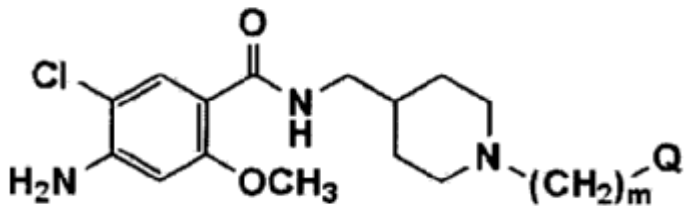
Claims

[Claim 1] A compound represented by formula 1:
[Formula 1]



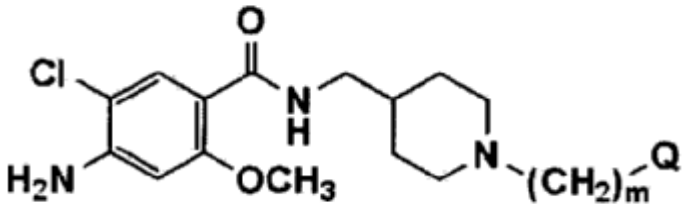
wherein m represents an integer of 1 to 10; and Q represents a heteroaromatic ring or phenyl, wherein the hetero~~r~~aromatic ring is unsubstituted or substituted with a substituent selected from the group consisting of alkyl, alkoxy, hydroxy, cyano, nitro and halogen and the ~~or~~ phenyl is ~~independently~~ substituted ~~by 0, 1, 2, or 3~~with a substituent~~s~~ selected from the group consisting of alkyl, alkoxy, hydroxy, cyano, nitro and halogen; or a pharmaceutically acceptable salt thereof.

[Claim 2] The compound of formula 1 or a pharmaceutically acceptable salt thereof according to claim 1, wherein m represents an integer of 1 to 5; and Q represents a heteroaromatic ring or phenyl wherein the hetero~~r~~aromatic ring is unsubstituted or substituted with a substituent selected from the group consisting of C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy and halogen, ~~or~~and the phenyl is ~~independently~~ substituted ~~by 0, 1, 2 or 3~~with a substituent~~s~~ selected from the group consisting of C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy and halogen, and wherein the heteroaromatic ring being a C_1-C_{12} aromatic ring or C_1-C_{12} bicyclic aromatic ring ~~independently~~ contains 1 to 4 hetero atoms selected from N, O or S~~;~~.

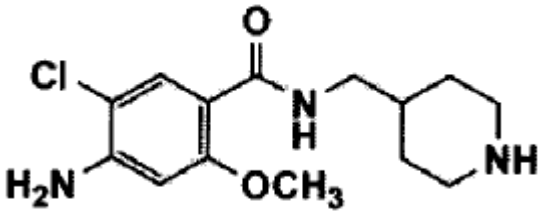
[Claim 3] The compound of formula 1 or a pharmaceutically acceptable salt thereof according to claim 1, wherein the compound of formula 1 or a pharmaceutically acceptable salt thereof is a compound selected from the group consisting of the following compounds:
(1) N-((1-(3-(1,2,4-triazol-1-yl)propyl)piperidin-4-yl)methyl)-4-amino-5-chloro-2-methoxybenzamide,
(2) N-((1-(3-(tetrazol-1-yl)propyl)piperidin-4-yl)methyl)-4-amino-5 -chloro-2-methoxybenzamide,
(3) N-((1-(3-(indol-1-yl)propyl)piperidin-4-yl)methyl)-4-amino-5 -chloro-2-methoxybenzamide,
(4) N-((1-(3-(2-methylimidazol-1-yl)propyl)piperidin-4-yl)methyl)-4 -amino-5-chloro-2-methoxybenzamide,
(5) N-((1-(5-(indol-1-yl)pentyl)piperidin-4-yl)methyl)-4-amino-5 -chloro-2-methoxybenzamide,
(6) N-((1-(5-(1,2,3-triazol-1-yl)pentyl)piperidin-4-yl)methyl)-4-amino -5-chloro-2-methoxybenzamide,
(7) N-((1-(3-(1,2,3-triazol-1-yl)propyl)piperidin-4-yl)methyl)-4-amino -5-chloro-2-methoxybenzamide,
(8) N-((1-(3-(1,2,3-triazol-2-yl)propyl)piperidin-4-yl)methyl)-4-amino -5-chloro-2-methoxybenzamide,
(9) N-((1-(pyridin-3-ylmethyl)piperidin-4-yl)methyl)-4-amino-5-chloro -2-methoxybenzamide,
(10) N-((1-((1-methylindol-3-yl)methyl)piperidin-4-yl)methyl)-4-amino -5-chloro-2-methoxybenzamide,
(11) N-((1-(imidazol-2-ylmethyl)piperidin-4-yl)methyl)-4-amino-5 -chloro-2-methoxybenzamide,
(12) N-((1-((1-methylpyrrol-2-yl)methyl)piperidin-4-yl)methyl)-4-amino -5-chloro-2-methoxybenzamide,
(13) N-((1-(4-fluorobenzyl)piperidin-4-yl)methyl)-4-amino-5-chloro-2 -methoxybenzamide,
(14) N-((1-(4-hydroxybenzyl)piperidin-4-yl)methyl)-4-amino-5-chloro-2 -methoxybenzamide,

