR^{1g}R^{1h}$, $-S(=O)_p-NR^{1i}R^{1j}$ or 3- to 8-membered heterocyclyl, wherein the alkyl, the carbocyclyl or the heterocyclyl is optionally further substituted with 0-5 substituents selected from F, Cl, Br, I, OH, CF_3, nitro, cyano, amino, C_{1-6} alkyl, C_{1-6} alkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} carbocyclyl or 3- to 8-membered heterocyclyl, and the heterocyclyl contains 1 to 3 heteroatoms optionally selected from N, O or S;

R^{1g}, R^{1h}, $R^{1i'}$ and R^{1j} are each independently selected from H or C_{1-6} alkyl;

or R^{1g} and R^{1h}, together with the nitrogen atoms to which they are attached, form a 3- to 10-membered heterocyclic ring, wherein the ring is optionally further substituted with a substituent selected from F, Cl, Br, I, OH, CF_3, cyano, nitro,

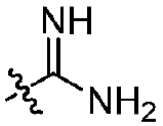
amino, C_{1-6} alkyl, C_{1-6} alkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl or $-S(=O)_p-C_{1-6}$ alkyl, and the heterocyclyl contains 1 to 3 heteroatoms selected from N, O or S;

q is selected from 0, 1, 2, 3 or 4;

p is selected from 0, 1 or 2;

a is selected from 0, 1, 2 or 3;

R^4 is independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl or $-(CH_2)q-C_{3-8}$ carbocyclyl, wherein the alkyl, the alkenyl, the alkynyl or the carbocyclyl is optionally further substituted with 0-5 substituents selected from F, Cl, Br, I, OH, CN, CF_3, NO_2, C_{1-6} alkyl, C_{1-6} alkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} carbocyclyl or 3- to 8-membered heterocyclyl, and the heterocyclyl contains 1 to 3 heteroatoms selected from N, O or S;

R^2, R^3, R^7 and R^8 are each independently selected from H, C_{1-6} alkyl, $-C(=O)O-C_{1-4}$ alkyl, $-C(=O)O-(CH_2)_q-C_{3-8}$ carbocyclyl, $-C(=O)O-(CH_2)_q$-3- to 8-membered heterocyclyl or , wherein the alkyl, the carbocyclyl or the heterocyclyl is optionally further substituted with 0-5 substituents selected from F, Cl, Br, I, OH, CF_3, nitro, cyano, amino, C_{1-6} alkyl, C_{1-6} alkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} carbocyclyl or 3- to 8-membered heterocyclyl, and the heterocyclyl contains 1 to 3 heteroatoms optionally selected from N, O or S;

b is selected from 0, 1, 2, 3, 4 or 5;

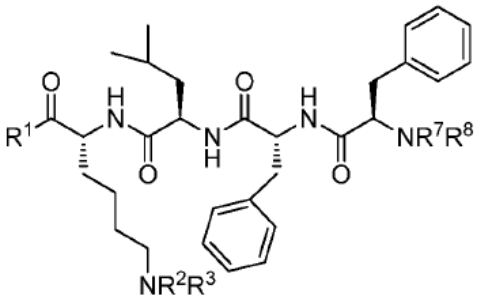
c is selected from 0, 1, 2, 3, 4 or 5;

R^5 and R^6 are each independently selected from F, Cl, Br, I, OH, CN, CF_3, cyano, nitro, C_{1-4} alkyl, $-OR^{5a}$, $-C(O)OR^{5b}$, $-SR^{5c}$, $-S(O)R^{5d}$, $-S(O)_2R^{5e}$ or $-NR^{5f}R^{5g}$;

R^{5a}, R^{5b}, R^{5c}, R^{5d}, R^{5e}, R^{5f} and R^{5g} are each independently selected from H or C1-4 alkyl;

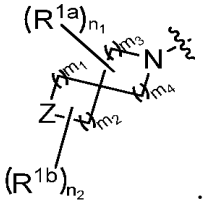
or R^{5f} and R^{5g}, together with the nitrogen atom to which they are attached, form a 5- to 6-membered heterocyclic ring, wherein the heterocyclyl contains 1 to 3 heteroatoms optionally selected from N, O or S.

