Title: ALKYLCARB AMOYL NAPHTHALENLOXY-OCTENOLYHYDROXYAMIDE DERIVATIVES HAVING INHIBITORY ACTIVITY AGAINST HISTONE DEACETYLASE AND PREPARATION THEREOF

Abstract: This invention discloses a novel alkylcarbamoyl naphthalenloxy octenolhydroxyamide derivative of formula (1) useful for inhibiting the enzyme activity of histone deacetylase, which leads to effective suppression of the cancer cell proliferation, a method for preparing same and a pharmaceutical composition comprising same.
ALKYLCARBAMOYL NAPHTHALENYLOXY-
OCTENOYLHYDROXYAMIDE DERIVATIVES HAVING
INHIBITORY ACTIVITY AGAINST HISTONE DEACETYLASE AND
PREPARATION THEREOF

FIELD OF THE INVENTION

The present invention relates to a novel alkylcarbamoyl
naphthalenyloxyoctenoyl hydroxyamide derivative, a method for preparing
same and an anticancer composition comprising same.

BACKGROUND OF THE INVENTION

Histones associate with DNAs in the nuclei of eukaryotic cells as basic
proteins and are subject to reversible acetylation at the amino group of the
lysine residue. The reversible acetylation is involved in the formation of
chromatin of a higher order structure, the cell division cycle and ultimately
the gene expression, and can be regulated by the dynamic balance established
between the opposing activities of histone acetyl transferases (HATs) and
histone deacetylases (HDACs): means enzymes neutralize or restore the
positive charges of lysine residues (e.g., 4 lysine residues in H4) by
acetylation/deacetylation to regulate the gene transcriptional level.

HDACs play an important role in cell cancerization or differentiation
and their expression is enhanced under conditions such as hypoxia, lowered
glucose, and cell cancerization, to inhibit the expression of cell proliferation
inhibitors. That is, histone deacetylation by HDAC causes cell proliferation,
while hyperacetylation of histone facilitates the inhibition of cell proliferation
and cell differentiation. Therefore, when HDACs are inhibited, cell
proliferation and angiogenesis can be controlled.

Abnormal histone deacetylation has been reported to cause acute
Zelent A. et. al. Oncogene 20: 7186, 2001). Specifically, abnormality in the
regulation of HDAC activity leads to oncoprotein's transcriptional
suppression and the formation of abnormal chromatin structures, which after causes normal cells to become cancer. Accordingly, HDAC has been one of the targets for the study of anticancer drugs as well as gene expression inhibitor and there have been attempts to develop ECDAC inhibitors as anticancer drugs.

Recent anticancer drug studies through chromatin modeling have shown that HDAC inhibitors such as suberoylanilide hydroxamic acid (SAHA) or apicidin inhibit the proliferation of cancer cells and induce cell differentiation (Munster P. N. et al., Cancer research 61: 8492, 2001; Han J. W. et. al. Cancer research 60: 6068, 2000).

Another HDAC inhibitor, n-butyrate was reported to be useful for the treatment of large intestine cancer. But it has to be used in such a high concentration in the order of milimolar (mM) that it disturbs the functions of other enzymes in cells, cytoskeleton, cell membrane, etc. Trichostatin A (TSA) which enhances the differentiation and suppresses the proliferation of Friend murine erythroleukemia cells has been reported to inhibit HDAC (Yoshida M. et al., Cancer research 47: 3688, 1987; Yoshida M. & Beppu T. Exp Cell Res. Ill: 122, 1988; Yoshida M. et al., J of Biol. Chem. 265: 17174, 1990).

Therefore, there has been a need for developing an improved HDAC inhibitor. The present inventors have unexpectedly found that a novel alkylcarbamoyl naphthalenloxyoctenoyl hydroxyamide derivative is an efficient inhibitor against cell proliferation which can be advantageously used for treating cancer.

**SUMMARY OF THE INVENTION**

It is an object of the present invention to provide a novel compound which efficiently inhibits the activity of histone deacetylases, thereby suppressing the proliferation of tumor cells, and a method for preparing same.

It is another object of the present invention to provide a pharmaceutical composition comprising the inventive compound as an active ingredient for preventing or treating cancers.
It is still another object of the present invention to provide a pharmaceutical composition comprising the inventive compound as an active ingredient for inhibition of the histone deacetylase activity.

In accordance with one aspect of the present invention, there is provided an alkylcarbamoyl naphthalenyloxyoctenoyl hydroxyamide derivative of formula (1) or a pharmaceutically acceptable salt thereof:

\[
\text{CONOH} \quad \text{(1)}
\]

wherein:
- \( R_1 \) is hydrogen or \( \text{C}_3 \)-alkyl;
- \( R_2 \) is \( \text{C}_6 \)-alkyl optionally having one or more substituents selected from the group consisting of di\( \text{C}_3 \)-alkylamino, oxopyrrolidinyl, pyrrolidinyl, piperidinyl, morpholinyl, \( \text{C}_3 \)-alkylpiperazinyl, cyano, hydroxy, imidazolyl, methoxy, tetrahydrofuran, \( \text{C}_{3-8} \) cycloalkenyl, and thiophenyl; \( \text{C}_{1-6} \) alkyl substituted with hydroxyphenyl, fluorophenyl, di\( \text{C}_{1-3} \) alkyl amino phenyl, methoxyphenyl and trifluoromethoxyphenyl; pyrrolidine substituted with \( \text{C}_{1-3} \) alkyl, \( \text{C}_{3-8} \) cycloalkyl, \( \text{C}_{3-8} \) cycloalkyl \( \text{C}_3 \)-alkyl, benzyl or \( \text{C}_{3-8} \) cycloalkylcarbonyl; piperidine substituted with \( \text{C}_{3-8} \) cycloalkyl or \( \text{C}_{1-6} \) alkyl; furan; pyridine substituted with (di\( \text{C}_{1-3} \) alkyl amino) \( \text{C}_{1-6} \) alkyl amino, methoxy, di\( \text{C}_{1-3} \) alkyl amino, morpholino \( \text{C}_3 \)-alkylamino, or \( \text{C}_3 \)-alkylpiperazinyl; or \( \text{C}_{3-8} \) cycloalkyl; or

\( R_1 \) and \( R_2 \) may optionally form a morpholinyl, piperidinyl or piperazinyl ring together with the nitrogen atom to which they are bonded.

In accordance with another aspect of the present invention, there is provided a method for preparing the compound of formula (1).

In accordance with still another aspect of the present invention, there is provided an anti-cancer composition and an inhibitor of histone deacetylase
activity comprising the compound of formula (1) or a pharmaceutically acceptable salt thereof as an active ingredient.

DETAILED DESCRIPTION OF THE INVENTION

Representative examples of preferred compounds as alkylcarbamoyl naphthalenylxoyoctenoyl hydroxyamide derivatives of formula (1) include:

(E)-N8-hydroxy-N1, N1-dimethyl-2-((naphthalen-1-yloxy)methyl)octenediamide,
(E)-N1-(2-(dimethylamino)ethyl)-N8-hydroxy-2-((naphthalen-1-yloxy)methyl)octenediamide,
(E)-N1-(2-(diethylamino)ethyl)-N8-hydroxy-N1-methyl-2-((naphthalene-1-yloxy)methyl)octenediamide,
(E)-N1-(2-(diethylamino)ethyl)-N8-hydroxy-2-((naphthalene-1-yloxy)methyl)octenediamide,
(E)-N8-hydroxy-2-((naphthalen-1-yloxy)methyl)-N1-(2-(pyrrolidin-1-yl)ethyl)octenediamide,
(E)-N1-(2-(diethylamino)ethyl)-N8-hydroxy-N1-methyl-2-((naphthalene-1-yloxy)methyl)octenediamide,
(E)-N8-hydroxy-2-((naphthalen-1-yloxy)methyl)octenediamide,
(E)-N8-hydroxy-2-((naphthalen-1-yloxy)methyl)-N1-(2-(piperidin-1-yl)ethyl)octenediamide,
(E)-N1-(2-(4-methylpiperazin-1-yl)-2-((naphthalene-1-yloxy)methyl)octenediamide,
(E)-N8-hydroxy-8-(4-methylpiperazin-1-yl)-7-((naphthalen-1-yloxy)methyl)-8-oxoocteneamide,
(E)-N8-hydroxy-N1-(2-(4-methylpiperazin-1-yl)ethyl)-2-((naphthalen-1-yloxy)methyl)octenediamide,
(E)-N1-(cyanomethyl)-N8-hydroxy-N1-methyl-2-((naphthalen-1-yloxy)methyl)octenediamide,
(E)-N8-hydroxy-N1-(2-hydroxyethy I)-N1-methyl-2-((naphthalen-1-yloxy)methyl)octenediamide,
(E)-N8-hydroxy-N1-methyl-N1-(1-methylpyrrolidin-3-yl)-2-((naphthalen-1-yloxy)methyl)octenediamide,
(E)-N₁-(3-(dimethylamino)propyl)-N₈-hydroxy-2-((naphthalen-1-yloxy)methyl)octenediamide,
(E)-N-hydroxy-8-morpholino-7-((naphthalen-1-yloxy)methyl)-8-oxoocteneamide,
(E)-N₈-hydroxy-N₁-(6-(4-methylpiperazin-1-yl)pyridin-3-yl)-2-((naphthalen-1-yloxy)methyl)octenediamide,
(E)-N₁-(6-(2-morpholinoethylamino)pyridin-3-yl)-N₈-hydroxy-2-((naphthalen-1-yloxy)methyl)octenediamide,
(E)-N₁-(6-(dimethylamino)pyridin-3-yl)-N₈-hydroxy-2-((naphthalen-1-yloxy)methyl)octenediamide,
(E)-N₁-(6-(2-(dimethylamino)ethylamino)pyridin-3-yl)-N₈-hydroxy-2-((naphthalen-1-yloxy)methyl)octenediamide,
(E)-N₁-(6-methoxypyridin-3-yl)-N₈-hydroxy-2-((naphthalen-1-yloxy)methyl)octenediamide,
(E)-N₁-(3-(1H-imidazol-1-yl)pro pyl)-N₈-hydroxy-2-((naphthalen-1-yloxy)methyl)octenediamide,
(E)-N₈-hydroxy-N₁-(4-hydroxyphenetyl)-2-((naphthalen-1-yloxy)methyl)-2-octenediamide,
(E)-N₁-(3-(dimethylamino)-2,2-dimethylpropyl)-N₈-hydroxy-2-((naphthalen-1-yloxy)methyl)octenediamide,
(E)-N₁-(2-(diisopropylamino)ethyl)-N₈-hydroxy-2-((naphthalen-1-yloxy)methyl)octenediamide,
(E)-N₈-hydroxy-N₁-(1-methoxypropan-2-yl)-2-((naphthalen-1-yloxy)methyl)-2-octenediamide,
(E)-N₈-hydroxy-N₁-(4-methoxybenzyl)-2-((naphthalen-1-yloxy)methyl)-2-octenediamide,
(E)-N₁-(4-fluorophenetyl)-N₈-hydroxy-2-((naphthalen-1-yloxy)methyl)-2-octenediamide,
(E)-N₈-hydroxy-2-((naphthalen-1-yloxy)methyl)-N₁-(tetrahydrofuran-2-yl)methyl)-2-octenediamide,
(E)-N₁-(2-cyclohexenylethyl)-N₈-hydroxy-2-((naphthalen-1-yloxy)methyl)-2-octenediamide,
(E)-N₈-hydroxy-2-((naphthalen-1-yloxy)methyl)-N₁-(3-(2-...
oxopyrrolidin-1-yl)propyl)-2-octenediamide,
(E)-N1-(furan-2-yl)-N8-hydroxy-2-((napthalen-1-yloxy)methyl)-2-octenediamide,
(E)-N1-(4-(dimethylamino)benzyl)-N8-hydroxy-2-((napthalen-1-yloxy)methyl)-2-octenediamide,
(E)-N8-hydroxy-N1-(2-methoxyethyl)-2-((napthalen-1-yloxy)methyl)-2-octenediamide,
(E)-N1-cyclohexyl-N8-hydroxy-2-((napthalen-1-yloxy)methyl)-2-octenediamide,
(E)-N8-hydroxy-2-((napthalen-1-yloxy)methyl)-N1-(4-methoxyphenetyl)-2-octenediamide,
(E)-N8-hydroxy-2-((napthalen-1-yloxy)methyl)-N1-(4-(trifluoromethoxy)benzyl)-2-octenediamide,
(E)-N1-l-(l-(cyclohexylmethyl)pyrrolidin-3-yl)-N8-hydroxy-2-((napthalen-1-yloxy)methyl)-2-octenediamide,
(E)-N1-l-(l-benzylpyrrolidin-3-yl)-N8-hydroxy-2-((napthalen-1-yloxy)methyl)-2-octenediamide,
(E)-N8-hydroxy-N1-(l-cyclohexylcarbonyl)pyrrolidin-3-yl)-N8-hydroxy-2-((napthalen-1-yloxy)methyl)-2-octenediamide,
(E)-N 1-(1-cyclopropylpiperidin-4-yl)-N8-hydroxy-2-((naphthalen-1-yloxy)methyl)-2-octenediamide,
(E)-N 1-(1-ethylpiperidin-4-yl)-N8-hydroxy-2-((naphthalen-1-yloxy)methyl)-2-octenediamide, and
(E)-N 1-(1-ethylpyrrolidin-3-yl)-N8-hydroxy-2-((naphthalen-1-yloxy)methyl)-2-octenediamide.

The inventive compound of formula (I) may be used in the form of a pharmaceutically acceptable addition salt formed with an inorganic acid or organic acid. Examples of the acid include hydrochloric, hydrobromic, sulfuric, phosphoric, nitric, acetic, glycolic, lactic, pyruvic, malonic, succinic, glutaric, fumaric, malic, mandelic, tartaric, citric, ascorbic, palmitic, maleic, hydroxy maleic, benzoic, hydroxybenzoic, phenylacetic, cinnamic, salicylic, methanesulfonic, benzenesulfonic, and toluenesulfonic acid.

And the inventive alkylcarbamoyl naphthalenyloxyoctenoyl hydroxyamide derivatives of formula (1) may be prepared by the method comprising the steps of:

1) treating a compound of formula (2) with sulfuric acid, and then with pyridinium chlorochromate (PCC) to obtain a compound of formula (3);
2) allowing the compound of formula (3) to react with an alkyl acrylate in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) to obtain a compound of the formula (4);
3) subjecting the compound of formula (4) to a reaction with tribromophosphine (PBr₃) to obtain a compound of formula (5);
4) bringing the compound of formula (5) to react with 1-naphthol to obtain a compound of formula (6);
5) hydrolyzing the compound of formula (6) in the presence of an inorganic or organic acid to obtain a compound of formula (7);
6) acylating the compound of formula (7) with an amine (R₁R₂NH or R₂NH₂) to obtain a compound of formula (8);
7) hydrolyzing the compound of formula (8) in the presence of an inorganic base to obtain a compound of formula (9);
8) acylating the compound of formula (9) with tetrahydropyranyloxyamine (NH₂OTHp) to obtain a compound of formula
(10); and
9) removing the tetrahydropyranyl group from the compound of formula (10) by trifluoroacetic acid (TFA) treatment.
Wherein:

R<sub>i</sub> and R<sub>2</sub> have the same meanings as defined in formula (1) above, and Y is C<sub>1-4</sub> alkyl.

The method described above may be represented by Reaction Scheme 1:

**Reaction Scheme 1**

Wherein:

R<sub>i</sub> and R<sub>2</sub> have the same meanings as defined in formula (1) above, and Y is C<sub>1-4</sub> alkyl.

In step 1) of Reaction Scheme 1, ε-caprolactone (formula 2) is dissolved in methanol and treated with concetrated sulfuric acid to form the 1, 6-hydroxy-hexanoic acid methylester of formula 3, which is then added to a pyridinium chlorochromate solution and reacted for 2 hrs to obtain 6-oxo-hexanoic acid methylester (formula 3).

Suitable for use in this step is a solvent such as dichloromethane, tetrahydrofuran, or dichloroethane.

In step 2), a hydroxy compound (formula 4) is obtained by the Baylis-
Hillman reaction carried out between a 6-oxo-hexanoic acid methylester (formula 3) and a C_{1-4} alkylacrylate in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) at 0-25 °C for 5-7 days, above ethyl acrylate, isobutyl acrylate, or t-butyl acrylate may be used as the alkyl acrylate.

The reaction step 3) is carried out using a bromination agent in an organic solvent. Representative examples of the organic solvent include ethylether, dichloromethane and hydrofuran, and representative examples of the bromination agent include PBr_3, CBr_4 and N-bromo succinic acid (NBS).

In step 4), the bromo compound (formula 5) is reacted with 1-naphthol to obtain an alcohol compound (formula 6) using acetone or acetonitrile as a solvent in the presence of potassium carbonate, sodium bicarbonate, or sodium carbonate.

The ester hydrolysis step 5) is carried out in the presence of an inorganic or organic acid in a solvent such as dichloromethane, tetrahydrofuran or N,N'-dimethylformamide. Representative examples of the inorganic acid include hydrochloric acid, sulfuric acid and phosphoric acid and representative examples of the organic acid include trifluoroacetic acid (TFA).

Acylation step 6) is carried out using N-Methanesulfonyloxy-6-trifluoromethylbenzotriazole (FMS), N-hydroxy-6-trifluorobenzotriazole (FOBT) or l-(3-diethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC·HCl) as an acylation agent in an aprotic solvent such as dimethylformamide, dimethylsulfoxide, tetrahydrofuran or dichloromethane.

The reaction in step 7) is preferably carried out using an aqueous alcohol or tetrahydrofuran solvent, and lithium hydroxide (LiOH-H_2O) or sodium hydroxide as the inorganic base.

The acylation in step 8) is carried out in an organic solvent in the presence of N-hydroxy-6-trifluorobenzotriazole (FOBT) and l-(3-diethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC-HCl). Representative examples of the organic solvent include N,N'-dimethylformamide, dimethylsulfoxide, tetrahydrofuran and dichloromethane.

Removing the tetrahydropyranyl group from the compound of formula...
in step 9) is carried out in a solvent such as methanol, ethanol, tetrahydrofuran or dichloromethane.

The starting material (formula 2) for preparing the alkylcarbamoyl naphthalenylxyloxyoctenoyl hydroxyamide derivatives of formula (1) is commercially available.

The inventive alkylcarbamoyl naphthalenylxyloxyoctenoyl hydroxyamide derivative of formula (1) efficiently inhibits the activity of histone deacetylase, resulting in the efficient suppression of the cancer-cell proliferation.

Accordingly, the present invention also provides an inhibitor of histone deacetylase activity comprising the compound of formula (1) or a pharmaceutically acceptable salt thereof as an active ingredient.

Further, the present invention provides an anti-cancer composition comprising the compound of formula (1) as an active ingredient and a pharmaceutically acceptable carrier.

The inventive pharmaceutical composition comprises the compound of formula (1) as an active ingredient in an amount ranging from 0.1 to 75 wt%, preferably 1 to 50 wt%, based on the total weight of the composition.