(15) N-((1-(2-(indol-3-yl)ethyl)piperidin-4-yl)methyl)-4-amino-5 -chloro-2-methoxybenzamide,
(16) N-((1-(3-(tetrazol-1-yl)propyl)piperidin-4-yl)methyl)-4-amino-5 -chloro-2-methoxybenzamide hydrochloride,
(17) N-((1-(5-(1,2,3-triazol-1-yl)pentyl)piperidin-4-yl)methyl)-4 -amino-5-chloro-2-methoxybenzamide hydrochloride,
(18) N-((1-(3-(1,2,3-triazol-1-yl)propyl)piperidin-4-yl)methyl)-4 -amino-5-chloro-2-methoxybenzamide hydrochloride,
(19) N-((1-((1-methylindol-3-yl)methyl)piperidin-4-yl)methyl)-4-amino -5-chloro-2-methoxybenzamide hydrochloride,
(20) N-((1-(4-fluorobenzyl)piperidin-4-yl)methyl)-4-amino-5-chloro-2 -methoxybenzamide hydrochloride,
(21) N-((1-(4-hydroxybenzyl)piperidin-4-yl)methyl)-4-amino-5-chloro-2 -methoxybenzamide hydrochloride, and a pharmaceutically acceptable salt thereof.

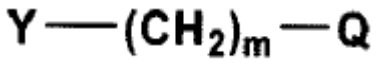
[Claim 4] A method for preparing a compound of formula 1 or a pharmaceutically acceptable salt thereof, comprising reacting a compound of formula 2 or a pharmaceutically acceptable salt thereof with a compound of formula 3 in the presence of a base to introduce the compound of formula 3 at an amine of the 1-position of the piperidine ring of the compound of formula 2 or the pharmaceutically acceptable salt thereof, thereby preparing the compound of formula 1.
[Formula 1]



[Formula 2]



[Formula 3]

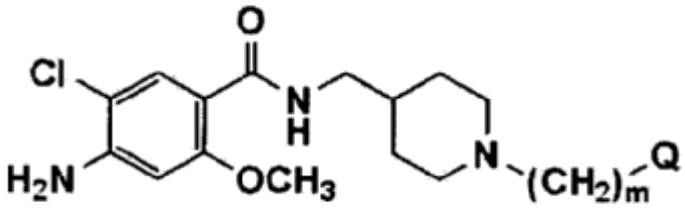


wherein the base is selected from potassium carbonate and potassium iodide, triethylamine or diisopropylethylamine, and wherein m and Q are as defined in claim 1, and Y represents a halogen atom or C_1-C_4 alkylsulfonate.

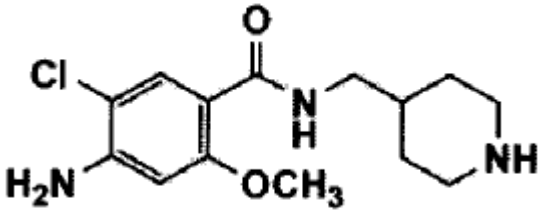
~~[Claim 5] The method according to claim 4, wherein the base is selected from potassium carbonate, potassium iodide, triethylamine , diisopropylethylamine and their mixture.~~

[Claim ~~6~~5] A method for preparing a compound of formula 1 or a pharmaceutically acceptable salt thereof, comprising reacting a compound of formula 2 or a pharmaceutically acceptable salt thereof with a compound of formula 11 in the presence of a reducing agent to prepare the compound of formula 1.