2. The use according to claim 1, characterized in that the compound is selected from formula (II):



(II)

wherein

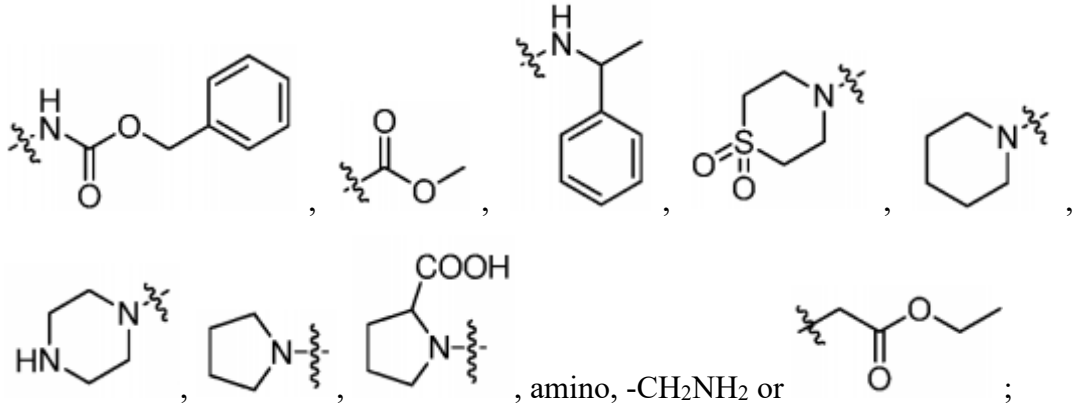
R_1 is selected from  ;

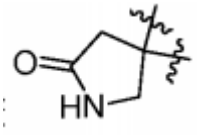
m1, m2, m3 and m4 are each independently selected from 0, 1 or 2; m1 and m2 are not both 0; m3 and m4 are not both 0;

n1 and n2 are each independently selected from 0 or 2;

Z is selected from $CR^{z1}R^{z2}$ or NR^{z3};

R^{1a} and R^{1b} are independently selected from F or NH_2;

R^{z1} and R^{z2} are each independently selected from H, carboxyl, , amino, $-CH_2NH_2$ or ;

or R^{z1} and R^{z2} can, together with the carbon atom to which they are attached, form a lactam  ;

R^{z3} is independently selected from H, $-C(=O)-C_{1-4}$ alkyl, $-C(=O)O-C_{1-4}$ alkyl, $-C(=O)-C_{3-6}$ carbocyclyl, $-C(=O)O-C_{3-6}$ carbocyclyl, $-S(=O)_p-C_{1-4}$ alkyl, $-S(=O)_p-C_{3-6}$ carbocyclyl, $-C(=O)NR^{1g}R^{1h}$, $-S(=O)_p-NR^{1i}R^{1j}$ or 3- to 6-membered heterocyclyl, wherein the alkyl, the carbocyclyl or the heterocyclyl is optionally

further substituted with 0-5 substituents selected from F, Cl, Br, I, OH, CF_3, nitro, cyano, amino, methyl, ethyl, methoxy, ethoxy, cyclopropyl or phenyl, and the heterocyclyl contains 1 to 3 heteroatoms optionally selected from N, O or S;