The pharmaceutical composition may be formulated for oral or parenteral administration. The formulation for oral administration may take various forms such as tablet, pill, powder, sachet, soft and hard capsule, solution, suspension, emulsion, syrup, granule and the like, which may contain conventional additives such as a diluent (e.g., lactose, dextrose, sucrose, mannitol, sorbitol, cellulose and/or glycine), a lubricant (e.g., silica, talc, stearic acid or its zinc, magnesium or calcium salt, and/or polyethylene glycol). A tablet form may also comprise a binder such as magnesium aluminum silicate, starch paste, gelatin, tragacanth, methyl cellulose, sodium carboxymethyl cellulose and/or polyvinylpyrrolidone, and optionally a disintegrant such as starch, agar, alginic acid or its sodium salt, an effervescent mixture, an absorbent, a colorant, a flavor and a sweetener. For parenteral administration, sterile injectable formulations such as istonic solution and suspension may be preferred.
The composition may be sterilized, additionally include preservatives, stabilizers, wetting agents, emulsifying agents, osmotic pressure-adjusting agents, buffering agents and the like, and may be formulated through a conventional mixing, granulating or coating procedures.

A typical daily dose of the compound of formula (1) ranges from about 2.5 to 100 mg/kg, preferably 5 to 60 mg/kg for mammals including a human subject, and can be orally or parenterally administered in a single dose or in divided doses.

The present invention is further described and illustrated in Examples provided below, which are, however, not intended to limit the scope of the present invention.

EXAMPLE

Preparation Example 1: 6-hydroxy-hexaenoic acid methyl ester

ε-Caprolactone (12.50 g, 109.51 mM) was dissolved in methanol (125 ml), a sulfuric acid solution (1 ml, 0.01 mM) was slowly added thereto, and the mixture was stirred at room temperature for 2 days. After the completion of the reaction, methanol was removed under a reduced pressure and ice water was poured thereinto. The resulting mixture was extracted with ethyl ether and the isolated organic layer was washed with saturated sodium bicarbonate and salt water in order. The resulting residue was subjected to column chromatography (ethyl acetic acid/n-hexane= 1/2) to obtain 10.18 g of the title compound (yield: 64%).

\[^{1}\text{H NMR} \ (200 \text{ MHz, CDCl}_3) \ \delta \ 1.23 \ (m, 2\text{H, CH}_2), \ 1.33-1.42 \ (m, 4\text{H, CH}_2\text{CH}_2), \ 1.44-1.74 \ (t, 4\text{H, CH}_2\text{CH}_2), \ 3.66 \ (s, 3\text{H, OCH}_3).\]

Preparation Example 2: 6-oxo-hexaenoic acid methyl ester (formula 3)

Pyridinium chlorochromate (16.27 g, 75.48 mM) was dissolved in dichloromethane (140 ml), 6-hydroxy-hexaenoic acid methyl ester (10.03 g,
68.61 mM) obtained in Preparation Example 1 in dichloromethane (20 ml)
was added dropwise thereto for 30 min, and the mixture was stirred at
25~30 °C for 2 hrs. After the completion of the reaction, the reaction
mixture was diluted with ethyl ether, and filtered. The filtrate was distilled
under a reduced pressure, concentrated and subjected to column
chromatography (ethyl acetic acid/n-hexane= 1/4), to obtain 5.77 g of the title
compound (yield: 59%).

\(^1\text{H} \text{NMR} \ (200 \text{ MHz, CDCl}_3) \delta 1.66 \ (m, 4H, CH}_2\text{CH}_2), \ 2.33 \ (m, 2H, CH}_2),
2.46 \ (m, 2H, CH}_2), \ 3.66 \ (s, 3H, OCH}_3), \ 9.74 \ (s, \text{ IH, CH}).

**Preparation Example 3: 3-hydroxy-2-methylene-dinonanoic acid 1-t-
butyl ester 9-methylester (formula 4)**

6-Oxo-hexaenoic acid methyl ester(20 g, 168.72 mM) obtained in
Preparation Example 2 was dissolved in the mixture of water and dioxane
(1:1) (100 mL), acrylic t-butyl ester (60.96 ml, 461.17 mM) was added
thereto, and 1,4-diazabicyclo[2.2.2]octane (DABCO) (15.56 g, 138.72 mM)
in the mixture of water and dioxane (1:1) (63 mL) were sequentially added
thereto, and the mixture was stirred for 7 days. After the completion of the
reaction, ice water was poured thereinto and the mixture was extracted with
ethyl ether. The extract was washed with 2 N hydrochloric acid, saturated
sodium bicarbonate and salt water in order, dried, concentrated under a
reduced pressure and subjected to column chromatography (ethyl acetic
acid/n-hexane= 1/9), to obtain 21.7 g of the title compound (yield: 57%).

\(^1\text{H} \text{NMR} \ (200 \text{ MHz, CDCl}_3) \delta 1.46 \ (m, 2H, \text{CH}_2), \ 1.47 \ (s, 9H, 3\text{CH}_3), \ 1.62
(m, 4H, CH}_2\text{CH}_2), \ 2.96 \ (m, 4H, CH}_2\text{CH}_2), \ 3.64 \ (s, 3H, OCH}_3), \ 5.67 \ (s, \text{ IH, CH}), \ 6.09 \ (s, \text{ IH, CH}).

**Preparation Example 4: 2-bromomethyl-2-dioctene acid 1-t-butyl ester 8-
methyl ester (formula 5)**
3-Hydroxy-2-methylene-dinonanoic acid 1-t-butyl ester 9-methyl ester (10.40 g, 38.20 raM) obtained in Preparation Example 3 was dissolved in ethyl ether (100 ml) and cooled to 0°C. Then, PBr₃ (3.93 ml, 42.02 mM) was slowly added thereto and stirred at room temperature for 1 hr. After the completion of the reaction, the reaction mixture was cooled to -10°C by pouring ice water, then extracted with ethyl ether. The extract was washed with salt water, dried over MgSO₄ and filtered. The solvent was removed under a reduced pressure and subjected to silica gel column chromatography (ethyl acetic acid/n-hexane = 1/9), to obtain 6.30 g of the title compound (yield: 49%).

¹H NMR (200 MHz, CDCl₃) δ 1.50 (s, 9H, CH₃), 1.65 (m, 4H, CH₂), 2.30 (m, 4H, CH₂), 3.66 (s, 3H, OCH₃), 4.27 (s, 2H, CH₂), 6.82 (m, IH, CH).

Preparation Example 5: 2-(naphthalen-1-yloxymethyl)-2-dioctene acid 1-t-butyl ester 8-methylester (formula 6)

2-Bromomethyl-2-dioctene acid 1-t-butyl ester 8-methylester (11.2 g 33.41 mM) obtained in Preparation Example 4 was dissolved in acetone(50 ml), potassium carbonate (6.93 g 50.11 mM) and 1-naphthol(5.30 g 36.75 mM) were added thereto, and the mixture was boiled for 3 hrs. After the completion of the reaction, the solvent was then removed under a reduced pressure at room temperature. The resulting residue was subjected to silica gel column chromatography (ethyl acetic acid/n-hexane= 1/15) to obtain 11.5 g of the title compound as a white solid (yield: 86%).

¹H NMR (200 MHz, CDCl₃) δ 1.45 (s, 9H, CH₃), 1.65 (m, 4H, CH₂), 2.30 (m, 4H, CH₂), 3.62 (s, 3H, OCH₃), 4.80 (s, 2H, CH₂), 6.64 (m, IH, ArH), 6.98 (m, IH, CH), 7.40 (m, 4H, ArH), 7.77 (m, IH, ArH), 8.19 (m, IH, ArH).

Preparation Example 6: 2-(naphthalen-1-yloxymethyl)-2-dioctene acid 8-methylester (formula 7)
2-(Naphthalen-1-yloxymethyl)-2-dioctene acid 1-t-butyl ester 8-methylester (5.00 g, 12.55 mM) obtained in Preparation Example 5 was dissolved in dichloromethane (60 ml), trifluoroacetic acid (6.77 ml, 87.83 mM) was slowly added thereto at 0°C, and the mixture was reacted at room temperature for 7 hrs. After the completion of the reaction, the solvent was then removed under a reduced pressure at room temperature. The resulting residue was subjected to silica gel column chromatography (ethyl acetic acid/n-hexane= 1/4) to obtain 2.08 g of the title compound (yield: 48%).

\[ \text{\textsuperscript{1}H NMR (200 MHz, CDCl}_3) \delta 1.46 (m, 2H, CH}_2, 1.59 (m, 2H, CH}_2, 2.26 (t, 2H, J = 7.1 Hz, CH}_2, 2.43 (q, 2H, J = 14.9, 7.5 Hz, CH}_2, 3.62 (s, 3H, OCH}_3, 4.94 (s, 2H, CH}_2, 6.89 (d, 1H, J = 7.3 Hz, CH), 7.27-7.47 (m, 5H, ArH), 7.80 (dd, 1H, J = 7.3, 1.7 Hz, ArH), 8.20 (t, 1H, J = 7.1, 1.7 Hz, ArH). \]

The amine compound (RjR\textsubscript{2}NH or R\textsubscript{2}NH\textsubscript{2}) for preparing the compound of formula 8 is commercially available, or can be readily synthesized by the conventional method.

Substituted pyrrolidine and piperidine may be synthesized as described in the Reaction Scheme B.

Reaction Scheme B
Wherein:

R is \( \text{C}_3\text{t}-\text{alkyl}, \text{C}_3\text{t}-\text{cycloalkyl}, \text{C}_3\text{t}-\text{cycloalkyl} \text{C}_1\text{t}-\text{alkyl}, \text{benzyl}, \text{or} \text{C}_3\text{t}-\text{gycloalkyl carbonyl}. \)

And procedures for preparation of the amine compounds are illustrated below.

**Preparation Example 1: \( t \)-butyl l-benzylpiperidin-4-ylcarbamate**

(formula 12)

l-Benzylpiperidine-4-amine (3g, 15.8mmol), the starting material, was dissolved in 1M aqueous sodium hydroxide solution (35.8 ml) and \( t \)-butanol (32 ml) in the 250 ml reaction vessel, \( t \)-butyl dicarbonate (\( (t\text{-Boc})_2\text{O;} 3.79 \text{ g}, 17.38 \text{ mmol} \)) was added thereto while stirring, and the mixture was reacted for 12 hrs. After the completion of the reaction, the reaction mixture was extracted with ethyl ether 2 times. The extract was washed with 0.1N hydrochloric acid solution and salt water in order. The resulting organic layer
was dried over anhydrous sodium sulfate, filtered, concentrated under a reduced pressure and then subjected to silica gel column chromatography to obtain 3.80 g of the title compound as a white solid (yield: 82.8%).

\[ ^1H \text{-NMR (200 MHz, CDCl}_3 \text{)} \delta 1.38 \text{ (s, 9H), 1.86-2.33 (m, 4H), 2.70 (m, 2H), 3.40 (m, 2H), 3.57 (br, IH), 4.12 (s, 2H), 7.43 (m, 3H), 7.55 (m, 2H).} \]

LC/MS (M+H): 291.

**Preparation Example II: /-butyl piperidin-4-ylcarbamate (formula 13)**

f-Butyl-l-benzylpiperidin-4-ylcarbamate (3.80 g, 13.1 mmol) obtained in Preparation Example I was dissolved in 26 ml of methanol in the 100 ml reaction vessel, catalytic quantities of 10% active palladium/carbon was added thereto, and reacted under the hydrogen for 12 hrs. After the completion of the reaction, the reduction mixture was filtered through a cellite pad to remove palladium/carbon and the solvent was removed under a reduced pressure. Then, the mixture was subjected to silica gel column chromatography to obtain 2.64 g of the title compound (yield: 99%).

\[ ^1H \text{-NMR (200 MHz, CD}_2\text{OD)} \delta 1.36 \text{ (s, 9H), 1.84-2.36 (m, 4H), 2.74 (m, 2H), 3.42 (m, 2H), 3.60 (br, IH).} \]

LC/MS (M+H): 201.

**Preparation Example III: /-butyl l-R-piperidin-4-ylcarbamate (formula 14)**

(III-l) /-butyl l-isopropylpiperidin-4-ylcarbamate (14a)

Method A: /-butyl piperidin-4-ylcarbamate (3 g, 15 mmol) obtained in Preparation Example II was dissolved in methanol (30ml) in the 100 ml reaction vessel, acetone (7.70 ml, 105 mmol) and acetic acid (0.45 ml, 7.5 mmol) were added thereto while stirring, 4 portions of NaCNBH \_3 \text{(1.88 mg, 30 mmol)} were added dropwise and reacted for 18 hrs. After the completion of the reaction, ice water was poured thereinto and then the mixture was
stirred and extracted with ethyl ether. The extract was washed with sodium bicarbonate and salt water in order. The resulting organic layer was dried over anhydrous sodium sulfate, filtered, concentrated under a reduced pressure and then subjected to silica gel column chromatography to obtain 2.644 g of title compound as a white solid (yield: 73.3%).

\[ ^1H \text{-NMR} \ (200 \text{ MHz, CDCl}_3) \delta 1.36 \ (d, \ J = 7.0 \text{ Hz, } 6\text{H}), \ 1.44 \ (s, \ 9\text{H}), \ 2.00 \ (m, \ 2\text{H}), \ 2.17 \ (m, \ 2\text{H}), \ 2.94 \ (m, \ 2\text{H}), \ 3.38 \ (m, \ 3\text{H}), \ 3.69 \ (m, \ 1\text{H}), \ 4.92 \ (br, \ 1\text{H}). \]

LC/MS (M+H): 243.

(III-2) f-butyl l-cydopropylpiperidiiM-ylcarbamate  (14b)

The procedure of Preparation Example (III-1) was repeated except for using bromocyclopropane instead of acetone as the amine substituent to obtain 0.72 g of the title compound as pale yellow oil (yield: 60%).

\[ ^1H \text{-NMR} \ (200 \text{ MHz, CDCl}_3) \delta 0.44 \ (m, \ 4\text{H}), \ 1.31 \ (m, \ 2\text{H}), \ 1.47 \ (s, \ 9\text{H}), \ 1.58 \ (m, \ 1\text{H}), \ 1.90 \ (m, \ 2\text{H}), \ 2.29 \ (m, \ 2\text{H}), \ 2.94 \ (m, \ 2\text{H}), \ 3.49 \ (br, \ 1\text{H}), \ 4.42 \ (br, \ 1\text{H}). \]

LC/MS (M+H): 241.

(III-3) f-butyl l-cyclopentylpiperidiiM-ylcarbamate  (14c)

The procedure of Preparation Example (III-1) was repeated except for using bromocyclophentane instead of acetone as the amine substituent to obtain 1.16 g of the title compound as pale yellow oil (yield: 86%).

\[ ^1H \text{-NMR} \ (200 \text{ MHz, CDCl}_3) \delta 1.45 \ (s, \ 9\text{H}), \ 1.50-1.80 \ (m, \ 8\text{H}), \ 1.81-2.18 \ (m, \ 6\text{H}), \ 2.50 \ (m, \ 1\text{H}), \ 2.94 \ (m, \ 2\text{H}), \ 3.48 \ (br, \ 1\text{H}), \ 4.41 \ (br, \ 1\text{H}). \]

LC/MS (M+H): 269.

(III-4) f-butyl l-methylpiperidin-4-y .carbamate (14d)
The procedure of Preparation Example (III-1) was repeated except for using iodomethane instead of acetone as the amine substituent to obtain 1.43 g of the title compound as pale yellow oil (yield: 79.4%).

\[ ^1H-NMR \text{ (200 MHz, CDCl}_3 \text{)} \delta 1.44 \text{ (s, 9H), 1.45 (m, 2H), 1.92 (m, 2H), 2.07 (m, 2H), 2.27 (s, 3H), 2.74 (m, 2H), 3.44 (br, IH), 4.43 (br, IH).} \]

LC/MS (M+H): 215.

(III-5) \(-\text{butyl 1-ethylpiperidin-4-ylcarbamate (14e)}\)

Method B: \(-\text{butyl piperidin-4-ylcarbamate (1.5 g, 7.49 mmol)}\) obtained in Preparation Example II was dissolved in N,N-dimethylformamide (19 ml) in the 25 ml reaction vessel, K$_2$CO$_3$ (2.07 g, 14.98 mmol, 2 eq.) and iodoethane (0.60 ml, 7.49 mmol, 1 eq.) were added thereto while stirring, heated from 0°C to room temperature and kept for 4 hrs. After the completion of the reaction, the solvent was distilled under a reduced pressure and the remaining was extracted with ethyl ester. The organic layer was washed with saturated sodium bicarbonate and salt water in order, dried over anhydrous magnesium sulfate, concentrated under a reduced pressure and then subjected to silica gel column chromatography to obtain 1.34 g of the title compound as pale yellow oil (yield: 78%).

\[ ^1H-NMR \text{ (200 MHz, CDCl}_3 \text{)} \delta 1.10 \text{ (t, } J = 7.4 \text{ Hz, 3H), 1.43 (m, 2H), 1.47 (s, 9H), 1.99 (m, 4H), 2.40 (q, } J = 7.2 \text{ Hz, 2H), 2.85 (m, 2H), 3.47 (br, IH), 4.43 (br, IH).} \]

LC/MS (M+H): 229.

Preparation Example IV: \(1-R\)-piperidin-4-amine (formula 15)

(IV-I) \(1\)-isopropylpiperidin-4-amine (15a)

The compound (14a) obtained in Preparation Example (III-1) (1.5 g, 7.49 mmol) was dissolved in methanol (20 ml) in the 250 ml reaction vessel, trifluoro acetic acid (4.06 ml, 54.5 mmol, 5 eq.) was added dropwise thereto
while stirring, and kept for 18 hrs. After the completion of the reaction, the mixture was concentrated under a reduced pressure, and then subjected to azeotropic distillation with CHCl$_3$ 3 times. The reaction mixture was basified with aqueous KOH solution (20 ml) and extracted with CHCl$_3$ 3 times. The extract was washed with salt water, dried, filtered and distilled under a reduced pressure, to obtain 1.23 g of the title compound as yellow oil (yield: 79.3%).

$^1$H-NMR (200 MHz, CDCl$_3$) $\delta$ 1.02 (d, J = 6.6 Hz, 6H), 1.38 (m, 2H), 1.56 (br, 2H), 1.80 (d, J = 11.8 Hz, 2H), 2.17 (m, 2H), 2.71 (m, 2H), 2.80 (m, 2H).

LC/MS (M+H): 143.

(IV-2) l-cyclopropylpiperidin-4-amine (15b)

The procedure of Preparation Example (IV-I) was repeated except for using the compound obtained in Preparation Example (III-2) as the starting material, to obtain 286 mg of the title compound as pale yellow oil (yield: 75%).

$^1$H-NMR (200 MHz, CDCl$_3$) $\delta$ 0.44 (m, 4H), 1.33 (m, 2H), 1.52 (m, IH), 1.76 (m, 2H), 2.20 (m, 2H), 2.66 (m, IH), 3.00 (m, 2H).

LC/MS (M+H): 141.

(IV-3) l-cyclopentylpiperidin-4-amine (15c)

The procedure of Preparation Example (IV-I) was repeated except for using the compound obtained in Preparation Example (III-3) as the starting material, to obtain 689 mg of the title compound as pale yellow oil (yield: 95%).

$^1$H-NMR (200 MHz, CDCl$_3$) $\delta$ 1.50-1.80 (m, 8H), 1.81-2.18 (m, 6H), 2.50 (m, 2H), 2.74 (m, 2H).

LC/MS (M+H): 169.
**IV-4**  l-methylpiperidin-4-amine  (15d)

The procedure of Preparation Example (IV-I) was repeated except for using the compound obtained in Preparation Example (III-4) as the starting material, to obtain 820 mg of the title compound as pale yellow oil (yield: 86%).