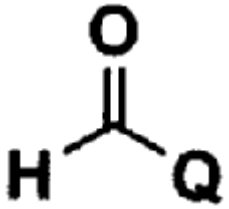
[Formula 1]



[Formula 2]



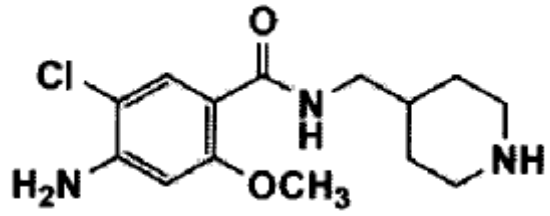
[Formula 11]



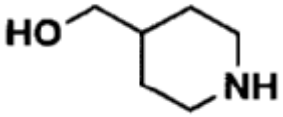
wherein the reducing agent is sodium cyanoborohydride and acetic acid, or sodium borohydride, and
wherein Q is as defined in claim 1, and m represents an integer of 1.

~~[Claim 7] The method according to claim 6, wherein the reducing agent is sodium cyanoborohydride and acetic acid, or sodium borohydride.~~

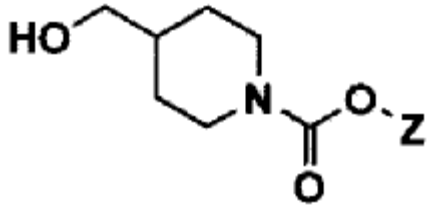
[Claim ~~8~~6] The method according to claim 4 or ~~6~~5, wherein the compound of formula 2 or the pharmaceutically acceptable salt thereof is prepared by:
(1) reacting a compound of formula 4 with an amine protecting group-introducing reagent to introduce an amine protecting group at an amine of the 1-position of the piperidine ring of the compound of formula 4, thereby obtaining a compound of formula 5;
(2) reacting hydroxy of the compound of formula 5 with N-bromosuccinimide and carbon tetrabromide, or with C_1-C_4 alkyl sulfonyl halide in the presence of a base to obtain a compound of formula 6;
(3) reacting a substituent Y of the compound of formula 6 with sodium azide to obtain a compound of formula 7;
(4) reducing the azido substituent of the compound of formula 7 into an amine in the presence of a reducing agent to obtain a compound of formula 8;
(5) reacting the compound of formula 8 with a compound of formula 9 in the presence of an amide bond formation-inducing reagent to obtain a compound of formula 10; and
(6) deprotecting the amine protecting group of the piperidine ring of the compound of formula 10 in the presence of a base or acid.
[Formula 2]



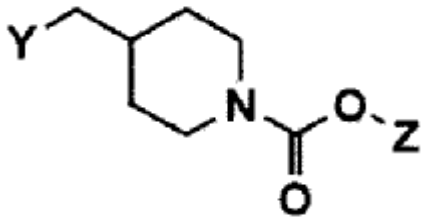
[Formula 4]



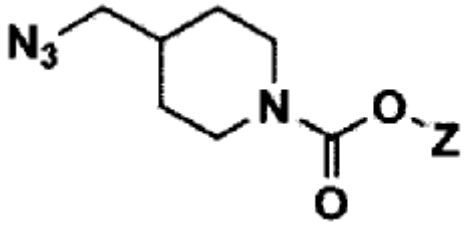
[Formula 5]



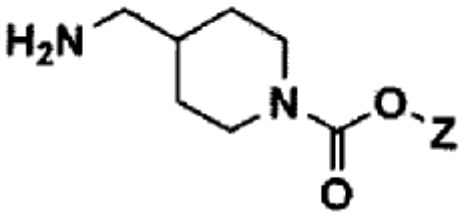
[Formula 6]



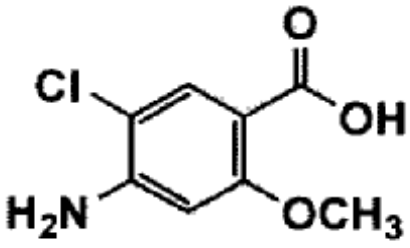
[Formula 7]



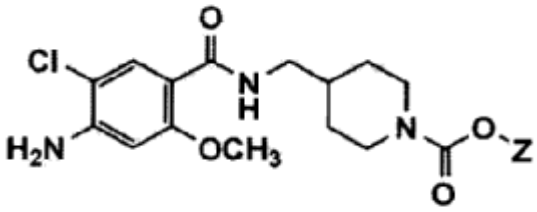
[Formula 8]



[Formula 9]



[Formula 10]



wherein the amine protecting group-introducing reagent of Step (1) is di-t-butyl dicarbonate or ethyl chloroformate in the presence of a triethylamine,
wherein the base of Step (2) is triethylamine or diisopropylethylamine,
wherein the reducing agent of Step (4) is triphenylphosphine or lithium aluminum hydride,
wherein the amide bond formation-inducing reagent of Step (5) is selected from N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride and 1-hydroxybenzotriazole in the presence of a base selected from triethylamine or diisopropylethylamine, ethyl chloroformate in the presence of a base selected from triethylamine or diisopropylethylamine, or carbodiimidazole in the absence of a base,
wherein the base or acid of Step (6) is selected from hydrochloric acid, trifluoroacetic acid or potassium hydroxide, and
wherein Y represents a halogen atom or C_1-C_4 alkylsulfonate, and Z represents C_1-C_4 alkyl.