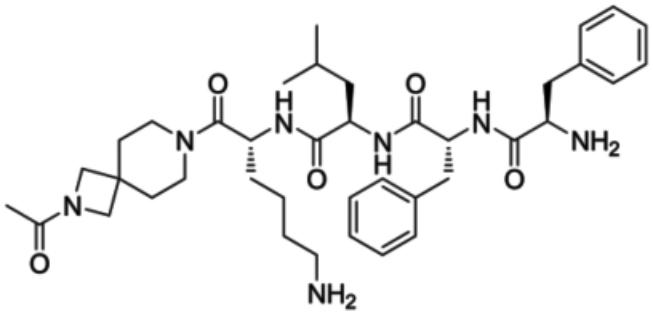
R^{1g}, R^{1h}, $R^{1i'}$ and R^{1j} are each independently selected from H or C_{1-4} alkyl;

or R^{1g} and R^{1h}, together with the nitrogen atom to which they are attached, form a 4- to 6-membered heterocyclic ring, wherein the ring is optionally further substituted with a substituent selected from F, CF_3, methyl, methoxy or $-S(=O)_p-C_{1-4}$ alkyl, and the heterocyclyl contains 1 to 3 heteroatoms selected from N, O or S;

p is selected from 2;

R^2, R^3, R^7 and R^8 are each independently selected from H, methyl or C(=O)O-tert-butyl.

3. The use according to claim 2, characterized in that the compound of formula (II) is selected from:



Compound 1.

4. The use according to claim 3, characterized in that the pharmaceutically acceptable salt is selected from propionate, mesylate, acetate, citrate, D-tartrate, besylate, phosphate, aspartate, L-tartrate, maleate, fumarate, benzoate, lactate, hydrochloride, formate, hydrobromide, sulphate, nitrate, phosphate, trifluoroacetate, succinate, mandelate, malonate, malate, 2-hydroxypropionate, oxalate, glycolate, salicylate, citrate, glutamate, cinnamate, p-toluenesulphonate, benzenesulphonate, ethanesulphonate or triflate.

5. The use according to claim 4, characterized in that an administration form is one or more of single administration, multiple administrations, continuous administration, and target-controlled infusion.

6. The use according to claim 4, characterized in that a route of administration is selected from oral administration, injection, infusion, transdermal absorption, buccal absorption, parenteral administration, rectal administration, transbuccal administration, intranasal administration, inhalation, topical delivery, subcutaneous administration, intraadipose administration, intraarticular administration, intraperitoneal administration or intrathecal administration; preferably intravenous injection, intravenous infusion, intraarterial injection, intramuscular injection, subcutaneous injection, intraarticular injection, intraperitoneal injection, intrathecal injection or intranasal administration.

7. The use according to claim 6, characterized in that the compound of formula (I) or the stereoisomer, hydrate, metabolite, solvate, pharmaceutically acceptable salt or eutectic thereof, and the composition thereof are administered before the end of surgery.

8. The use according to any one of claims 1-7, characterized by further comprising a second drug, wherein the second drug is selected from one or more of antiemetic agents or analgesic agents.

9. The use according to claim 8, characterized in that

the antiemetic agent is selected from tropisetron, ondansetron, granisetron, dolasetron, azasetron, ramosetron, palonosetron, aprepitant, fosaprepitant, rolapitant, casopitant, vetipitant, dimenhydrinate, promethazine, scopolamine, gabapentin, pregabalin, midazolam and ephedrine;

the analgesic agent is selected from morphine, fentanyl, sufentanil, oxycodone, hydromorphone, pethidine, butorphanol, nalbuphine, dezocine, pentazocine, buprenorphine, flurbiprofen axetil, ketorolac, lornoxicam, diclofenac, parecoxib, celecoxib, paracetamol, tramadol, dexmedetomidine, ketamine, esketamine, gabapentin and pregabalin.

10. The use according to any one of claims 5-9, characterized in that an effective dose of the compound is selected from 1 ng-30 mg, 0.01 **μg-10 mg**, 0.1

μg-1 mg, 1 **μg-1000 μg**, 10 **μg-800 μg**, 10 **μg-600 μg**, 10 **μg-400 μg** and 10 **μg-200 μg**, and effective doses of the hydrate, metabolite, solvate, pharmaceutically acceptable salt or eutectic of the compound, and the composition thereof are converted based on the effective dose of the compound.

11. The use according to claim 10, characterized in that an effective dose for intravenous injection is selected from 40 **μg-400 μg** and 60 **μg-180 μg**.