$^1$H-NMR  (200 MHz, CDCl$_3$)  $\delta$ 1.37 (m, 2H), 1.78 (m, 2H), 1.99 (m, 2H), 2.27 (s, 3H), 2.70 (m, IH), 2.81 (m, 2H).

**LC/MS (M+H): 115.**

**IV-5**  l-ethylpiperidin-4-amine  (15e)

The procedure of Preparation Example (IV-I) was repeated except for using the compound obtained in Preparation Example (III-5) as the starting material, to obtain 672 mg of the title compound as pale yellow oil (yield: 89%).

$^1$H-NMR  (200 MHz, CDCl$_3$)  $\delta$ 1.08 (t, J = 7.2 Hz, 3H), 1.37 (m, 2H), 1.81-2.08 (m, 4H), 2.37 (q, J = 7.2 Hz, 2H), 2.65 (m, IH), 2.87 (m, 2H).

**LC/MS (M+H): 129.**

**Preparation Example V: *-butyl l-benzylpyrrolidin-3-ylcarbamate** (formula 17)

The starting material (10 g, 0.57 mmol) was dissolved in 3M aqueous sodium hydroxide solution (21 ml) and $^-$-butanol (114 ml) in the 500 ml reaction vessel, $r$-butyl dicarbonate ($r$-Boc)$_2$O; 13.07 g, 59.9 mmol) was added thereto while stirring, kept for 12 hrs. After the completion of the reaction, the reaction mixture was extracted with ethyl acetate 2 times. The extract was washed with 0.1N hydrochloric acid solution and salt water in order. The resulting organic layer was dried over anhydrous sodium sulfate,
filtered, concentrated under a reduced pressure and then subjected to silica gel column chromatography to obtain 15.25 g of the title compound as a white solid (yield: 97%).

1H-NMR (200 MHz, CDCl₃) δ 1.43 (s, 9H), 2.27 (m, 2H), 2.57 (m, 3H), 2.75 (m, IH), 3.59 (s, 2H), 4.16 (br, IH), 4.85 (br, IH), 7.30 (m, 5H).

LC/MS (M+H): 277.

Preparation Example VI: tf-butyl pyrrolidin-3-ylcarbamate (formula 18)

The starting material (15.75 g, 57.0 mmol) was dissolved in methanol and tetrabutylfuran (4:1) (114 ml) in the 100 ml reaction vessel, catalytic quantities of 10% active palladium/carbon was added thereto, and reacted under the hydrogen for 12 hrs. After the completion of the reaction, the reduction mixture was filtered through a cellite pad to remove palladium/carbon and the solvent was removed therefrom under a reduced pressure. Then, the mixture was subjected to silica gel column chromatography to obtain 9.51 g of the title compound (yield: 99%).

1H-NMR (200 MHz, CDCl₃) δ 1.41 (s, 9H), 2.26 (m, 2H), 2.55 (m, 3H), 2.74 (m, IH), 4.84 (br, IH).

LC/MS (M+H): 187.

Preparation Example VII: f-butyl l-R-pyrrolidin-3-ylcarbamate (formula 19)

(VII-I) /-butyl l-cyclopropylpyrrolidin-3-ylcarbamate (19a)

Method A: tf-butyl pyrrolidin-3-ylcarbamate (1.24 g, 6.7 mmol) was dissolved in methanol (14 ml) in the 250 ml reaction vessel, acetone (3.44 ml, 46.9 mmol) and acetic acid (0.19 ml, 3.35 mmol) were added thereto while stirring, and 4 portions of NaCNBH₃ (842 mg, 13.4 mmol) were added thereto dropwise and kept for 18 hrs. After the completion of the reaction, ice water...
was poured thereinto and then the mixture was stirred and extracted with ethyl acetate. The extract was washed with sodium bicarbonate and salt water in order. The resulting organic layer was dried over anhydrous sodium sulfate, filtered, concentrated under a reduced pressure and then subjected to silica gel column chromatography to obtain 897 g of title compound as a white solid (yield: 58%).

\[ ^1\text{H-NMR (200 MHz, CDCl}_3 \text{)} \delta 1.40 (d, J = 6.6 \text{ Hz, } 6\text{Hz}), 1.44 (s, 9\text{H}), 2.12 (m, \text{IH}), 2.48 (m, \text{IH}), 3.27 (m, 3\text{H}), 3.39 (m, 3\text{H}), 3.57 (m, \text{IH}), 4.38 (m, \text{IH}), 5.41 (m, \text{IH}). \]

LC/MS (M+H): 229.

(VII-2) **f-butyl l-cyclopropylpyrrolidin-S-ylcarbamate** (19b)

The procedure of Preparation Example (VII-1) was repeated except for using bromocyclopropane instead of acetone as the amine substituent to obtain 7.17 g of the title compound as pale yellow oil (yield: 59%).

\[ ^1\text{H-NMR (200 MHz, CDCl}_3 \text{)} \delta 0.40 (m, 4\text{H}), 1.44 (s, 9\text{H}), 1.60 (m, 2\text{H}), 2.19 (m, \text{IH}), 2.57 (m, 2\text{H}), 2.81 (m, 2\text{H}), 4.14 (br, \text{IH}), 4.80 (br, \text{IH}). \]

LC/MS (M+H): 227.

(VII-3) **f-butyl l-cyclohexylpyrrolidin-S-ylcarbamate** (19c)

The procedure of Preparation Example (VII-1) was repeated except for using cyclohexanone instead of acetone as the amine substituent to obtain 1.10 g of the title compound as pale yellow oil (yield: 77%).

\[ ^1\text{H-NMR (200 MHz, CDCl}_3 \text{)} \delta 1.23 (m, 2\text{H}), 1.41 (m, 2\text{H}), 1.46 (s, 9\text{H}), 1.78 (m, 2\text{H}), 1.89 (m, 2\text{H}), 2.06 (m, 3\text{H}), 2.44 (m, \text{IH}), 2.76 (m, \text{IH}), 3.04 (m, \text{IH}), 3.24 (m, 2\text{H}), 3.49 (m, \text{IH}), 4.34 (m, \text{IH}), 5.33 (m, \text{IH}). \]

LC/MS (M+H): 269.
Method B: The starting material (1.5 g, 8.05 mmol) was dissolved in N,N-dimethylformamide (20 ml) at 0°C in the 100 ml reaction vessel, K₂CO₃ (2.23 g, 16.1 mmol, 2 eq.) and iodoethane (0.64 ml, 8.05 mmol, 1 eq.) were added thereto while stirring, heated from 0°C to room temperature, and kept for 12 hrs. After the completion of the reaction, the solvent was distilled under a reduced pressure and the remaining was extracted with ethyl ester. The extract was washed with saturated sodium bicarbonate and salt water in order. The resulting organic layer was washed with saturated sodium bicarbonate and salt water, dried over anhydrous magnesium sulfate, concentrated under a reduced pressure and then subjected to silica gel column chromatography to obtain 1.13 g of the title compound as pale yellow oil (yield: 66%).

¹H-NMR (200 MHz, CDCl₃) δ 1.10 (t, J = 7.4 Hz, 3H), 1.44 (s, 9H), 1.69 (m, IH), 2.27 (m, 2H), 2.48 (q, J = 7.0 Hz, 2H), 2.57 (m, IH), 2.81 (m, IH), 4.16 (br, IH), 4.86 (br, IH).

LC/MS (M+H): 215.

(VII-5) f-butyl l-(cyclohexanecarbonyl)pyrrolidin-3-ylcarbamate (19e)

Method C: The starting material (1 g, 5.4 mmol) was dissolved in dichloromethane (14 ml) at 0°C in the 50 ml reaction vessel, triethyl amine (0.83 ml, 5.94 mmol, 1.1 eq.) and cyclohexylcarbonyl chloride (0.79 ml, 5.94 mmol, 1.1) were added thereto while stirring, heated from 0°C to room temperature, and kept for 4 hrs. After the completion of the reaction, the solvent was distilled under a reduced pressure and the remaining was extracted with dichloromethane. The extract was washed with sodium bicarbonate and salt water in order. The resulting organic layer was washed with saturated sodium bicarbonate and salt water, dried over anhydrous magnesium sulfate, concentrated under a reduced pressure and then subjected to silica gel column chromatography to obtain 1.57 g of the title compound as
pale yellow oil (yield: 98%).

$^1$H-NMR (200 MHz, CDCl$_3$) $\delta$ 1.26 (m, 4H), 1.46 (s, 9H), 1.79 (m, 6H), 1.98 (m, IH), 2.08-2.49 (m, 2H), 3.39 (m, IH), 3.59 (m, 2H), 3.73 (m, IH), 4.22 (m, IH), 4.63 (m, IH).

LC/MS (M+H): 297.

Preparation Example VIII: 1-R- pyrrolidine-3-amine (formula 20)

(VIII-I) 1- isopropyl pyrrolidine-3-amine (20a)

The compound (14a) obtained in Preparation Example (VII-I) (0.90 g, 3.9 mmol) was dissolved in dichloromethane (10 ml) in the 50 ml reaction vessel, trifluoro acetic acid (1.45 ml, 1.95 mmol, 5 eq.) was slowly added thereto dropwise while stirring, followed by reacting for 18 hrs. After the completion of the reaction, the mixture was distilled and concentrated under a reduced pressure, and then subjected to azeotropic distillation with CHCl$_3$ 3 times. The reaction mixture was basified with aqueous 2N potassium hydroxide solution (20 ml) and extracted with CHCl$_3$ 3 times. The extract was washed with salt water, dried, filtered and distilled under a reduced pressure, to obtain 433 mg of the title compound as yellow oil (yield: 86%).

$^1$H-NMR (200 MHz, CDCl$_3$) $\delta$ 1.38 (d, $J = 6.6$ Hz, 6Hz), 2.11 (m, IH), 2.47 (m, IH), 3.15 (m, IH), 3.29 (m, 4H), 3.57 (m, IH).

LC/MS (M+H): 129.

(VIII-2) 1-cyclopropyl pyrrolidine-3-amine (20b)

The procedure of Preparation Example (VIII-I) was repeated except for using the compound obtained in Preparation Example (VII-2) as the starting material, to obtain 477 mg of the title compound as pale yellow oil (yield: 79%).
\[ ^1H-NMR \ (200\ MHz, \ CDCl_3) \ \delta \ 0.41 \ (m, \ 4H), \ 1.55 \ (m, \ 2H), \ 2.16 \ (m, \ IH), \ 2.40 \ (m, \ IH), \ 2.68 \ (m, \ IH), \ 2.80 \ (m, \ IH), \ 2.93 \ (m, \ IH), \ 3.47 \ (m, \ IH). \]

LC/MS(M+H): 127.

(VIII-3) 1-cyclohexyl pyrrolidine-3-amine (20c)

The procedure of Preparation Example (VIII-I) was repeated except for using the compound obtained in Preparation Example (VII-3) as the starting material, to obtain 513 mg of the title compound as pale yellow oil (yield: 74%).

\[ ^1H-NMR \ (200\ MHz, \ CDCl_3) \ \delta \ 1.19 \ (m, \ 4H), \ 1.39-1.62 \ (m, \ 4H), \ 1.72 \ (m, \ IH), \ 1.93 \ (m, \ 3H), \ 2.14 \ (m, \ IH), \ 2.31 \ (m, \ IH), \ 2.58-2.78 \ (m, \ 2H), \ 2.85 \ (m, \ IH), \ 3.47 \ (m, \ IH). \]

LC/MS (M+H): 169.

(VIII-4) 1-ethyl pyrrolidine-3-amine (20d)

The procedure of Preparation Example (VIII-I) was repeated except for using the compound obtained in Preparation Example (VII-4) as the starting material, to obtain 477 mg of the title compound as pale yellow oil (yield: 79%).

\[ ^1H-NMR \ (200\ MHz, \ CDCl_3) \ \delta \ 1.13 \ (t, \ J = 7.2\ Hz, \ 3H), \ 1.51 \ (m, \ 2H), \ 2.31 \ (m, \ 2H), \ 2.47 \ (m, \ 3H), \ 2.73 \ (m, \ IH), \ 3.54 \ (m, \ IH). \]

LC/MS(M+H): 115.

(VIII-5) (3-amino pyrrolidin-1-yl)(cyclohexyl)methanone (20e)

The procedure of Preparation Example (VIII-I) was repeated except for using the compound obtained in Preparation Example (VII-5) as the starting material, to obtain 1.51 g of the title compound as pale yellow oil (yield: 99%).
H-NMR (200 MHz, CDCl₃) δ 1.26 (m, 4H), 1.79 (m, 6H), 1.98 (m, 1H), 2.08-2.49 (m, 2H), 3.39 (m, 1H), 3.59 (m, 2H), 3.73 (m, 1H).

LC/MS (M+H): 197.

Example 1: (E)-N8-hydroxy-N1,N1-dimethyl-2-((naphthalen-1-yloxy)methyl)octenediamide (formula 1)

(l-2):(E)-8-(dimethylamino)-7-((naphthalen-1-yloxy)methyl)-8-oxo-6-octene acid methylester (formula 8)

2-(Naphthalen-1-yloxy)methyl)-2-dioctene acid 8-methylester (423 mg, 1.24 mM) obtained in Preparation Example 6 was dissolved in dimethylformamide (4 ml) and cooled to 0°C, followed by adding triethylamine (520 µl, 3.72 mM) and N-Methanesulfonyloxy-6-trifluorobenzotriazole (418 mg, 1.49 mM), and stirring at 0°C for 30 min. A dimethylaminehydrochloride (111 mg, 1.36 mM) was slowly added there to, and stirred at room temperature for 1 hr. After the completion of the reaction, ice water was poured there into and the mixture was extracted with ethyl acetate. The extract was successively washed with 1 N hydrochloric acid, sodium bicarbonate and salt water, dried over anhydrous magnesium sulfate, and filtered. The solvent was removed under a reduced pressure and resulting residue was subjected to silica gel column chromatography (ethyl acetic acid/n-hexane= 2/1), to obtain 437 mg of the title compound (yield: 95%).

³H NMR (300 MHz, CDCl₃) δ 1.46 (m, 2H, CH₂), 1.59 (m, 2H, CH₂), 2.43 (q, 4H, J = 14.9, 7.5 Hz, CH₂), 3.02 (s, 6H, N(CH₃)₂), 3.63 (s, 3H, OCH₃), 4.95 (s, 2H, CH₂), 5.84 (t, IH, J = 14.8, 6.5 Hz, CH), 6.85 (d, IH, J = 7.4 Hz, ArH), 7.36-7.47 (m, 4H, ArH), 7.79 (t, IH, J = 9.05, 1.4 Hz, ArH), 8.10 (t, IH, J = 8.8, 7.5 Hz, ArH).

(l-2):(E)-8-(dimethylamino)-7-((naphthalen-1-yloxy)methyl)-8-oxo-6-
octene acid (formula 9)

(E)-8-(dimethylamino)-7-((naphthalen-l-yloxy)methyl)-8-oxo-6-
octene acid methylester (437 mg, 1.18 mM) obtained in Example (1-1) was
dissolved in 30% aqueous ethanol solution (4 ml), whereto a monohydrated
sodium lithium (248 mg, 5.90 mM) and tetrahydrofuran (4 ml) were added.
The reaction mixture was stirred at room temperature for 10 min and at 50°C
for 3 hrs. After the completion of the reaction, the reaction mixture was
cooled to room temperature by pouring ice water and the solvent was
removed under a reduced pressure. The reaction solution was cooled to 5°C
and 2 N hydrochloric acid was added thereto to adjust its pH to 4. The
resulting mixture was filtered and dried over anhydrous magnesium sulfate,
to obtain 413 mg of the title compound as a white solid (yield: 99%).

(l-3):(E)-N8-hydroxy-Nl,Nl-dimethyl-2-((naphthalen-l-yloxy)methyl)
octenediamide (formula 1)

(E)-8-(dimethylamino)-7-((naphthalen-l-yloxy)methyl)-8-oxo-6-
octene acid (413 mg, 1.16 mM) obtained in Example (1-2) was dissolved in
dimethylformamide (4 ml) and cooled to 0°C, whereto triethylamine (240 µL,
1.74 mM) and N-methanesulfonyloxy-6-trifluorobenzotriazole (391 mg, 1.39
mM) were added, followed by stirring for 20 min. And then, N-t-
butyldimethylsilyloxyamine (256 mg, 1.74 mM) was added thereto and
stirred at room temperature for 1 hr. After the completion of the reaction,
ice water was poured thereinto and the mixture was extracted with ethyl
acetate. The extract was successively washed with sodium bicarbonate, dried
over anhydrous sodium sulfate, and filtered. The solvent was removed and
resulting residue was subjected to silica gel column chromatography, to
obtain 280 mg of the title compound as a white solid (yield: 65%).

1H NMR (300 MHz, MeOH-d4) δ 1.46 (m, 2H, CH₂), 1.59 (m, 2H, CH₂),
2.43 (q, 4H, J = 14.9, 7.4 Hz, CH₂), 3.02 (s, 6H, N(CH₃)₂), 4.94 (s, 2H, CH₂),
5.84 (t, IH, J = 14.8, 6.5 Hz, CH), 6.85 (d, IH, J = 7.4 Hz, ArH), 7.36-7.47
Example 2: (E)-N1-(2-(dimethylamino)ethyl)-N8-hydroxy-2-((naphthalen-1-yloxy)methyl)octenediamide

(2-1): (E)-8-(2-(dimethylamino)ethylamino)-7-((naphthalen-1-yloxy)methyl)-8-oxo-6-octene acid methylester

The procedure of Example (1-1) was repeated except for using 2-(dimethylamino)ethylamine instead of dimethylaminehydrochloride as the amine to obtain 428 mg of the title compound (yield: 86%).

1H NMR (300 MHz, CDCl3) δ 1.51 (m, 2H, CH2), 1.63 (m, 2H, CH2), 2.03 (s, 6H, N(CH3)2), 2.23 (m, 4H, CH2CH2), 2.38 (m, 2H, CH2), 2.37 (q, J = 11.1, 5.7 Hz, CH2), 3.62 (s, 3H, OCH3), 4.92 (s, 2H, CH2), 6.85 (t, J = 15.3, 7.6 Hz, CH), 6.91 (d, J = 7.0 Hz, ArH), 7.44 (m, 4H, ArH), 7.78 (dd, J = 9.3, 7.5 Hz, ArH).

(2-2): (E)-8-(2-(dimethylamino)ethylamino)-7-((naphthalen-1-yloxy)methyl)-8-oxo-6-octene acid

The procedure of Example (1-2) was repeated except for using the compound obtained in Example (2-1) as the starting material, to obtain 335 mg of the title compound (yield: 81%).

1H NMR (300 MHz, MeOH-d4) δ 1.52 (m, 2H, CH2), 1.64 (m, 2H, CH2), 2.20 (m, 2H, CH2), 2.27 (s, 6H, N(CH3)2), 2.38 (m, 2H, CH2), 2.55 (m, 2H, CH2), 3.42 (m, 2H, CH2), 4.97 (s, 2H, CH2), 6.67 (s, J = 7.0 Hz, ArH), 6.99 (t, J = 7.0 Hz, ArH), 7.41 (m, 4H, ArH), 7.77 (d, J = 7.0, 1.8 Hz, CH), 8.74 (t, J = 7.2 Hz, ArH).