~~[Claim 9] The method according to claim 8, wherein the amine protecting group-introducing reagent of Step (1) is di-t-butyl dicarbonate or ethyl chloroformate in the presence of a tertiary amine base.~~

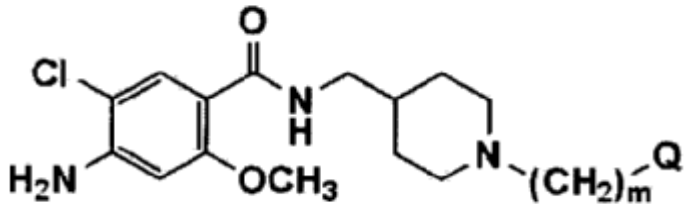
[Claim ~~10~~7] The method according to claim ~~8~~6, wherein the C_1-C_4 alkyl sulfonyl halide of Step (2) is methane sulfonyl chloride, methane sulfonyl bromide or methane sulfonyl fluoride.

~~[Claim 11] The method according to claim 8, wherein the reducing agent of Step (4) is triphenylphosphine or lithium aluminum hydride.~~

~~[Claim 12] The method according to claim 8, wherein the amide bond formation-inducing reagent of Step (5) is selected from N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride and 1-hydroxybenzotriazole in the presence of a base, ethyl chloroformate in the presence of a base, or carbodiimidazole in the absence of a base.~~

~~[Claim 13] The method according to claim 8, wherein the base or acid of Step (6) is selected from hydrochloric acid, trifluoroacetic acid or potassium hydroxide.~~

[Claim ~~14~~8] A 5-HT_4 receptor agonist comprising a compound of formula 1:
[Formula 1]



wherein m represents an integer of 1 to 10; and Q represents a heteroaromatic ring or phenyl, wherein the hetero~~r~~aromatic ring is unsubstituted or substituted with a substituent selected from the group consisting of alkyl, alkoxy, hydroxy, cyano, nitro and halogen and the~~or~~ phenyl is ~~independently~~ substituted ~~by 0, 1, 2, or 3~~with a substituent~~s~~ selected from the group consisting of alkyl, alkoxy, hydroxy, cyano, nitro and halogen, and wherein the 5-HT_4 receptor agonist effective in the prevention or treatment of a disease selected from gastroesophageal reflux disease, gastrointestinal disease, gastric motility disorder, non-ulcer dyspepsia, functional dyspepsia, irritable bowel syndrome (IBS), constipation, dyspepsia, esophagitis, gastroesophageal disease, nausea, central nervous system disease, Alzheimer's disease, cognitive impairment, emesis, migraine, neurological disease, pain, cardiovascular disorder, cardiac failure, cardiac arrhythmia, diabetes or apnea syndrome; or a pharmaceutically acceptable salt thereof, as an active ingredient.

[Claim ~~15~~9] The agonist according to claim ~~14~~8, wherein m represents an integer of 1 to 5; and Q represents a heteroaromatic ring or phenyl wherein the hetero~~r~~aromatic ring is unsubstituted or substituted with a substituent selected from the group consisting of C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy and halogen ~~or~~and the phenyl is ~~independently~~ substituted ~~by 0, 1, 2 or 3~~with a substituent~~s~~ selected from the group consisting of C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy and halogen, and wherein the heteroaromatic ring being a C_1-C_{12} aromatic ring or C_1-C_{12} bicyclic aromatic ring ~~independently~~ contains 1 to 4 hetero atoms selected from N, O or S.

[Claim ~~16~~10] The agonist according to claim ~~14~~8, wherein the compound of formula 1 or a pharmaceutically acceptable salt thereof is a compound selected from the group consisting of the following compounds:
(1) N-((1-(3-(1,2,4-triazol-1-yl)propyl)piperidin-4-yl)methyl)-4-amino-5-chloro-2-methoxybenzamide,
(2) N-((1-(3-(tetrazol-1-yl)propyl)piperidin-4-yl)methyl)-4-amino- 5-chloro-2-methoxybenzamide,
(3) N-((1-(3-(indol-1-yl)propyl)piperidin-4-yl)methyl)-4-amino- 5-chloro-2-methoxybenzamide,
(4) N-((1-(3-(2-methylimidazol-1-yl)propyl)piperidin-4-yl)methyl)- 4-amino-5-chloro-2-methoxybenzamide,
(5) N-((1-(5-(indol-1-yl)pentyl)piperidin-4-yl)methyl)-4-amino- 5-chloro-2-methoxybenzamide,
(6) N-((1-(5-(1,2,3-triazol-1-yl)pentyl)piperidin-4-yl)methyl)-4-amino-5-chloro-2-methoxybenzamide,
(7) N-((1-(3-(1,2,3-triazol-1-yl)propyl)piperidin-4-yl)methyl)-4-amino-5-chloro-2-methoxybenzamide,
(8) N-((1-(3-(1,2,3-triazol-2-yl)propyl)piperidin-4-yl)methyl)-4-amino-5-chloro-2-methoxybenzamide,
(9) N-((1-(pyridin-3-ylmethyl)piperidin-4-yl)methyl)-4-amino-5-chloro -2-methoxybenzamide,
(10) N-((1-((1-methylindol-3-yl)methyl)piperidin-4-yl)methyl)-4-amino -5-chloro-2-methoxybenzamide,
(11) N-((1-(imidazol-2-ylmethyl)piperidin-4-yl)methyl)-4-amino- 5-chloro-2-methoxybenzamide,
(12) N-((1-((1-methylpyrrol-2-yl)methyl)piperidin-4-yl)methyl)-4-amino-5-chloro-2-methoxybenzamide,
(13) N-((1-(4-fluorobenzyl)piperidin-4-yl)methyl)-4-amino-5-chloro- 2-methoxybenzamide,
(14) N-((1-(4-hydroxybenzyl)piperidin-4-yl)methyl)-4-amino-5-chloro- 2-methoxybenzamide,

(15) N-((1-(2-(indol-3-yl)ethyl)piperidin-4-yl)methyl)-4-amino- 5-chloro-2-methoxybenzamide,
(16) N-((1-(3-(tetrazol-1-yl)propyl)piperidin-4-yl)methyl)-4-amino- 5-chloro-2-methoxybenzamide hydrochloride,
(17) N-((1-(5-(1,2,3-triazol-1-yl)pentyl)piperidin-4-yl)methyl)- 4-amino-5-chloro-2-methoxybenzamide hydrochloride,
(18) N-((1-(3-(1,2,3-triazol-1-yl)propyl)piperidin-4-yl)methyl)- 4 -amino-5-chloro-2-methoxybenzamide hydrochloride,
(19) N-((1-((1-methylindol-3-yl)methyl)piperidin-4-yl)methyl)-4- amino -5-chloro-2-methoxybenzamide hydrochloride,
(20) N-((1-(4-fluorobenzyl)piperidin-4-yl)methyl)-4-amino-5-chloro -2 -methoxybenzamide hydrochloride,
(21) N-((1-(4-hydroxybenzyl)piperidin-4-yl)methyl)-4-amino-5-chloro -2 -methoxybenzamide hydrochloride and a pharmaceutically acceptable salt thereof.

~~[Claim 17] The agonist according to any one of claims 14 to 16, wherein the 5-HT_4 receptor agonist is a composition for the prevention or treatment of a disease selected from gastroesophageal reflux disease, gastrointestinal disease, gastric motility disorder, non-ulcer dyspepsia, functional dyspepsia, irritable bowel syndrome (IBS), constipation, dyspepsia, esophagitis, gastroesophageal disease, nausea, central nervous system disease, Alzheimer's disease, cognitive impairment, emesis, migraine, neurological disease, pain, cardiovascular disorder, cardiac failure, cardiac arrhythmia, diabetes or apnea syndrome.~~

~~[Claim 18] A method for the prevention, treatment or alleviation of a disease due to attenuated efficacy of a 5-HT_4 receptor, comprising administering a 5-HT_4 receptor agonist containing a compound of formula 1 of any one of claims 1 to 3 or a pharmaceutically acceptable salt thereof as an active ingredient to a mammal including a human in need of 5-HT_4 receptor agonistic effects.~~

~~[Claim 19] The method according to claim 18, wherein the 5-HT_4 receptor agonist is a composition for the prevention or treatment of a disease selected from gastroesophageal reflux disease, gastrointestinal disease, gastric motility disorder, non-ulcer dyspepsia, functional dyspepsia, irritable bowel syndrome (IBS), constipation, dyspepsia, esophagitis, gastroesophageal disease, nausea, central nervous system disease, Alzheimer's disease, cognitive impairment, emesis, migraine, neurological disease, pain, cardiovascular disorder, cardiac failure, cardiac arrhythmia, diabetes or apnea syndrome.~~