(2-3): (E)-N1-(2-(dimethylamino)ethyl)-N8-hydroxy-2-((naphthalen-1-yloxy)methyl)octenediamide
The procedure of Example (1-3) was repeated except for using the compound obtained in Example (2-2) as the starting material, to obtain 134 mg of the title compound (yield: 88%).

\[ ^1H \text{NMR (200 MHz, MeOH-}d_4) \delta 1.58 (m, 4H, CH}_2CH_2), 2.40 (m, 2H, CH_2), 2.82 (s, 6H, N(CH}_3)_2), 3.30 (m, 4H, CH}_2CH_2), 3.62 (m, 2H, CH_2), 5.01 (s, 2H, CH_2), 6.70 (t, IH, J = 15.2, 7.4 Hz, CH), 7.04 (d, IH, J = 1.2 Hz, ArH), 7.44 (m, 4H, ArH), 7.81 (m, IH, ArH), 8.19 (m, ArH).\]

**Example 3:** (E)-Nl-(2-(dimethylamino)ethyl)-N8-hydroxy-Nl-methyl-2-((naphthalen-1-yloxy)methyl)octenediamide

(3-1): (E)-8-((2-(dimethylamino)ethyl)(methyl)amino)-7-((naphthalen-1-yloxy)methyl)-8-oxo-6-octene acid methylester

The procedure of Example (1-1) was repeated except for using (2-(dimethylamino)ethyl)(methyl)amine instead of dimethylaminehydrochloride as the amine to obtain 351 mg of the title compound (yield: 77%).

\[ ^1H \text{NMR (200 MHz, CDCl}_3) \delta 1.6 (m, 4H, CH}_2CH_2), 2.2 (m, 8H, CH}_2CH_2CH}_2CH_2CH_2CH_2), 3.05 (s, 3H, NCH}_3), 3.55 (m, 2H, CH}_2), 3.70 (s, 3H, OCH}_3), 5.00 (s, 2H, Ph CH_2), 5.80 (s, IH, CH), 6.89 (d, IH, J = 1.4 Hz, ArH), 7.48 (m, 4H, ArH), 7.80 (dd, IH J = 6.0, 2.0 Hz, ArH), 8.20 (m, IH, ArH).\]

(3-2): (E)-8-((2-(dimethylamino)ethyl)(methyl)amino)-7-((naphthalen-1-yloxy)methyl)-8-oxo-6-octene acid

The procedure of Example (1-2) was repeated except for using the compound obtained in Example (3-1) as the starting material, to obtain 224 mg of the title compound (yield: 92%).

\[ ^1H \text{NMR (200 MHz, MeOH-}d_4) \delta 1.6 (m, 4H}_5 CH}_2CH_2), 2.4 (m, 6H,}
CH₂CH₂CH₂, 2.50 (m, 4H, CH₂CH₂), 2.80 (m, 2H, CH₂), 3.01 (s, 3H, NCH₃), 3.29 (m, IH, CH), 3.65 (m, IH, CH), 4.95 (s, 2H, PhCH₂), 6.00 (m, IH, CH), 7.00 (t, IH, J = 16.6, 9.4 Hz, ArH), 7.46 (m, 4H, ArH), 7.82 (m, IH, ArH), 8.18 (m, IH₅ArH).

(3-3):(E)-Nl-(2-(dimethylamino)ethyl)-N8-hydroxy-Nl-methyl-2-((naphthalene-l-yloxy)methyl)octenediamide

The procedure of Example (1-3) was repeated except for using the compound obtained in Example (3-2) as the starting material, to obtain 155 mg of the title compound (yield: 68%).

¹H NMR (200 MHz, MeOH-d₄) δ 1.48 (m, 2H, CH₂), 1.58 (m, 2H, CH₂), 2.4 (m, 6H, CH₂CH₂CH₂), 2.49 (m, 4H, CH₂CH₂), 2.81 (m, 2H, CH₂), 3.02 (s, 3H, NCH₃), 3.28 (m, IH, CH), 3.64 (m, IH, CH), 4.95 (s, 2H, PhCH₂), 6.02 (m, IH, CH), 7.00 (d, IH, J = 8.2 Hz, ArH), 7.44 (m, 4H, ArH), 7.80 (m, IH, ArH), 8.17 (m, IH, ArH).

Example 4: (E)-Nl-(2-(diethylamino)ethyl)-N8-hydroxy-2-((naphthalene-l-yloxy)methyl)octenediamide

(4-l):(E)-8-(2-(diethylamino)ethylamino)-7-((naphthalene-l-yloxy)methyl)-8-oxo-6-octene acid methylester

The procedure of Example (1-1) was repeated except for using 2-(diethylamino)ethylamine instead of dimethylaminehydrochloride as the amine to obtain 164 mg of the title compound (yield: 37%).

¹H NMR (200 MHz, CDCl₃) δ 1.24 (m, 6H, CH₂CH₂CH₂), 1.60 (m, 4H, CH₂CH₂), 2.14 (t, 2H, J = 14.2, 7.4 Hz, CH₂), 2.40 (m, 2H₅CH₂), 3.14 (m, 6H, CH₂CH₂CH₂CH₂), 3.50 (s, 2H, CH₂), 3.86 (s, 3H, OCH₃), 5.02 (s, 2H₅CH₂), 6.73 (t, IH, J = 14.6, 7.2 Hz, CH), 7.01 (d, IH, J = 7.4 Hz₅ArH), 7.40 (m, 4H₅ArH), 7.76 (d, IH, J = 7.4 Hz₅ArH), 8.18 (dd, IH₅J = 7.4, 2.8 Hz, ArH).
(4-2):(E)-8-(2-(diethylamino)ethylamino)-7-((naphthalen-1-yloxy)methyl)-8-oxo-6-octene acid

The procedure of Example (1-2) was repeated except for using the compound obtained in Example (4-1) as the starting material, to obtain 130 mg of the title compound (yield: 81%).

\[^1\text{H NMR (200 MHz, MeOH-d}_4\text{)} \delta 1.24 (m, 6H, CH}_2\text{CH}_2\text{CH}_2), 1.60 (m, 4H, CH}_2\text{CH}_2\text{), 2.12 (m, 2H, JCH}_2\text{), 2.36 (m, 2H, CH}_2\text{), 3.14 (m, 6H, CH}_2\text{CH}_2\text{CH}_2), 3.50 (s, 2H, CH}_2\text{), 5.01 (s, 2H, CH}_2\text{), 6.72 (d, IH, J = 7.4 Hz, CH), 7.02 (d, IH, J = 7.4 Hz, ArH), 7.40 (m, 4H, ArH), 7.80 (dd, IH, J = 7.6, 1.8 Hz, ArH), 8.16 (d, IH, J = 7.2 Hz, ArH).\]

(4-3):(E)-Nl-(2-(diethylamino)ethyl)-2-((naphthalen-1-yloxy)methyl)-N8-(tetrahydro-2H-pyran-2-yloxy)octenediamide

(E)-8-(2-(diethylamino)ethylamino)-7-((naphthalen-1-yloxy)methyl)-8-oxo-6-octene acid (311 mg, 0.71 mM) obtained in Example (4-2) was dissolved in dimethylformamide (3 ml), whereto triethylamine (150 µl, 1.07 mM) was added, followed by cooling to 0°C. N-hydroxy-6-trifluoro-6-trifluorobenzotriazole (159 mg, 0.78 mM), l-(3-diethylaminopropyl)-3-ethylcarbodiimidhydrochloride (177 mg, 0.92 mM) and tetrahydropyranyl oxyamine (125 mg, 1.07 mM) were added thereto, and the mixture was stirred at room temperature for 18 hrs. After the completion of the reaction, ice water was poured thereinto and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated sodium bicarbonate and salt water in order, dried over anhydrous magnesium sulfate, and concentrated under a reduced pressure. The resulting residue was subjected to silica gel column chromatography, to obtain 320 mg of the title compound (yield: 87%).

\[^1\text{H NMR (200 MHz, MeOH-d}_4\text{)} \delta 0.80 (m, 6H, CH}_2\text{CH}_2\text{CH}_2), 1.80 (m, 12H,
\( \text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2 \), 2.10 (s, IH, CH\(_2\)), 2.35 (m, 6H, CH\(_3\)CH\(_3\)), 2.58 (m, 2H, CH\(_2\)), 3.40 (m, 2H, CH\(_2\)), 3.60 (m, IH, CH), 3.94 (m, IH, CH), 4.96 (s, 2H, CH\(_2\)), 6.80 (d, IH, \( J = 7.4 \text{ Hz}, \text{CH} \)), 6.98 (d, IH, \( J = 6.8 \text{ Hz}, \text{ArH} \)), 7.42 (m, 4H, ArH), 7.80 (m, IH, ArH), 8.21 (dd, IH, \( J = 12.6, 6.4 \text{ Hz}, \text{ArH} \)).

(4-4): (E)-Nl-(2-(diethylamino)ethyl)-N8-hydroxy-2-((naphthalen-1-yloxy)methyl)octenediamide

(E)-Nl-(2-(diethylamino)ethyl)-2-((naphthalen-1-yloxy)methyl)-N8-(tetrahydro-2H-pyran-2-yloxy)octenediamide (320 mg, 0.62 mM) obtained in Example (4-4) was dissolved in dichloromethane (10 ml), where to trifluoroacetic acid (0.46 ml, 6.20 mM) was added slowly at 0°C, followed by reacting at room temperature for 18 hrs. After the completion of the reaction, the solvent was then removed under a reduced pressure at room temperature. The resulting residue was subjected to silica gel column chromatography (methylalcohol/dichloromethane=1/9) to obtain 261 mg of the title compound (yield: 95%).

\(^1\text{H} \text{NMR} \ (200 \text{ MHz, MeOH-d}_4) \ \delta \ 1.24 \ (m, \ 6\text{H}, \ \text{CH}_2\text{CH}_2\text{CH}_2), \ 1.60 \ (m, \ 4\text{H}, \ \text{CH}_2\text{CH}_2), \ 2.14 \ (t, \ 2\text{H}, \ J = 13.8, \ 7.0 \text{ Hz}, \ \text{CH}_2), \ 2.40 \ (q, \ 2\text{H}, \ J = 14.4, \ 7.0 \text{ Hz}, \ \text{CH}_2), \ 3.12 \ (m, \ 6\text{H}, \ \text{CH}_2\text{CH}_2\text{CH}_2), \ 3.51 \ (s, \ 2\text{H}, \ \text{CH}_2), \ 5.02 \ (s, \ 2\text{H}, \ \text{CH}_2), \ 6.73 \ (t, \ \text{IH}, \ J = 14.8, \ 7.4 \text{ Hz}, \ \text{CH}), \ 7.02 \ (d, \ \text{IH}, \ J = 6.4 \text{ Hz}, \ \text{ArH}), \ 7.41 \ (m, \ 4\text{H}, \ \text{ArH}), \ 7.80 \ (dd, \ \text{IH}, \ J = 5.6, \ 2.0 \text{ Hz}, \ \text{ArH}), \ 8.18 \ (dd, \ \text{IH}_3, \ J = 7.0, \ 3.8 \text{ Hz}, \ \text{ArH}).

Example 5: (E)-Nl-(2-(diethylamino)ethyl)-N8-hydroxy-Nl-methyl-2-((naphthalen-1-yloxy)methyl)octenediamide

(5-1): (E)-8-((2-(diethylamino)ethyl)(methyl)amino)-7-((naphthalen-1-yloxy)methyl)-8-oxo-6-octene acid methylester

The procedure of Example (1-1) was repeated except for using (2-(diethylamino)ethyl)(methyl)amine instead of dimethylaminehydrochloride as the amine to obtain 483 mg of the title compound (yield: 71%).
\(^1\text{H NMR (300 MHz, CDCl}_3\text{)}\) \(\delta\) 1.11 (m, 6H, \(\text{CH}_2\text{CH}_2\text{CH}_2\)), 1.40 (m, 2H, \(\text{CH}_2\)), 1.65 (m, 2H, \(\text{CH}_2\)), 2.28 (m, 8H, \(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3\)), 2.90 (s, 2H, \(\text{CH}_2\)), 3.00 (s, 3H, NCH\(_3\)), 3.57 (s, 2H, \(\text{CH}_2\)), 3.66 (s, 3H, OCH\(_3\)), 4.93 (s, 2H, \(\text{CH}_2\)), 6.85 (d, IH, \(J = 7.8\) Hz, CH), 6.99 (m, IH, ArH), 7.41 (m, 4H, ArH), 7.75 (m, IH, ArH), 8.14 (m, IH, NH), 8.17 (m, IH, ArH).

(5-2): (E)-N\(_2\)-(2-(diethylamino)ethyl)(methyl)amino)-7-((naphthalen-1-yl)oxy)methyl)-8-oxo-6-octene acid

The procedure of Example (1-2) was repeated except for using the compound obtained in Example (5-1) as the starting material, to obtain 300 mg of the title compound (yield: 65%).

\(^1\text{H NMR (300 MHz, MeOH-d}_4\text{)}\) \(\delta\) 1.05 (m, 6H, \(\text{CH}_2\text{CH}_2\text{CH}_2\)), 1.38 (m, 2H, \(\text{CH}_2\)), 1.50 (m, 2H, \(\text{CH}_2\)), 2.17 (m, 4H, \(\text{CH}_2\text{CH}_2\)), 2.99 (m, 6H, \(\text{CH}_3\text{CH}_3\)), 3.16 (s, 3H, NCH\(_3\)), 3.60 (m, 2H, \(\text{CH}_2\)), 4.87 (s, 2H, \(\text{CH}_2\)), 5.86 (d, IH, \(J = 7.4\) Hz, CH), 6.82 (d, IH, \(J = 7.4\) Hz, ArH), 7.28 (m, 4H, ArH), 7.64 (t, IH, \(J = 9.4\), 6.1 Hz, ArH), 7.92 (d, IH, \(J = 9.7\) Hz, ArH).

(5-3): (E)-N\(_1\)-(2-(diethylamino)ethyl)-2-((naphthalen-1-yl)oxy)methyl)-N\(_8\)-(tetrahydro-2H-pyran-2-yl)oxy)-2-octenediamide

The procedure of Example (4-3) was repeated except for using the compound obtained in Example (5-2) as the starting material, to obtain 320 mg of the title compound (yield: 87%).

\(^1\text{H NMR (300 MHz, MeOH-d}_4\text{)}\) \(\delta\) 1.00 (m, 6H, \(\text{CH}_2\text{CH}_2\text{CH}_2\)), 1.54 (m, 4H, \(\text{CH}_2\text{CH}_2\)), 1.73 (m, 8H, \(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\)), 2.14 (d, 2H, \(J = 7.0\) Hz, \(\text{CH}_2\)), 2.36 (d, 2H, \(J = 7.4\) Hz, \(\text{CH}_2\)), 2.58 (d, 2H, \(J = 6.8\) Hz, \(\text{CH}_2\)), 3.07 (m, 6H, \(\text{CH}_3\text{CH}_3\)), 3.32 (s, 3H, NCH\(_3\)), 3.55 (m, 2H, \(\text{CH}_2\)), 3.98 (m, IH, CH), 5.05 (s, 2H, \(\text{CH}_2\)), 5.94 (m, IH, CH), 7.01 (d, IH, \(J = 7.4\) Hz, ArH), 7.48 (m, 4H, ArH), 7.82 (t, IH, \(J = 9.1\), 2.0 Hz, ArH), 8.11 (dd, IH, \(J = 7.4\), 2.3 Hz, ArH).
(E)-Nl-(2-(diethylamino)ethyl)-N8-hydroxy-Nl-methyl-2-((naphthalen-1-yloxy)methyl)octenediamide

The procedure of Example (4-4) was repeated except for using the compound obtained in Example (5-3) as the starting material, to obtain 285 mg of the title compound (yield: 93%).

\[ \text{1H NMR (300 MHz, MeOH-d$_4$)} \delta 1.10 (m, 6H, CH$_2$CH$_2$CH$_2$), 1.13 (m, 2H, CH$_2$), 1.58 (m, 2H, CH$_2$), 2.02 (t, 2H, J = 14.1, 7.0 Hz, CH$_2$), 2.28 (d, 2H, J = 7.2 Hz, CH$_2$), 3.07 (m, 6H, CH$_3$CH$_3$), 3.21 (s, 3H, NCH$_3$), 3.64 (m, 2H, CH$_2$), 4.96 (s, 2H, CH$_2$), 5.93 (s, 1H, CH), 6.90 (d, 1H, J = 7.2 Hz, ArH), 7.36 (m, 4H, ArH), 7.71 (dd, 1H, J = 8.0, 3.7 Hz, ArH), 7.98 (d, 1H, J = 9.4 Hz, ArH); MS (LC, 70 eV) m/z 456 (M+1), 382.

Example 6: (E)-N8-hydroxy-2-((naphthalen-1-yloxy)methyl)-Nl-(2-(pyrrolidin-1-yl)ethyl)octenediamide

(6-1): (E)-7-((naphthalen-1-yloxy)methyl)-8-oxo-8-(2-(pyrrolidin-1-yl)ethyl)octenediamide

The procedure of Example (1-1) was repeated except for using 2-(pyrrolidin-1-yl)ethylamine instead of dimethylaminehydrochloride as the amine to obtain 74 mg of the title compound (yield: 29%).

\[ \text{1H NMR (200 MHz, CDCl$_3$)} \delta 1.50 (d, 2H, J = 7.4 Hz, CH$_2$), 1.62 (d, 2H, J = 7.4 Hz, CH$_2$), 1.89 (m, 4H, CH$_2$), 2.09 (m, 2H, CH$_2$), 2.35 (m, 2H, CH$_2$), 3.13 (m, 5H, CHCH$_2$CH$_2$), 3.32 (s, 1H, CH), 3.58 (t, 2H, J = 12.1, 6.1 Hz, CH$_2$), 3.96 (s, 3H, OCH$_3$), 4.96 (s, 2H, CH$_2$), 6.80 (d, 1H, J = 7.4 Hz, CH), 6.98 (d, 1H, J = 7.4 Hz, ArH), 7.45 (m, 4H, ArH), 7.80 (m, 1H, ArH), 8.21 (m, 1H, ArH).

(6-2): (E)-7-((naphthalen-1-yloxy)methyl)-8-oxo-8-(2-(pyrrolidin-1-yl)

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thylamino)-6-octeiie acid

The procedure of Example (1-2) was repeated except for using the compound obtained in Example (6-1) as the starting material, to obtain 69 mg of the title compound (yield: 96%).

$^1$H NMR (200 MHz, MeOH-d$_4$) δ 1.50 (d, 2H, J = 7.2 Hz, CH$_2$), 1.60 (d, 2H, J = 7.2 Hz, CH$_2$), 1.88 (m, 4H, CH$_2$), 2.08 (m, 2H, CH$_2$), 2.34 (m, 2H, CH$_2$), 3.14 (m, 5H, CHCH$_2$CH$_2$), 3.34 (s, IH, CH), 3.58 (t, 2H, J = 12.1, 6.1 Hz, CH$_2$), 4.96 (s, 2H, CH$_2$), 6.80 (d, IH, J = 7.0 Hz, CH), 6.98 (d, IH, J = 7.2 Hz, ArH), 7.45 (m, 4H, ArH), 7.80 (m, IH, ArH), 8.21 (m, IH, ArH).

(6-3):(E)-2-((naphthalen-1-yloxy)methyl)-Nl-(2-(pyrrolidin-1-yl)ethyl)-N8-(tetrahydro-2H~pyran-2-yloxy)octenediamide

The procedure of Example (6-2) was repeated except for using the compound obtained in Example (4-3) as the starting material, to obtain 87 mg of the title compound (yield: 85%).

$^1$H NMR (200 MHz, MeOH-d$_4$) δ 1.50 (m, 8H, CH$_2$CH$_2$CH$_2$CH$_2$), 1.80 (m, 4H, CH$_2$CH$_2$), 2.01 (m, 2H, CH$_2$), 2.40 (m, 4H, CH$_2$CH$_2$), 2.59 (m, 5H, CHCH$_2$CH$_2$), 2.78 (m, 2H, CH$_2$), 3.50 (m, 3H, CHCH$_2$), 3.90 (s, IH, CH), 4.96 (s, 2H, CH$_2$), 6.80 (d, IH, J = 7.2 Hz, CH), 6.98 (d, IH, J = 7.4 Hz, ArH), 7.45 (m, 4H, ArH), 7.80 (m, IH, ArH), 8.21 (m, IH, ArH).

(6-4):(E)-N8-hydroxy-2-((naphthalen-1-yloxy)methyl)-Nl-(2-(pyrrolidin-1-yl)ethyl)octenediamide

The procedure of Example (4-4) was repeated except for using the compound obtained in Example (6-3) as the starting material, to obtain 72 mg of the title compound (yield: 84%).

$^1$H NMR (300 MHz, MeOH-d$_4$) δ 1.51 (d, 2H, J = 7.0 Hz, CH$_2$), 1.62 (d, 2H,
\( J = 7.9 \text{ Hz}, \text{CH}_2 \), 1.89 (m, 4H, \text{CH}_2\text{CH}_2), 2.09 (m, 2H, \text{CH}_2), 2.35 (m, 2H, \text{CH}_2), 3.13 (m, 5H, \text{CHCH}_2\text{CH}_2), 3.32 (s, \text{IH}, \text{CH}), 3.58 (t, 2H, J = 12.1, 6.1 Hz, \text{CH}_2), 5.01 (s, 2H, \text{CH}_2), 6.70 (s, \text{IH}, \text{CH}), 7.00 (d, \text{IH}, J = 7.2 \text{ Hz, ArH}), 7.45 (m, 4H, \text{ArH}), 7.80 (t, \text{IH}, J = 8.4, 1.8 Hz, \text{ArH}), 8.12 (t, \text{IH}, J = 9.4, 7.5 Hz, \text{ArH}); \text{MS} \ (\text{LC}, 700 \text{ eV}) \ m/z \ 440 \text{(M+)}), 425, 328, 313, 242, 210, 192.

**Example 7**: (E)-N8-hydroxy-2-((naphthalen-1-yl)oxy)methyl)-N1-(2-(piperidin-1-yl)ethyl)octenediamide

The procedure of Example (1-1) was repeated except for using 2-(piperidin-1-yl)ethylamine instead of dimethylaminehydrochloride as the amine to obtain 290 mg of the title compound (yield: 94%).

\(^1\text{H} \text{NMR} \ (200 \text{ MHz, CDCl}_3) \delta 1.10 \text{ (m, 2H, CH}_2\text{), 1.21 (m, 2H, CH}_2\text{), 1.60 (m, 4H, CH}_2\text{), 2.01 (m, 2H, CH}_2\text{), 2.21 (m, 5H, CHCH}_2\text{CH}_2\text{), 2.38 (m, 5H, CHCH}_2\text{CH}_2\text{), 3.41 (t, 2H, J = 11.4, 5.8 Hz, CH), 3.65 (s, 3H, OCH}_2\text{), 4.95 (s, 2H, CH}_2\text{), 6.81 (d, \text{IH}, J = 7.8 Hz, CH), 6.95 (d, \text{IH}, J = 7.0 \text{ Hz, ArH}), 7.10 \text{(brs, IH, NH), 7.45 (m, 4H, ArH), 7.80 (q, IH, J = 5.8, 2.4 Hz, ArH), 8.21 (dd, IH, J = 7.0, 3.4 Hz, ArH).}

**Example 7-l**: (E)-7-((naphthalen-1-yl)oxy)methyl)-8-oxo-8-(2-(piperidin-1-yl)thylamino)-6-octene acid methylester

The procedure of Example (1-2) was repeated except for using the compound obtained in Example (7-1) as the starting material, to obtain 256 mg of the title compound (yield: 94%).

\(^1\text{H} \text{NMR} \ (300 \text{ MHz, MeOH-d}_4) \delta 1.44 \text{ (m, 4H, CH}_2\text{CH}_2\text{), 1.64 (m, 2H, CH}_2\text{), 2.12 (m, 2H, CH}_2\text{), 2.26 (m, 2H, CH}_2\text{), 3.08 (m, 1OH, CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{), 3.51 (d, 2H, J = 6.0 Hz, CH), 4.91 (s, 2H, CH}_2\text{), 6.61 (s, \text{IH, CH), 6.91 (d, IH,} \)
\( J = 6.2 \text{ Hz, ArH} \), 7.31 (m, 4H, ArH), 7.68 (dd, IH, \( J = 6.8, 3.4 \text{ Hz, ArH} \)), 8.00 (dd, IH, \( J = 7.0, 3.4 \text{ Hz, ArH} \))

\( 7-3 \) : (E)-2-((naphthalen-1-yloxy)methyl)-Nl-(2-(piperidin-1-yl)ethyl)-N8-(tetrahydro-2H-pyran-2-yloxy)octenediamide

The procedure of Example (4-3) was repeated except for using the compound obtained in Example (7-2) as the starting material, to obtain 288 mg of the title compound (yield: 91%).

\(^1\)H NMR (300 MHz, MeOH-d\(_4\)) \( \delta \) 1.42 (m, 2H, CH\(_2\)), 1.45 (m, 4H, CH\(_2\)CH\(_2\)), 1.60 (m, 8H, CH\(_2\)CH\(_2\)CH\(_2\)CH\(_2\)), 2.09 (s, 2H, CH\(_2\)), 2.29 (m, 1OH, CH\(_2\)CH\(_2\)CH\(_2\)CH\(_2\)CH\(_2\)), 3.21 (m, 2H, CH\(_2\)), 3.47 (m, 2H, CH\(_2\)), 3.89 (t, IH, \( J = 7.2 \text{ Hz, CH} \)), 4.90 (s, 2H, CH\(_2\)), 6.50 (s, IH, CH), 6.90 (d, IH, \( J = 7.2 \text{ Hz, ArH} \)), 7.33 (m, 4H, ArH), 7.70 (t, IH, \( J = 9.0, 1.4 \text{ Hz, ArH} \)), 8.02 (d, IH, \( J = 8.2 \text{ Hz, ArH} \)).

\( 7-4 \) : (E)-N8-hydroxy-2-((naphthalen-1-yloxy)methyl)-Nl-(2-(piperidin-1-yl)ethyl)octenediamide

The procedure of Example (4-4) was repeated except for using the compound obtained in Example (7-3) as the starting material, to obtain 213 mg of the title compound (yield: 94%).

\(^1\)H NMR (300 MHz, MeOH-d\(_4\)) \( \delta \) 1.41 (m, 4H, CH\(_2\)CH\(_2\)), 1.65 (m, 4H, CH\(_2\)CH\(_2\)), 2.10 (t, 2H, \( J = 14.3, 7.0 \text{ Hz, CH} \)), 2.41 (d, 2H, \( J = 7.2 \text{ Hz, CH} \)), 2.89 (m, 2H, CH\(_2\)), 3.22 (t, 2H, \( J = 11.8, 5.9 \text{ Hz, CH} \)), 3.32 (m, 2H, CH\(_2\)), 3.52 (d, 2H, \( J = 11.8 \text{ Hz, CH} \)), 3.65 (t, \( J = 11.8, 5.8 \text{ Hz, 2H, CH} \)), 5.04 (s, 2H, CH\(_2\)), 6.70 (s, IH, CH), 7.05 (t, IH, \( J = 7.3, 1.0 \text{ Hz, ArH} \)), 7.45 (m, 4H, ArH), 7.83 (d, IH, \( J = 7.2 \text{ Hz, ArH} \)), 8.13 (d, IH, \( J = 7.2 \text{ Hz, ArH} \)).

Example 8: (E)-N8-hydroxy-Nl-(2-morpholinoethyl)-2-((naphthalen-1-yloxy)methyl)octenediamide
(8-1): (E)-8-(2-morpholinoethylamino)-7-((naphthalen-l-yloxy)methyl)-8-oxo-6-octene acid methylester

The procedure of Example (1-1) was repeated except for using 2-morpholinoethylamine instead of dimethylaminehydrochloride as the amine to obtain 266 mg of the title compound (yield: 91%).

\[ \text{H NMR (200 MHz, CDCl}_3 \text{)} \delta 1.45 (m, 2H, CH}_2, 1.64 (m, 2H}_5 \text{CH}_2, 2.20 (m, 4H, CH}_2\text{CH}_2, 2.25 (m, 4H, CH}_2\text{CH}_2, 2.40 (m, 2H, CH}_2, 3.07 (t, 2H, J = 8.6, 4.2 Hz, CH), 3.42 (t, 2H, J = 10.6, 5.4 Hz, CH}_2, 3.61 (s, 3H}_5 \text{OCH}_3, 4.89 (s, 2H, CH}_2, 6.90 (s, IH, CH}_5, 6.94 (d, IH}_5 J = 7.8 Hz, ArH), 7.45 (m, 4H, CH}_5 \text{ArH), 7.82 (dd, IH}_5 J = 7.8, 2.4 Hz, ArH), 8.19 (dd, IH}_5 J = 7.8, 2.8 Hz, ArH). \]

(8-2): (E)-8-(2-morpholinoethylamino)-7-((naphthalen-l-yloxy)methyl)-8-oxo-6-octene acid

The procedure of Example (1-2) was repeated except for using the compound obtained in Example (8-1) as the starting material, to obtain 250 mg of the title compound (yield: 96%).

\[ \text{H NMR (300 MHz, MeOH-d}_4 \text{)} \delta 1.50 (m, 2H, CH}_2, 1.62 (m, 2H}_5 \text{CH}_2, 2.24 (m, 4H, CH}_2\text{CH}_2, 2.38 (m, 4H}_5 \text{CH}_2\text{CH}_2, 2.58 (m, 2H}_5 \text{CH}_2, 3.32 (q, 2H}_5 J = 3.1, 1.5 Hz, CH}_5, 3.43 (m, 4H, CH}_2\text{CH}_2, 4.96 (s, 2H}_5 \text{CH}_2, 6.71 (s, IH}_5 \text{CH}_5, 7.01 (d, IH, J = 7.3 Hz, ArH), 7.43 (m, 4H, ArH), 7.80 (t, IH, J = 7.1, 5.5 Hz, ArH), 8.19 (d, IH, J = 7.6 Hz, ArH); MS (LC_5 70 eV) m/z 416 (M+l), 403, 346, 313, 298, 204, 102. \]

(8-3):(E)-N8-hydroxy-Nl-(2-morpholinoethyl)-2-((naphthalen-l-yloxy)ethyl)octenediamide

The procedure of Example (1-3) was repeated except for using the compound obtained in Example (8-2) as the starting material, to obtain 155
mg of the title compound (yield: 90%).

$^1$HNMR (300 MHz, MeOH-$d_4$) $\delta$ 1.48 (m, 2H, CH$_2$), 1.59 (m, 2H, CH$_2$), 2.25 (m, 4H, CH$_2$CH$_2$), 2.38 (m, 4H, CH$_2$CH$_2$), 2.56 (m, 2H, CH$_2$), 3.30 (d, 2H, J = 7.5 Hz, CH), 3.42 (m, 4H, CH$_2$CH$_2$), 5.01 (s, 2H, CH$_2$), 6.78 (s, IH, CH), 7.00 (d, IH, J = 7.4 Hz, ArH), 7.45 (m, 4H, ArH), 7.78 (d, IH, J = 7.4 Hz, ArH), 8.14 (d, IH, J = 7.6 Hz, ArH); MS (LC, 70 eV) $m/z$ 416 (M+I), 403, 346, 313, 298, 204, 102.

Example 9: (E)-N-hydroxy-8-(4-methylpiperazin-1-yl)-7-((naphthalen-1-yl oxy)methyl)-8-oxoocteneamide

(9-1): (E)-8-(4-methylpiperazin-1-yl)-7-((naphthalen-1-yl oxy)methyl)-8-oxo-6-octene acid methylester

The procedure of Example (1-1) was repeated except for using A-methylpiperazin-1-ylamine instead of dimethylaminehydrochloride as the amine to obtain 175 mg of the title compound (yield: 41%).

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 1.46 (m, 2H, CH$_2$), 1.53 (m, 2H, CH$_2$), 2.17 (m, 4H, CH$_2$CH$_2$), 2.34 (m, 8H, CH$_2$CH$_2$CH$_2$CH$_2$CH$_2$CH$_2$), 3.64 (s, 3H, NCH$_3$), 3.75 (s, 3H, OCH$_3$), 4.98 (s, 2H, CH$_2$), 5.78 (t, IH, J = 15.0, 7.5 Hz, CH), 6.84 (d, IH, J = 7.5 Hz, ArH), 7.44 (m, 4H, ArH), 7.79 (t, IH, J = 8.7, 1.2 Hz, ArH), 8.13 (d, IH, J = 7.8 Hz, ArH).

(9-2): (E)-8-(4-methylpiperazin-1-yl)-7-((naphthalen-1-yl oxy)methyl)-8-oxo-6-octene acid

The procedure of Example (1-2) was repeated except for using the compound obtained in Example (9-1) as the starting material, to obtain 168 mg of the title compound (yield: 100%).

$^1$H NMR (300 MHz, MeOH-$d_4$) $\delta$ 1.55 (m, 2H, CH$_2$), 1.68 (m, 2H, CH$_2$), 2.32
(m, HH, CHCH₂CH₂CH₂CH₂CH₂), 3.31 (m, IH, CH), 3.66 (s, 3H, NCH₃), 5.09 (s, 2H, CH₂), 5.92 (s, IH, CH), 6.97 (dd, IH, J = 6.5, 6.5 Hz, ArH), 7.46 (m, 4H, ArH), 7.81 (d, IH, J = 7.8 Hz, ArH), 8.16 (d, IH, J = 7.8 Hz, ArH).

(9-3):(E)-8-(4-methylpiperazin-1-yl)-7-((naphthalen-1-yl)oxy)methyl)-8-oxo-N-(tetrahydro-2H-pyran-2-yl)oxy)-6-octeneamide

The procedure of Example (4-3) was repeated except for using the compound obtained in Example (9-2) as the starting material, to obtain 317 mg of the title compound (yield: 83%).

¹H NMR (300 MHz, MeOH-d₄) δ 1.54 (m, 4H, CH₂), 1.72 (m, 4H, CH₂), 2.17 (m, 8H, CH₂CH₂CH₂CH₂), 2.37 (m, 6H, CH₂CH₂CH₂), 3.32 (q, 2H, J = 3.2, 1.6 Hz, CH₂), 3.57 (s, 3H, NCH₃), 3.92 (m, IH, CH), 5.08 (s, 2H, CH₂), 5.86 (s, IH, CH), 6.96 (d, IH, J = 7.3 Hz, ArH), 7.45 (m, 4H, ArH), 7.80 (d, IH, J = 7.3 Hz, ArH), 8.14 (d, IH, J = 7.3 Hz, ArH).

(9-4):(E)-N-hydroxy-8-(4-methylpiperazin-1-yl)-7-((naphthalen-1-yl)oxy)methyl)-8-oxoocteneamide

The procedure of Example (4-4) was repeated except for using the compound obtained in Example (9-3) as the starting material, to obtain 287 mg of the title compound (yield: 92%).

¹H NMR (300 MHz, MeOH-d₄) δ 1.52 (m, 2H, CH₂), 1.57 (m, 2H, CH₂), 2.13 (t, 2H, J = 14.3, 7.1 Hz, CH₂), 2.37 (q, 2H, J = 14.4, 7.1 Hz, CH₂), 2.61 (m, 4H, CH₂CH₂), 3.32 (m, 2H, CH₂), 3.76 (m, 2H₅CH₂), 3.80 (s, 3H, NCH₃), 5.10 (s, 2H, CH₂), 5.96 (s, IH, CH), 6.97 (d, IH, J = 7.3 Hz, ArH), 7.47 (m, 4H, ArH), 7.83 (t, IH, J = 9.1, 4.0 Hz, ArH), 8.13 (t, IH, J = 9.2, 5.1 Hz, ArH); MS (LC, 70 eV) m/z 426 (M+1), 407, 325, 293, 281, 326, 149, 102.

Example 10: (E)-N8-hydroxy-N1-(2-(4-methylpiperazin-1-yl)ethyl)-2-
The procedure of Example (1-1) was repeated except for using 2-(4-methylpiperazin-1-yl)ethylamine instead of dimethylaminehydrochloride as the amine to obtain 225 mg of the title compound (yield: 48%).

\[ \text{1H NMR (300 MHz, CDCl}_3 \delta 1.53 (m, 2H}_5 \text{CH}_2), 1.66 (m, 4H}_5 \text{CH}_2, 1.92 (m, 4H, CH}_2 \text{CH}_2), 2.31 (m, 8H}_5 \text{CH}_2 \text{CH}_2 \text{CH}_2), 2.42 (s, 3H, NCH}_3), 3.40 (q, 2H, J = 10.5, 5.4 Hz, CH}_2), 3.63 (s, 3H, OCH}_3), 4.87 (s, 2H}_5 \text{CH}_2), 6.95 (dd, IH, J = 15.6, 7.8 Hz, CH), 7.05 (s, 1H}_5 \text{ArH}), 7.45 (m, 4H, ArH)\]

\[ \text{7.80 (dd, IH, J = 6.9, 1.8 Hz, ArH), 8.19 (t, IH, J = 9.6, 7.8 Hz, ArH).} \]

The procedure of Example (1-2) was repeated except for using the compound obtained in Example (10-1) as the starting material, to obtain 157 mg of the title compound (yield: 76%).

\[ \text{1H NMR (300 MHz, MeOH-d}_4 \delta 1.24 (s, 1H}_5 \text{CH), 1.54 (m, 4H, CH}_2 \text{CH}_2), 2.20 (m, 4H}_5 \text{CH}_2 \text{CH}_2), 2.29 (m, 4H, CH}_2 \text{CH}_2), 2.51 (m, 4H, CH}_2 \text{CH}_2), 3.05 (m, 1H, CH), 3.24 (s, 3H}_5 \text{NCH}_3), 3.34 (m, 2H}_5 \text{CH}_2), 4.94 (s, 2H, CH}_2), 6.69 (s, 1H}_5 \text{CH), 7.01 (dd, 1H}_5 \text{J = 7.2, 1.0 Hz}_5 \text{ArH}), 7.42 (m, 4H}_5 \text{ArH) 7.75 (d, 1H, J = 7.2 Hz, ArH), 8.08 (d, 1H, J = 1.7 Hz, ArH).} \]

The procedure of Example (4-3) was repeated except for using the compound obtained in Example (10-2) as the starting material, to obtain 137

\[ \text{((naphthalen-l-yloxy)methyl)octenediamide} \]

\[ \text{(1O-^-E^S-Cl^-methylpiperazin-l-yOethylamino^-T^-naphthalen-l-yloxy)methyl)-8-oxo-6-octene acid methylester} \]
mg of the title compound (yield: 54%).

$^1\text{H} \text{NMR}$ (300 MHz, MeOH-d$_4$) $\delta$ 1.54 (m, 4H, CH$_2$CH$_2$), 1.64 (m, 6H, CHCH$_2$CH$_2$), 2.11 (m, 5H, CHCH$_2$CH$_2$), 2.41 (m, 8H, CH$_2$CH$_2$CH$_2$CH$_2$), 3.27 (s, 3H, NCH$_3$), 3.34 (m, 3H, CHCH$_2$), 3.50 (m, 2H, CH$_2$), 3.85 (t, IH, $J = 7.2, 1.8$ Hz, CH), 4.96 (s, 2H, CH$_2$), 6.70 (s, IH, CH), 7.01 (d, IH, $J = 7.2$ Hz, ArH), 7.43 (m, 4H, ArH), 7.79 (dd, IH, $J = 6.6, 1.7$ Hz, ArH), 8.10 (t, IH, $J = 8.9, 7.2$ Hz, ArH).

(10-4): (E)-N8-hydroxy-Nl-(2-(4-methylpiperazin-l-yl)ethyl)-2-((naphthalen-l-yloxy)methyl)octenediamide

The procedure of Example (4-4) was repeated except for using the compound obtained in Example (10-3) as the starting material, to obtain 118 mg of the title compound (yield: 76%).

$^1\text{H} \text{NMR}$ (300 MHz, MeOH-d$_4$) $\delta$ 1.53 (d, 2H, $J = 7.7$ Hz, CH$_2$), 1.65 (d, 2H, $J = 7.0$ Hz, CH$_2$), 2.10 (t, 2H, $J = 14.3$, 7.0 Hz, CH$_2$), 2.39 (t, 2H, $J = 14.2$, 7.3 Hz, CH$_2$), 2.72 (d, 2H, $J = 8.2$ Hz, CH$_2$), 2.95 (d, 2H, $J = 5.4$ Hz, CH$_2$), 3.12 (m, 6H, CH$_2$CH$_2$CH$_2$), 3.32 (s, 3H, NCH$_3$), 3.56 (t, 2H, $J = 11.2$, 5.6 Hz, CH$_2$), 5.02 (s, 2H, CH$_2$), 6.75 (t, IH, $J = 15.0$, 7.2 Hz, CH), 7.05 (d, IH, $J = 7.2$ Hz, ArH), 7.46 (m, 4H, ArH), 7.82 (d, IH, $J = 7.5$ Hz, ArH), 8.14 (d, IH, $J = 8.5$ Hz, ArH).

Example 11: (E)-Nl-(cyanomethyl)-N8-hydroxy-Nl-methyl-2-((naphthalen-l-yloxy)methyl)octenediamide

(II-I): (E)-8-((cyanomethyl)(cyanomethyl)amino)-7-((naphthalen-l-yloxy)methyl)-8-oxo-6-octene acid methylester

The procedure of Example (1-1) was repeated except for using cyanomethylamine as instead of dimethylaminehydrochloride the amine to obtain 299 mg of the title compound (yield: 76%).
1H NMR (200 MHz, CDCl₃) δ 1.35 (m, 2H, CH₂), 1.60 (m, 2H, CH₂), 2.31 (m, 4H, CH₂CH₂), 3.11 (s, 3H, NCH₃), 3.67 (s, 3H, OCH₃), 4.38 (s, 2H, CH₂), 4.97 (s, 2H, CH₂), 5.98 (s, IH, CH), 6.85 (d, IH, J = 4.6 Hz, ArH), 7.37 (t, IH, J = 10.6, 5.2 Hz, ArH), 7.47 (m, 3H, ArH), 7.79 (dd, IH, J = 6.2, 1.4 Hz, ArH), 8.06 (d, IH, J = 4.6 Hz, ArH).

(II-2):(E)-8-((cyanomethyl)(cyanomethyl)amino)-7-((naphthalen-1-yloxy)methyl)-8-oxo-6-octene acid

The procedure of Example (1-2) was repeated except for using the compound obtained in Example (11-1) as the starting material, to obtain 250 mg of the title compound (yield: 84%).

1H NMR (300 MHz, MeOH-d₄) δ 1.37 (m, 2H, CH₂), 1.61 (m, 2H, CH₂), 2.31 (m, 4H, CH₂CH₂), 3.31 (s, 3H, NCH₃), 4.16 (d, 2H, J = 8.5 Hz, CH₂), 5.01 (s, 2H, CH₂), 6.21 (m, IH, CH), 6.98 (d, IH, J = 7.0 Hz, ArH), 7.44 (m, 4H, ArH), 7.81 (t, IH, J = 8.8, 2.8 Hz, ArH), 8.13 (d, IH, J = 13.6 Hz, ArH).


The procedure of Example (4-3) was repeated except for using the compound obtained in Example (11-2) as the starting material, to obtain 222 mg of the title compound (yield: 64%).

1H NMR (300 MHz, MeOH-d₄) δ 1.48 (m, 4H, CH₂CH₂), 1.71 (m, 4H, CH₂CH₂), 1.92 (m, 4H, CH₂CH₂), 2.32 (m, 4H, CH₂CH₂), 3.21 (s, 3H, NCH₃), 3.73 (t, IH, J = 7.2 Hz, CH₂), 4.39 (s, 2H, CH₂), 5.06 (s, 2H, CH₂), 6.18 (m, IH, CH), 7.20 (d, IH, J = 7.0 Hz, ArH), 7.64 (m, 4H, ArH), 8.09 (dd, IH, J = 14.8, 7.2 Hz, ArH), 8.13 (m, IH, ArH).

(II-4):(E)-N₁-(cyanomethyl)-N₈-hydroxy-N₁-methyl-2-((naphthalen-1-
The procedure of Example (4-4) was repeated except for using the compound obtained in Example (11-3) as the starting material, to obtain 170 mg of the title compound (yield: 75%).

\[ \text{NMR (300 MHz, MeOH-}^{d_4}) \delta \] 1.34 (d, 2H, J = 7.7 Hz, CH\(_2\)), 1.50 (d, 2H, J = 6.7 Hz, CH\(_2\)), 1.89 (d, 2H, J = 7.2 Hz, CH\(_2\)), 2.25 (q, 2H, J = 16.2, 7.9 Hz, CH\(_2\)), 3.20 (s, 3H, NCH\(_3\)), 3.91 (d, 2H, J = 7.6 Hz, CH\(_2\)), 4.98 (s, 2H, CH\(_2\)), 5.98 (d, IH, J = 14.7 Hz, CH), 6.86 (d, IH, J = 6.7 Hz, ArH), 7.35 (m, 4H, ArH), 7.56 (t, IH, J = 9.1, 3.4 Hz, ArH), 7.98 (m, 1H, ArH).

Example 12: (E)-N\(_8\)-hydroxy-N\(_1\)-(2-hydroxyethyl)-N\(_1\)-methyl-2-((naphthalen-1-yloxy)methyl)octenediamide

The procedure of Example (1-1) was repeated except for using 2-hydroxyethylamine instead of dimethylaminehydrochloride as the amine to obtain 366 mg of the title compound (yield: 93%).

\[ \text{NMR (300 MHz, CDCl}_3 \] \( \delta \) 1.51 (m, 2H, CH\(_2\)), 1.68 (m, 2H, CH\(_2\)), 2.29 (m, 4H, CH\(_2\)CH\(_2\)), 3.08 (s, 3H, NCH\(_3\)), 3.66 (m, 4H, CH\(_2\)CH\(_2\)), 3.81 (S, 3H, OCH\(_3\)), 4.96 (s, 2H, CH\(_2\)), 6.86 (d, IH, J = 7.0 Hz, CH), 7.26 (s, IH, ArH), 7.44 (m, 4H, ArH), 7.77 (d, IH, J = 7.2 Hz, ArH), 8.15 (d, IH, J = 7.2 Hz, ArH).

Example 12: (E)-8-((2-hydroxyethyl)(methyl)amino)-7-((naphthalen-1-yloxy)methyl)-8-oxo-6-octene acid methylester

The procedure of Example (1-2) was repeated except for using the compound obtained in Example (12-1) as the starting material, to obtain 320 mg of the title compound (yield: 68%).
mg of the title compound (yield: 88%).

\(^1\)H NMR (300 MHz, MeOH-\(d_4\)) \(\delta\) 1.30 (m, 4H, CH\(_2\)CH\(_2\)), 2.08 (m, 4H, CH\(_2\)CH\(_2\)), 3.07 (s, 3H, NCH\(_3\)), 3.09 (m, 4H, CH\(_2\)CH\(_2\)), 4.74 (s, 2H, CH\(_2\)), 6.77 (t, IH, J = 7.2, 1.2 Hz, CH), 6.95 (s, IH, ArH), 7.20 (m, 4H, ArH), 7.56 (t, IH, J = 7.0, 1.9 Hz, ArH).

(12-3): (E)-N\(_8\)-hydroxy-Nl-(2-hydroxyethyl)-Nl-methyl-2-((naphthalen-1-yloxy)methyl)octenediamide

The procedure of Example (1-3) was repeated except for using the compound obtained in Example (12-2) as the starting material, to obtain 262 mg of the title compound (yield: 90%).

\(^1\)H NMR (300 MHz, MeOH-\(d_4\)) \(\delta\) 1.32 (m, 4H, CH\(_2\)CH\(_2\)), 2.06 (m, 4H, CH\(_2\)CH\(_2\)), 3.08 (s, 3H, NCH\(_3\)), 3.13 (m, 4H, CH\(_2\)CH\(_2\)), 4.92 (s, 2H, CH\(_2\)), 6.78 (t, IH, J = 7.4, 1.8 Hz, CH), 6.92 (s, IH, ArH), 7.28 (m, 4H, ArH), 7.56 (d, IH, J = 7.4 Hz, ArH), 7.88 (d, IH, J = 7.4 Hz, ArH); MS (LC, 70 eV) \(m/z\) 448 (M+1), 305, 204.

Example 13: (E)-N\(_8\)-hydroxy-Nl-methyl-Nl-(l-methylpyrrolidin-3-yl)-2-((naphthalen-1-yloxy)methyl)octenediamide

(13-1): (E)-8-(methyl(l-methylpyrrolidin-3-yl)amino)-7-((naphthalen-1-yloxy)methyl)-8-oxo-6-octene acid methylester

The procedure of Example (1-1) was repeated except for using l-methylpyrrolidin-3-ylamine instead of dimethylaminehydrochloride as the amine to obtain 355 mg of the title compound (yield: 91%).

\(^1\)H NMR (200 MHz, CDCl\(_3\)) \(\delta\) 1.42 (m, 4H, CH\(_2\)CH\(_2\)), 1.80 (m, 4H, CH\(_2\)CH\(_2\)), 2.20 (m, 4H, CH\(_2\)CH\(_2\)), 2.98 (s, 3H, NCH\(_3\)), 3.61 (s, 3H, NCH\(_3\)), 3.80 (s, 3H, OCH\(_3\)), 4.82 (s, 2H, CH\(_2\)), 4.96 (s, 2H, CH\(_2\)), 5.81 (m, IH, CH), 6.82 (m, IH,
ArH) 3 7.45 (m, 4H ArH), 7.80 (m, IH ArH) 3 8.15 (m, IH ArH).

(13-2):(E)-8-(methyl(1-methylpyrrolidin-3-yl)amino)-7-((naphthalen-1-yloxy)methyl)-8-oxo-6-octene acid

The procedure of Example (1-2) was repeated except for using the compound obtained in Example (13-1) as the starting material, to obtain 320 mg of the title compound (yield: 86%).

${}^1H$ NMR (300 MHz, MeOH-d$_4$) $\delta$ 1.42 (m, 4H CH$_2$CH$_2$), 1.76 (m, 4H, CH$_2$CH$_2$), 2.22 (m, 4H$_5$ CH$_2$CH$_2$), 2.88 (s, 3H, NCH$_3$), 3.58 (s, 3H$_5$NCH$_3$), 4.80 (s, 2H, CH$_2$), 4.99 (s, 2H, CH$_2$), 5.84 (m, IH, ArH) 5 7.44 (m, 4H$_5$ArH) 5 7.80 (m, IH$_5$ArH) 5 8.12 (m, IH$_5$ArH).

(13^rCE^NS-hydroxy-Nl-methyl-Nl-Cl-methylpyrrolidin-S-yl)-l-((naphthalen-l-yloxy)methyl)octenediamide

The procedure of Example (1-3) was repeated except for using the compound obtained in Example (13-2) as the starting material, to obtain 188 mg of the title compound (yield: 41%).

${}^1H$ NMR (300 MHz, MeOH-d$_4$) $\delta$ 1.42 (m, 4H$_5$ CH$_2$CH$_2$), 1.80 (m, 4H$_5$ CH$_2$CH$_2$), 2.20 (m, 4H$_5$ CH$_2$CH$_2$), 2.98 (s, 3H$_5$NCH$_3$), 3.60 (s, 3H$_5$NCH$_3$), 3.80 (s, 3H, OCH$_2$), 5.00 (s, 2H, CH$_2$), 4.96 (s, 2H, CH$_2$), 5.82 (m, IH, CH), 6.84 (m, IH, ArH), 7.44 (m, 4H$_5$ArH) 5 7.78 (m, IH$_5$ArH) 5 8.14 (m, IH$_5$ArH).

Example 14: (E)-Nl-(3-(dimethylamino)propyl)-N8-hydroxy-2-((naphthalen-l-yloxy)methyl)octenediamide

(14-l):(E)-7-(3-(dimethylamino)propylcarbamoyl)-8-(naphthalen-l-yloxy)octane acid methylester

The procedure of Example (1-1) was repeated except for using 3-
(dimethylamino)propylamine instead of dimethylaminehydrochloride as the amine to obtain 467 mg of the title compound (yield: 73%).

\[ {^1}H\text{ NMR (200 MHz, CDCl}_3\text{)} \delta 1.45 \text{ (m, 2H, CH}_2\text{), 1.64 \text{ (m, 4H, CH}_2\text{CH}_2\text{), 2.01 \text{ (s, 6H, N(CH}_3\text)_2\text{), 2.25 \text{ (m, 6H, CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{), 3.40 \text{ (m, 2H, CH}_2\text{), 3.60 \text{ (s, 3H, OCH}_3\text{), 4.96 \text{ (s, 2H, CH}_2\text{), 6.81 \text{ (t, 1H, J = 15.4 Hz, CH), 6.94 \text{ (t, 1H, J = 7.4 Hz, ArH)}, 7.43 \text{ (m, 4H, ArH), 7.79 \text{ (m, 1H, ArH), 8.19 \text{ (dd, 1H, J = 6.8, 3.6 Hz, ArH).}}}}\]

(14-2):(E)-7-(3-(dimethylamino)propylcarbamoyl)-8-(naphthalen-1-yloxy)octane acid

The procedure of Example (1-2) was repeated except for using the compound obtained in Example (14-1) as the starting material, to obtain 154 mg of the title compound (yield: 83%).

\[ {^1}H\text{ NMR (300 MHz, MeOH-d}_4\text{)} \delta 1.30 \text{ (m, 2H, CH}_2\text{), 1.64 \text{ (d, 2H, J = 6.9 Hz, CH}_2\text{), 1.94 \text{ (m, 2H, CH}_2\text{), 2.27 \text{ (t, 2H, J = 14.2 Hz, CH}_2\text{), 2.39 \text{ (d, 2H, J = 7.2 Hz, CH}_2\text{), 2.74 \text{ (s, 6H, N(CH}_3\text)_2\text{), 3.03 \text{ (t, 1H, J = 15.0 Hz, CH}_2\text{), 3.33 \text{ (m, 2H, CH}_2\text{), 5.05 \text{ (s, 2H, CH}_2\text{), 6.66 \text{ (s, 1H, CH), 7.03 \text{ (dd, 1H, J = 7.2 Hz, ArH)}, 7.46 \text{ (m, 4H, ArH), 7.80 \text{ (d, 1H, J = 6.9 Hz, ArH), 8.14 \text{ (d, 1H, J = 7.0 Hz, ArH).}}}}\]

(14-3):(E)-Nl-(3-(dimethylamino)propyl)-2-((naphthalen-1-yloxy)methyl)-N8-(tetrahydro-2H-pyran-2-yloxy)octenediamide

The procedure of Example (4-3) was repeated except for using the compound obtained in Example (14-2) as the starting material, to obtain 160 mg of the title compound (yield: 89%).

\[ {^1}H\text{ NMR (200 MHz, MeOH-d}_4\text{)} \delta 1.59 \text{ (m, 13H, CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{), 1.90 \text{ (s, 6H, N(CH}_3\text)_2\text{), 2.23 \text{ (m, 6H, CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{), 3.41 \text{ (q, 2H, J = 11.8 Hz, CH}_3\text{CH}_2\text{), 3.61 \text{ (m, 1H, CH}, 3.91 \text{ (m,}}\]
IH, CH), 4.87 (s, 2H, CH2), 6.82 (d, IH, J = 7.4 Hz, CH), 6.89 (d, IH, J = 6.8 Hz, ArH), 7.44 (m, 4H, ArH), 7.79 (dd, IH, J = 5.2, 3.2 Hz, ArH), 8.16 (t, IH, J = 9.4, 6.4 Hz, ArH).

(14-4): (E)-Nl-(3-(dimethylamino)propyl)-N8-hydroxy-2-((naphthalen-1-yloxy)methyl)octenediamide

The procedure of Example (4-4) was repeated except for using the compound obtained in Example (14-3) as the starting material, to obtain 142 mg of the title compound (yield: 92%).

1H NMR (300 MHz, MeOH-d4) δ 1.52 (t, 2H, J = 7.5, 4.1 Hz, CH2), 1.64 (d, 2H, J = 7.1 Hz, CH2), 1.92 (t, 2H, J = 13.8, 7.5 Hz, CH2), 2.10 (t, IH, J = 14.2, 7.0 Hz, CH2), 2.37 (d, 2H, J = 7.2 Hz, CH2), 2.72 (s, 6H, N(CH3)2), 3.01 (t, 2H, J = 14.8, 7.3 Hz, CH2), 3.35 (m, 3H, CHCH2), 5.03 (s, 2H, CH2), 6.62 (t, IH, J = 15.0, 7.5 Hz, CH), 7.02 (d, IH, J = 7.1 Hz, ArH), 7.46 (m, 4H, ArH), 7.80 (dd, IH, J = 6.2, 1.9 Hz, ArH), 8.14 (t, IH, J = 8.9, 6.9 Hz, ArH); MS (LC, 70 eV) m/z 429 (M+1), 413, 301, 256, 224.

Example 15: (E)-N-hydroxy-8-morpholino-7-((naphthalen-1-yloxy)methyl)-8-oxoocteneamide

(15-1): (E)-8-morpholino-7-((naphthalen-1-yloxy)methyl)-8-oxooctene acid methylester

The procedure of Example (1-1) was repeated except for using morpholinoamine instead of dimethylaminehydrochloride as the amine to obtain 416 mg of the title compound (yield: 67%).

1H NMR (200 MHz, CDCl3) δ 1.45 (m, 2H, CH2), 1.63 (m, 2H, CH2), 2.25 (m, 4H, CH2CH2), 3.60 (m, 8H, CH2CH2CH2CH2), 3.71 (s, 3H, OCH3), 5.01 (s, 2H, CH2), 5.82 (t, IH, J = 15.0, 7.8 Hz, CH), 6.84 (dd, IH, J = 7.2, 1.2 Hz, ArH), 7.46 (m, 4H, ArH), 7.79 (m, IH, ArH), 8.13 (dd, IH, J = 4.0, 3.2 Hz,
(15-2): (E)-8-morpholino-7-((naphthalen-1-yl)oxy)methyl)-8-oxooctene acid

The procedure of Example (1-2) was repeated except for using the compound obtained in Example (15-1) as the starting material, to obtain 85 mg of the title compound (yield: 89%).

\[ \text{H NMR (300 MHz, MeOH-d}_4) \delta 1.45 (m, 2H, CH}_2, 1.63 (m, 2H, CH}_2, 2.24 (m, 4H, CH}_2CH}_2, 3.58 (m, 8H, CH}_2CH}_2CH}_2CH}_2, 5.02 (s, 2H, CH}_2, 5.86 (t, IH, J = 15.2, 7.6 Hz, CH), 6.82 (dd, IH, J = 7.4, 1.2 Hz, ArH), 7.45 (m, 4H, ArH), 7.80 (d, IH, J = 7.4 Hz, ArH), 8.13 (t, IH, J = 7.4, 3.4 Hz, ArH). \]

(15-3): (E)-8-morpholino-7-((naphthalen-1-yl)oxy)methyl)-8-oxo-N-(tetrahydro-2H-pyran-2-yloxy)octeneamide

The procedure of Example (4-3) was repeated except for using the compound obtained in Example (15-2) as the starting material, to obtain 92 mg of the title compound (yield: 88%).

\[ \text{H NMR (200 MHz, MeOH-d}_4) \delta 1.54 (m, 5H, CH CH}_2CH}_2, 1.68 (m, 4H, CH}_2CH}_2, 2.18 (m, 2H, CH}_2, 2.40 (m, 2H, CH}_2, 3.25 (m, 5H, CHCH}_2CH}_2, 3.59 (m, 6H, CH}_2CH}_2CH}_2, 3.99 (m, IH, CH), 5.08 (s, 2H, CH}_2, 5.90 (t, IH, J = 15.0, 7.6 Hz, CH), 6.97 (t, IH, J = 7.0, 5.8 Hz, ArH), 7.48 (m, 4H, ArH), 7.91 (dd, IH, J = 12.6, 3.0 Hz, ArH), 8.13 (t, IH, J = 7.0, 4.0 Hz, ArH). \]

(15-4): (E)-N-hydroxy-8-morpholino-7-((naphthalen-1-yl)oxy)methyl)-8-oxooctenediamide

The procedure of Example (4-4) was repeated except for using the compound obtained in Example (15-3) as the starting material, to obtain 64 mg of the title compound (yield: 72%).
\[ \text{Example 16: (E)-N8-hydroxy-N1-(6-(4-methylpiperazin-1-yl)pyridin-3-yl)-2-((naphthalen-1-yloxy)methyl)octenediamide} \]

(16-1): (E)-8-(6-(4-methylpiperazin-1-yl)pyridin-3-ylamino)-7-((naphthalen-1-yloxy)methyl)-8-oxo-6-octene acid methylester

The procedure of Example (1-1) was repeated except for using 6-(4-methylpiperazin-1-yl)pyridin-3-ylamine instead of dimethylaminehydrochloride as the amine to obtain 216 mg of the title compound (yield: 37%).

\[ \text{1H NMR (300 MHz, MeOH-d}_4\text{) } \delta 1.53 \text{ (s, 2H, CH}_2\text{), 1.68 \text{ (m, 2H, CH}_2\text{), 2.13 (t, 2H, J = 14.1, 7.0 Hz, CH}_2\text{), 2.35 (q, 2H, J = 14.6, 7.3 Hz, CH}_2\text{), 3.33 (m, 2H, CH}_2\text{), 3.53 (m, 6H, CH}_2\text{CH}_2\text{CH}_2\text{), 5.06 (s, 2H, ArH), 5.86 (t, IH, J = 14.9, 7.4 Hz, CH)), 6.97 (t, IH, J = 7.2, 2.4 Hz, ArH), 7.45 (m, 4H, ArH), 7.80 (dd, IH, J = 5.6, 2.6 Hz, ArH), 8.13 (dd, IH, J = 6.2, 2.6 Hz, ArH); MS (LC, 70 eV) m/z 413 (M+1), 380, 309, 293, 265, 236, 149, 121.} \]

(16-2): (E)-8-(6-(4-methylpiperazin-1-yl)pyridin-3-ylamino)-7-((naphthalen-1-yloxy)methyl)-8-oxo-6-octene acid methylester

The procedure of Example (1-2) was repeated except for using the compound obtained in Example (16-1) as the starting material, to obtain 249 mg of the title compound (yield: 94%).

\[ \text{1H NMR (300 MHz, MeOH-d}_4\text{) } \delta 1.45 \text{ (m, 2H), 1.67 (m, 2H), 2.30 (t, 2H),} \]

52
2.94 (s, 3H), 3.33 (m, 4H)3.83 (br, 4H), 4.45 (t, IH), 4.56 (d, IH), 7.03 (d, IH)7.41 (m, 4H), 7.76 (m, 2H), 7.92 (d, IH), 8.12 (m, 2H), 8.49 (s, IH); MS (LC, 70 eV) m/z 503 (M+ 1).

(16-3): (E)-N8-hydroxy-Nl-(6-(4-methylpiperezin-l-yl)pyridin-3-yl)-2-((naphthalen-l-yloxy)methyl)octenediamide

The procedure of Example (1-3) was repeated except for using the compound obtained in Example (16-2) as the starting material, to obtain 132 mg of the title compound (yield: 72%).

1H NMR (300 MHz, MeOH-d4) δ 1.45 (m, 2H), 1.67 (m, 2H), 2.11 (t, 2H), 2.94 (s, 3H), 3.33 (m, 4H), 3.83 (br, 4H), 4.45 (t, IH), 4.56 (d, IH), 7.03 (d, IH), 7.41 (m, 4H), 7.76 (m, 2H), 7.92 (d, IH), 8.12 (m, 2H), 8.49 (s, IH); MS (LC, 70 eV) m/z 518 (M+ 1).

Example 17: (E)-Nl-(6-(2-morpholinoethylamino)pyridin-3-yl)-N8-hydroxy-2-((naphthalen-l-yloxy)methyl)octenediamide

(17-1): (E)-7-(6-(2-morpholinoethylamino)pyridin-3-ylcarbamoyl)-8-(naphthalen-l-yloxy)-6-octene acid methylester

The procedure of Example (1-1) was repeated except for using 6-(2-morpholinoethylamino)pyridin-3-yl instead of dimethylaminehydrochloride amine as the amine to obtain 350 mg of the title compound (yield: 64%).

1H NMR (300 MHz, MeOH-d4) δ 1.45 (m, 2H), 1.63 (m, 2H), 1.91 (m, 2H), 2.29 (t, 2H), 2.88 (m, 6H), 3.52 (t, 2H), 3.69 (s, 3H), 3.81 (m, 4H), 4.34 (t, IH), 4.78 (d, IH), 6.60 (d, IH), 7.42 (m, 6H), 7.66 (d, IH), 7.74 (m, IH), 8.12 (m, IH), 8.24 (s, IH); MS (LC, 70 eV) m/z 547 (M+1).

(17-2): (E)-7-(6-(2-morpholinoethylamino)pyridin-3-ylcarbamoyl)-8-(naphthalen-l-yloxy)-6-octene acid
The procedure of Example (1-2) was repeated except for using the compound obtained in Example (17-1) as the starting material, to obtain 207 mg of the title compound (yield: 87%).

\[ ^1H \text{NMR (300 MHz, MeOH-d}^4) \delta 1.45 (m, 2H), 1.63 (m, 2H), 1.91 (m, 2H), 2.29 (t, 2H), 2.88 (m, 6H), 3.52 (t, 2H), 3.81 (m, 4H), 4.34 (t, IH), 4.78 (d, IH), 6.60 (d, IH), 7.42 (m, 6H), 7.66 (d, IH), 7.74 (m, IH), 8.12 (m, IH), 8.24 (s, IH); MS (LC, 70 eV) m/z 533 (M+1). \]

17-3): (E)-Nl-(6-(2-morpholinoethylamino)pyridin-3-yl)-N8-hydroxy-2-((naphthalen-1-yloxy)methyl)octenediamide

The procedure of Example (1-3) was repeated except for using the compound obtained in Example (17-2) as the starting material, to obtain 171 mg of the title compound (yield: 48%).

\[ ^1H \text{NMR (300 MHz, DMSO-d}^6) \delta 1.39 (m, 2H), 1.54 (m, 2H), 1.78 (m, 2H), 1.96 (t, 2H), 3.35 (m, 6H), 3.69 (m, 2H), 3.81 (m, 4H), 4.38 (t, IH), 4.52 (d, IH), 6.87 (d, IH), 7.45 (m, 6H), 7.82 (m, 2H), 8.03 (m, IH), 8.38 (s, IH), 10.07 (s, IH), 10.39 (s, IH); MS (LC, 70 eV) m/z 548 (M+1). \]

Example 18: (E)-Nl-(6-(dimethylamino)pyridin-3-yl)-N8-hydroxy-2-((naphthalen-1-yloxy)methyl)octenediamide

The procedure of Example (1-1) was repeated except for using not dimethylaminehydrochloride but 6-(dimethylamino)pyridin-3-ylamine as the amine to obtain 256 mg of the title compound (yield: 63%).

\[ ^1H \text{NMR (300 MHz, CDCl}_3) \delta 1.64 (m, 4H), 2.36 (m, 4H), 3.07 (s, 6H), 3.68 (s, 3H), 5.06 (s, 2H), 6.52 (d, IH), 6.98 (m, 2H), 7.44 (t, IH), 7.53 (m, 3H), \]

54
7.87 (m, 2H), 8.11 (d, IH), 8.27 (m, IH); MS (LC, 70 eV) m/z 462 (M+1).

(18-2): (E)-7-(6-(dimethylamino)pyridin-3-ylcarbamoyl)-8-(naphthalen-1-yloxy)-6-octene acid

The procedure of Example (1-2) was repeated except for using the compound obtained in Example (18-1) as the starting material, to obtain 190 mg of the title compound (yield: 76%).

\[
\begin{align*}
^1H \text{ NMR (300 MHz, MeOH-d}_4) & \delta 1.61 (m, 4H), 2.28 (t, 2H), 2.44 (q, 2H), \\
& 3.08 (s, 6H), 5.12 (s, 2H), 6.71 (m, 2H), 7.05 (d, IH), 7.44 (m, 4H), 7.79 (m, 2H), 8.23 (m, 2H); \\
& MS (LC, 70 eV) m/z 448 (M+1).
\end{align*}
\]

(18-3): (E)-N1-(6-(dimethylamino)pyridin-3-yl)-N8-hydroxy-2-((naphthalen-1-yloxy)methyl)octenediamide

The procedure of Example (1-3) was repeated except for using the compound obtained in Example (18-2) as the starting material, to obtain 90 mg of the title compound (yield: 46%).

\[
\begin{align*}
^1H \text{ NMR (300 MHz, MeOH-d}_4) & \delta 1.66 (m, 4H), 2.11 (t, 2H), 2.43 (q, 2H), \\
& 3.06 (s, 6H), 5.10 (s, 2H), 6.68 (m, 2H), 7.07 (d, IH), 7.44 (m, 4H), 7.78 (m, 2H), 8.20 (m, 2H); \\
& MS (LC, 70 eV) m/z 463 (M+1).
\end{align*}
\]

Example 19: (E)-N1-(6-(2-(dimethylamino)ethylamino)pyridin-3-yl)-N8-hydroxy-2-((naphthalen-1-yloxy)methyl)octenediamide

(19-1): (E)-8-(6-(2-(dimethylamino)ethylamino)pyridin-3-ylamino)-7-((naphthalen-1-yloxy)methyl)-8-oxo-6-octene acid methylester

The procedure of Example (1-1) was repeated except for using 6-(2-(dimethylamino)ethylamino)pyridin-3-ylamine instead of dimethylaminehydrochloride as the amine to obtain 307 mg of the title
compound (yield: 31%).

\(^1\text{H} \text{NMR} \ (300 \ \text{MHz}, \ \text{CDCl}_3) \ \delta \ 1.65 \ (m, \ 4H), \ 2.08 \ (m, \ 2H), \ 2.31 \ (s, \ 6H), \ 2.38 \ (m, \ 2H), \ 2.59 \ (t, \ 2H), \ 3.35 \ (q, \ 2H), \ 3.67 \ (s, \ 3H), \ 5.06 \ (s, \ 2H), \ 6.44 \ (d, \ \text{IH}), \ 7.03 \ (m, \ 2H), \ 7.45 \ (t, \ \text{IH}), \ 7.53 \ (m, \ 3H), \ 7.75 \ (dd, \ \text{IH}), \ 7.85 \ (dd, \ \text{IH}), \ 8.06 \ (d, \ \text{IH}), \ 8.24 \ (m, \ 2H); \ \text{MS} \ (\text{LC}, \ 70 \ \text{eV}) \ m/z \ 505 \ (M+1).

\textbf{(19-2): (E)-8-(6-(2-(dimethylamino)ethylamino)pyridin-3-ylamino)-7-((naphthalen-1-yloxy)methyl)-8-oxo-6-octene acid}

The procedure of Example (1-2) was repeated except for using the compound obtained in Example (19-1) as the starting material, to obtain 226 mg of the title compound (yield: 75%).

\(^1\text{H} \text{NMR} \ (300 \ \text{MHz}, \ \text{MeOH-d}_4) \ \delta \ 1.64 \ (m, \ 4H), \ 2.27 \ (t, \ 2H), \ 2.47 \ (m, \ 2H), \ 2.91 \ (s, \ 6H), \ 3.28 \ (q, \ 2H), \ 3.65 \ (t, \ 2H), \ 5.11 \ (s, \ 2H), \ 6.66 \ (d, \ \text{IH}), \ 6.72 \ (t, \ \text{IH}), \ 7.08 \ (d, \ \text{IH}), \ 7.44 \ (m, \ 4H), \ 7.67 \ (dd, \ \text{IH}), \ 7.78 \ (dd, \ \text{IH}), \ 8.15 \ (dd, \ \text{IH}), \ 8.29 \ (m, \ \text{IH}); \ \text{MS} \ (\text{LC}, \ 70 \ \text{eV}) \ m/z \ 491 \ (M+1).

\textbf{(19-3): (E)-N1-(6-(2-(dimethylamino)ethylamino)pyridin-3-yl)-N8-hydroxy-2-((naphthalen-1-yloxy)methyl)octenediamide}

The procedure of Example (1-3) was repeated except for using the compound obtained in Example (19-2) as the starting material, to obtain 11 mg of the title compound (yield: 5%).

\(^1\text{H} \text{NMR} \ (300 \ \text{MHz}, \ \text{MeOH-d}_4) \ \delta \ 1.64 \ (m, \ 4H), \ 2.11 \ (t, \ 2H), \ 2.50 \ (s, \ 6H), \ 2.52 \ (m, \ 2H), \ 2.83 \ (t, \ 2H), \ 4.11 \ (t, \ 2H), \ 5.13 \ (s, \ 2H), \ 6.78 \ (m, \ \text{IH}), \ 7.06 \ (d, \ \text{IH}), \ 7.45 \ (m, \ 4H), \ 7.58 \ (dd, \ \text{IH}), \ 7.78 \ (dd, \ \text{IH}), \ 8.06 \ (dd, \ \text{IH}), \ 8.13 \ (d, \ \text{IH}), \ 8.74 \ (d, \ \text{IH}); \ \text{MS} \ (\text{LC}, \ 70 \ \text{eV}) \ m/z \ 506 \ (M+1).

\textbf{Example 20: (E)-N8-hydroxy-N1-(6-methoxypyridin-3-yl)-2-((naphthalen-1-yloxy)methyl)octenediamide}
(20-1): 7-(6-methoxy-pyridin-3-ylcarbamoyl)-8-(naphthalen-1-ylamino)-6-octene acid methylester

The procedure of Example (1-1) was repeated except for using (6-methoxypyridin-3-yl)amine instead of dimethylaminehydrochloride as the amine to obtain 1.67 mg of the title compound (yield: 42%).

1H NMR (300 MHz, CDCl₃) δ 1.54-1.73 (m, 4H), 2.29-2.37 (m, 4H), 3.63 (S, 3H), 3.85 (S, 3H), 6.65 (m, 1H), 6.82-6.98 (m, 2H), 7.39-7.52 (m, 4H), 7.81-7.91 (m, 3H), 8.10 (m, 1H), 9.29 (S, 1H).

(20-2): 7-(6-methoxy-pyridin-3-ylcarbamoyl)-8-(naphthalen-1-ylamino)-6-octene acid

The procedure of Example (1-2) was repeated except for using the compound obtained in Example (20-1) as the starting material, to obtain 670 mg of the title compound (yield: 40%).

(20-3): (E)-N₁-hydroxy-N₈-(6-methoxypyridin-3-yl)-2-((naphthalen-1-yl)oxy)methyl)octenediamide

The procedure of Example (1-3) was repeated except for using the compound obtained in Example (20-2) as the starting material, to obtain 482 mg of the title compound (yield: 69%).

1H NMR (300 MHz, MeOH-d₄) δ 1.45-1.59 (m, 4H), 1.97 (m, 2H), 2.40 (m, 2H), 3.80 (S, 3H), 4.17 (S, 2H), 6.15 (S, IH), 6.55 (m, 2H), 6.78 (d, J = 9.0 Hz, IH), 7.13(d, J = 7.7 Hz, IH), 7.24-7.41 (m, 3H), 7.74 (d, J = 8.8 Hz, IH), 7.91 (m, IH), 8.10 (S, IH), 8.38 (S, IH), 9.84 (S, IH), 10.37 (S, IH).

Example 21: (E)-N₁-(3-(1H-imidazo1-1-yl)propyl)-N₈-hydroxy-2-((naphthalen-1-yl)methyl)octenediamide
(21-1):(E)-8-(3-(1H-imidazol-1-yl)propylamino)-7-((naphthalen-1-yl)methyl)-8-oxo-6-octene acid methylester

The procedure of Example (1-1) was repeated except for using 3-(1H-imidazol-1-yl)propylamine instead of dimethylaminehydrochloride as the amine to obtain 449 mg of the title compound (yield: 77%).

\[ ^1 \text{H NMR (300 MHz, CDCl}_3) \delta 1.53-1.84 (m, 4H), 2.05 (m, 2H), 2.39 (m, 4H), 3.42 (q, J = 6.3Hz, 2H), 3.72 (s, 3H), 3.98 (t, J=7.0Hz, 2H), 5.02 (s, 2H), 6.72 (t, J = 6.0 Hz, IH) \]
\[ 6.88-7.07 (m, 4H), 7.36-7.65(m, 4H), 7.90(d, J = 6.7 Hz, IH), 8.22 (d, J = 7.3 Hz, IH). \]

LC/MS (M+H): 450.23.

(21-2):(E)-8-(3-(1H-imidazol-1-yl)propylamino)-7-((naphthalen-1-yl)methyl)-8-oxo-6-octene acid

The procedure of Example (1-2) was repeated except for using the compound obtained in Example (21-1) as the starting material, to obtain 350 mg of the title compound (yield: 85%).

(21-3):(E)-Nl-(3-(1H-imidazol-1-yl)propyl)-2-((naphthalen-1-yl)methyl)-N8-(tetrahydro-2H-pyran-2-yloxy)-2-octenediamide

The procedure of Example (4-3) was repeated except for using the compound obtained in Example (21-2) as the starting material, to obtain 220 mg of the title compound (yield: 63%).

\[ ^1 \text{H NMR (200 MHz, CDCl}_3) \delta 1.40-1.75 (m, HH), 1.81 (t, J = 6.4 Hz, 2H), 1.96 (m, 2H), 2.15 (m, 2H), 3.19 (q, J = 6.1 Hz, 2H), 3.38 (d, J = 11.8 Hz, IH), 3.76 (t, J = 6.9 Hz, 3H), 4.74 (s, 2H), 6.46 (m, IH), 6.67 (m, 2H) \]
\[ 6.83 (m, 2H) 7.32 (m, 5H) 7.65 (d, J = 6.5 Hz, IH), 7.96 (d, J = 7.7 Hz, IH), 9.33 \] (br, IH).

LC/MS (M+H): 535.28.
(21-4):(E)-Nl-(3-(1H-imidazoI-1-yl)propyl)-N8-hydroxy-2-((naphthalen-1-yl)oxy)methyl)octenediamide

The procedure of Example (4-4) was repeated except for using the compound obtained in Example (21-3) as the starting material, to obtain 63 mg of the title compound (yield: 37%).

HPLC purification: 46mg (purity : 97%)

1H NMR (300 MHz, MeOH-d₄) δ 1.52 (m, 2H), 1.68 (m, 2H), 2.03 (t, J = 6.6Hz, 2H), 2.11 (t, J = 6.6 Hz, 2H), 2.35 (q, J = 7.2Hz, 2H), 5.04 (s, 2H), 6.57 (t, J = 6.3 Hz, 2H), 7.01 (d, J = 7.2 Hz, IH), 7.18 (s, IH), 7.26 (s, IH), 7.43 (m, 4H), 7.78 (d, J = 7.8Hz, IH), 8.09 (s, IH), 8.13 (d, J =5.1 Hz, IH).

LC/MS (M+H): 451.23.

Example 22: (E)-N8-hydroxy-Nl-(4-hydroxyphenetyl)-2-((naphthalen-1-yl)oxy)methyl)-2-octenediamide

(22-1):(E)-8-(4-hydroxyphenetylamino)-7-((naphthalen-1-yl)oxy)methyl)-8-oxo-6-octene acid methylester

The procedure of Example (1-1) was repeated except for using 4-hydroxyphenetylamine instead of dimethylaminehydrochloride as the amine to obtain 461 mg of the title compound (yield: 95%).

1H NMR (300 MHz, CDCl₃) δ 1.50-1.80 (m, 4H), 2.38 (m, 4H), 2.82 (t, J = 6.9Hz, 2H), 3.63 (m, 2H), 3.72 (s, 3H), 4.92 (s, 2H), 6.44 (br, IH), 6.53-6.59 (t, J = 5.4 Hz, IH), 6.66 (d, J = 8.4 Hz, 2H), 6.95 (m, 4H), 7.37 (m, 4H), 7.90 (d, J = 9.1Hz, IH), 8.12 (d, J = 9.7 Hz, IH).

LC/MS (M+H): 412.20.

(22-2):(E)-8-(4-hydroxyphenetylamino)-7-((naphthalen-1-yl)oxy)methyl)-8-oxo-6-octene acid
The procedure of Example (1-2) was repeated except for using the compound obtained in Example (22-1) as the starting material, to obtain 439 mg of the title compound (yield: 92%).

\[ ^1\text{H NMR (}300\text{ MHz, MeOH-d}_4\text{)} \delta 1.52 (m, 2H, CH\_2), 1.64 (m, 2H, CH\_2), 2.20 (m, 2H, CH\_2), 2.27 (s, 6H, N(CH\_3)_2), 2.38 (m, 2H, CH\_2), 2.55 (m, 2H, CH\_2), 3.42 (m, 2H, CH\_2), 4.97 (s, 2H, CH\_2), 6.67 (s, 1H, CH), 6.99 (t, IH, J = 7.0, 1.8 Hz, ArH), 7.41 (m, 4H, ArH), 7.77 (d, IH, J = 7.0, 1.8 Hz, ArH), 8.14 (d, IH, J = 7.2 Hz, ArH). \]  

(22-3): (E)-N\text{I}-(4-hydroxyphenetyl)-2-((naphthalen-1-yloxy)methyl)-N\text{I}-((tetrahydro-2H-pyran-2-yloxy)-2-octenediamide)

The procedure of Example (4-3) was repeated except for using the compound obtained in Example (22-2) as the starting material, to obtain 394 mg of the title compound (yield: 75%).

\[ ^1\text{H NMR (}200\text{ MHz, CDCl}_3\text{)} \delta 1.42-1.85 (m, 12H), 2.04 (m, 2H), 2.22 (m, 2H), 2.71 (t, J = 6.4 Hz, 2H), 3.50 (m, 3H), 3.92 (m, IH), 4.79 (s, 2H), 4.92 (m, IH), 6.38 (t, J = 5.4 Hz, IH), 6.67 (m, 3H), 6.86 (m, 3H) 7.18 (br, IH), 7.44 (m, 4H), 7.77 (m, IH), 8.00 (m, IH), 8.93 (br, IH). \]  


(22-4): (E)-N\text{I}-4-hydroxy-N\text{I}-(4-hydroxyphenetyl)-2-((naphthalen-1-yloxy)methyl)-2-octenediamide

The procedure of Example (4-4) was repeated except for using the compound obtained in Example (22-3) as the starting material, to obtain 121 mg of the title compound (yield: 78%).

HPLC purification: 61mg (purity: 95%)

\[ ^1\text{H NMR (}200\text{ MHz, MeOH-d}_4\text{)} \delta 1.48-1.72 (m, 4H), 2.08 (t, J = 7.2 Hz, 2H), \]
2.34 (q, J = 6.8 Hz, 2H), 2.73 (t, J = 7.2 Hz, 2H), 3.45 (t, J = 7.0 Hz, 2H), 4.98 (s, 2H), 6.53 (t, J = 7.4 Hz, 1H), 6.63 (d, J = 7.8 Hz, 2H), 6.97 (d, J = 8.2 Hz, 3H), 7.43 (m, 4H), 7.78 (d, J = 7.0 Hz, 1H), 8.10 (d, J = 9.2 Hz, 1H).

LC/MS (M+H): 413.20.

Example 23: (E)-Nl-(3-(dimethylamino)-2,2-dimethylpropyl)-N8-hydroxy-2-((naphthalen-l-yloxy)methyl)octenediamide

(23-1):(E)-8-(3-(dimethylamino)-2,2-dimethylpropylamino)-7-((naphthalen-l-yloxy)methyl)-8-oxo-6-octene acid methylester

The procedure of Example (1-1) was repeated except for using 3-(dimethylamino)-2,2-dimethylpropylamine instead of dimethyaminehydrochloride as the amine to obtain 454 mg of the title compound (yield: 75%).

1H NMR (200 MHz, CDCl₃) δ 0.87 (s, 6H), 1.45-1.73 (m, 4H), 1.85 (s, 6H), 2.11 (s, 2H), 2.27 (m, 2H), 3.25 (d, J = 4.4 Hz, 2H), 3.60 (s, 3H), 4.87 (s, 2H), 6.92 (m, 2H), 7.42 (m, 4H), 7.72 (d, J = 7.4 Hz, 1H), 8.19 (d, J = 9.0 Hz, 1H).

LC/MS (M+H): 405.27.

(23-2):(E)-8-(3-(dimethylamino)-2,2-dimethylpropylamino)-7-((naphthalen-l-yloxy)methyl)-8-oxo-6-octene acid

The procedure of Example (1-2) was repeated except for using the compound obtained in Example (23-1) as the starting material, to obtain 339 mg of the title compound (yield: 93%).

1H NMR (200 MHz, MeOH-d₄) δ 1.6 (m, 4H, CH₂CH₂), 2.4 (m, 6H, CH₂CH₂CH₂), 2.50 (m, 4H, CH₂CH₂), 2.80 (m, 2H, CH₂), 3.01 (s, 3H, NCH₃), 3.29 (m, 1H, CH), 3.65 (m, 1H, CH), 4.95 (s, 2H, PhCH₂), 6.00 (m, 1H, CH), 7.00 (t, J = 16.6, 9.4 Hz, ArH), 7.46 (m, 4H, ArH), 7.82 (m, 1H, ArH), 8.18 (m, 1H, ArH).
(23-3):(E)-Nl-(3-(dimethylamino)-2,2-dimethylpropyl)-2-((naphthalen-1-yloxy)methyl)-N8-(tetrahydro-2H-pyran-2-yloxy)-2-octenediamide

The procedure of Example (4-3) was repeated except for using the compound obtained in Example (23-2) as the starting material, to obtain 304 mg of the title compound (yield: 52%).

$^1$H NMR (200 MHz, CDCl$_3$) δ 0.88 (s, 6H), 1.49-1.82 (m, 10H), 1.86 (s, 6H), 2.02 (m, 2H), 2.13 (s, 2H), 2.31 (q, J = 7.4 Hz, 2H), 3.27 (d, J = 4.6 Hz, 2H), 3.58 (m, 1H), 3.93 (m, 1H), 4.88 (s, 2H), 4.90 (m, 1H), 6.95 (t, J = 7.4 Hz, 2H), 7.45 (m, 4H), 7.78 (d, J = 6.0 Hz, 1H), 8.21 (d, J = 7.0 Hz, 1H), 8.48 (br, 1H), 8.62 (br, 1H).

LC/MS (M+H): 490.32.

(23-4):(E)-Nl-(3-(dimethylamino)-2,2-dimethylpropyl)-N8-hydroxy-2-((naphthalen-1-yloxy)methyl)octenediamide

The procedure of Example (4-4) was repeated except for using the compound obtained in Example (23-3) as the starting material, to obtain 144 mg of the title compound (yield: 74%).

HPLC purification: 101mg (purity: 92%)

$^1$H NMR (200 MHz, MeOH-d$_4$) δ 0.98 (s, 6H), 1.54 (m, 2H), 1.6 (m, 2H), 2.12 (t, J = 7.4 Hz, 2H), 2.40 (s, 6H), 2.46 (m, 4H), 3.26 (s, 2H), 6.71 (t, J = 8.2 Hz, 1H), 7.04 (m, 4H), 7.45 (m, 4H), 7.80 (d, J = 7.8 Hz, 1H), 8.13 (d, J = 8.6 Hz, 1H).


Example 24: (E)-Nl-(2-(diisopropylamino)ethyl)-N8-hydroxy-2-((naphthalen-1-yloxy)methyl)octenediamide

(24-l):(E)-8-(2-(diisopropylamino)ethylamino)-8-oxo-7-((naphthalen-1-
The procedure of Example (1-1) was repeated except for using 2-(diisopropylamino)ethylamine instead of dimethylaminehydrochloride as the amine to obtain 420 mg of the title compound (yield: 89%).

\[\text{1H NMR (200 MHz, CDCl}_3\text{)} \delta 0.87 \text{ (d, J = 7.0 Hz, 12H), 1.51 (m, 2H), 1.64 (m, 2H), 2.26 (m, 4H), 2.57 (t, J = 6.0 Hz, 2H), 2.86 (m, 2H), 3.31 (q, J = 5.6 Hz, 2H), 3.61 (s, 3H), 4.90 (s, 3H), 6.90 (m, 3H), 7.44 (m, 4H), 7.77 (d, J = 7.2 Hz, 1H), 8.17 (d, J = 7.0 Hz, 1H).} \]

\[\text{LC/MS (M+H): 419.28.}\]

(24-2):(E)-8-(2-(diisopropylamino)ethylamino)-8-oxo-7-((naphthalen-1-ylxy)methyl)-6-octene acid

The procedure of Example (1-2) was repeated except for using the compound obtained in Example (24-1) as the starting material, to obtain 420 mg of the title compound (yield: 78%).

(24-3):(E)-N1-(2-(diisopropylamino)ethyl)-N8-(tetrahydro-2H-pyran-2-ylxy)methyl)-2-octenediamide

The procedure of Example (4-3) was repeated except for using the compound obtained in Example (24-2) as the starting material, to obtain 319 mg of the title compound (yield: 50%).

\[\text{1H NMR (200 MHz, CDCl}_3\text{)} \delta 0.95 \text{ (br, 9H), 1.50-1.95 (m, 10H), 2.10 (m, 2H), 2.31 (q, J = 6.8 Hz, 2H), 2.67 (m, 2H), 2.96 (s, 2H), 3.46 (m, 2H), 3.57 (m, 2H), 3.97 (m, 1H), 4.93 (s, 2H), 4.94 (m, 1H), 6.87 (m, 3H), 7.49 (m, 4H), 7.78 (d, J = 6.8 Hz, 1H), 8.15 (d, J = 8.6 Hz, 1H).} \]

\[\text{LC/MS (M+H): 504.34.}\]

(24-4):(E)-N1-(2-(diisopropylamino)ethyl)-N8-hydroxy-2-((naphthalen-1-ylxy)methyl)-6-octene acid methylester
The procedure of Example (4-4) was repeated except for using the compound obtained in Example (24-3) as the starting material, to obtain 145 mg of the title compound (yield: 85%).

HPLC purification: 59 mg (purity: 92%)

\[
\begin{align*}
\text{\[^1\text{H NMR} (200\text{ MHz, MeOH-d}_4)\text{ }]} & \quad \delta 1.32 (t, J = 6.2\text{ Hz}, 9\text{H}), \quad 1.46-1.78 (m, 4\text{H}), \\
& \quad 2.10 (t, J = 7.0\text{ Hz}, 2\text{H}), \quad 2.41 (q, J = 6.8\text{ Hz}, 2\text{H}), \quad 3.23 (t, J = 6.2\text{ Hz}, 2\text{H}), \\
& \quad 3.63 (t, J = 7.0\text{ Hz}, \text{IH}), \quad 3.74 (m, 2\text{H}), \quad 5.05 (s, 2\text{H}), \quad 6.76 (t, J = 6.6\text{ Hz}, \text{IH}), \\
& \quad 7.02 (d, J = 7.0\text{ Hz}, \text{IH}), \quad 7.45 (m, 4\text{H}), \quad 7.80 (d, J = 7.6\text{ Hz}, \text{IH}), \quad 8.12 (d, J = 7.8\text{ Hz}, \text{IH}).
\end{align*}
\]

LC/MS (M+H): 420.28.

**Example 25:** (E)-N8-hydroxy-Nl-(l-methoxypropan-2-yl)-2-((naphthalen-1-yloxy)methyl)-2-octenediamide

(25-1):(E)-8-(l-methoxypropan-2-ylamino)-7-((naphthalen-1-yloxy)methyl)-8-oxo-6-octene acid methylester

The procedure of Example (1-1) was repeated except for using 1-methoxypropan-2-ylamine instead of dimethylaminehydrochloride as the amine to obtain 413 mg of the title compound (yield: 83%).

\[
\begin{align*}
\text{\[^1\text{H NMR} (200\text{ MHz, CDCl}_3)\text{ }]} & \quad \delta 1.15 (d, J = 6.8\text{ Hz}, 3\text{H}), \quad 1.50 (m, 2\text{H}), \quad 1.63 (m, 2\text{H}), \\
& \quad 2.29 (m, 4\text{H}), \quad 3.15 (s, 3\text{H}), \quad 3.31 (d, J = 4.0\text{ Hz}, 2\text{H}), \quad 3.62 (s, 3\text{H}), \quad 4.24 (m, \text{IH}), \\
& \quad 4.93 (s, 2\text{H}), \quad 6.64 (d, J = 7.8\text{ Hz}, \text{IH}), \quad 6.84 (t, J = 7.8\text{ Hz}, \text{IH}), \quad 6.91 (d, J = 7.2\text{ Hz}, \text{IH}), \\
& \quad 7.46 (m, 4\text{H}), \quad 7.83 (m, 4\text{H}), \quad 8.19 (m, \text{IH}).
\end{align*}
\]

LC/MS (M+H): 414.22.

(25-2):(E)-8-(l-methoxypropan-2-ylamino)-7-((naphthalen-1-yloxy)methyl)-8-oxo-6-octene acid
The procedure of Example (1-2) was repeated except for using the compound obtained in Example (25-1) as the starting material, to obtain 346 mg of the title compound (yield: 81%).

(25-3):(E)-Nl-(l-methoxypropan-2-yl)-2-((naphthalen-l-yloxy)methyl)-N8-(tetrahydro-2H-pyran-2-yloxy)-2-octenediamide

The procedure of Example (4-3) was repeated except for using the compound obtained in Example (25-2) as the starting material, to obtain 289 mg of the title compound (yield: 75%).

\[ ^1H \text{NMR} \ (200 \text{ MHz, CDCl}_3) \delta 1.17 \ (d, J = 6.8 \text{ Hz}, 3H), 1.41-1.89 \ (m, 10H), 2.09 \ (m, 2H), 2.31 \ (q, J = 7.0 \text{ Hz}, 2H), 3.17 \ (s, 3H), 3.57 \ (m, IH), 3.93 \ (m, IH), 4.24 \ (m, IH), 4.93 \ (m, IH), 6.69 \ (d, J = 7.8 \text{ Hz}, IH), 6.84 \ (t, J = 6.6 \text{ Hz}, IH), 6.91 \ (d, J = 7.8 \text{ Hz}, IH), 7.41 \ (m, 4H), 7.80 \ (d, J = 7.8 \text{ Hz}, IH), 8.19 \ (d, J = 7.8 \text{ Hz}, IH). \]

LC/MS (M+H): 499.27.

(25-4):(E)-N8-hydroxy-Nl-(l-methoxypropan-2-yl)-2-((naphthalen-l-yloxy)methyl)-2-octenediamide

The procedure of Example (4-4) was repeated except for using the compound obtained in Example (25-3) as the starting material, to obtain 125 mg of the title compound (yield: 88%).

HPLC purification: 63mg (purity: 97%)

\[ ^1H \text{NMR} \ (200 \text{ MHz, DMSO-d}_4) \delta 1.07 \ (d, J = 7.0 \text{ Hz}, 3H), 1.45 \ (m, 2H), 1.51 \ (m, 2H), 1.96 \ (t, J = 7.0 \text{ Hz}, 2H), 2.29 \ (m, 2H), 3.24 \ (s, 3H), 3.36 \ (s, 2H), 4.09 \ (m, IH), 4.96 \ (s, 2H), 6.51 \ (t, J = 7.8 \text{ Hz}, IH), 7.07 \ (d, J = 6.8 \text{ Hz}, IH), 7.47 \ (m, 4H), 7.86 \ (m, 2H), 8.06 \ (d, J = 9.0 \text{ Hz}, IH), 8.70 \ (br, 4H), 10.35 \ (br, IH). \]

LC/MS (M+H): 415.22.
Example 26: (E)-N8-hydroxy-Nl-(4-methoxybenzyl)-2-((naphthalen-l-yloxy)methyl)-2-octenediamide

(26-1):(E)-8-(4-methoxybenzylamino)-7-((naphthalen-l-yloxy)methyl)-8-oxo-6-octene acid methylester

The procedure of Example (1-1) was repeated except for using 4-methoxybenzylamine instead of dimethylaminehydrochloride as the amine to obtain 461 mg of the title compound (yield: 98%).

\[ \text{HNM}R \ (200 \text{ MHz, } \text{CDCl}_3) \delta 1.49 (m, 2H), 1.59 (m, 2H), 2.29 (m, 4H), 3.62 (s, 3H), 3.77 (s, 3H), 4.44 (d, J = 5.8 Hz, 2H), 4.94 (s, 2H), 6.75 (m, 3H), 6.88 (d, J = 7.4 Hz, 2H), 7.15 (d, J = 8.6 Hz, 2H), 7.44 (m, 4H), 7.78 (d, J = 7.4 Hz, 1H), 7.99 (d, J = 7.4 Hz, 1H). \]

LC/MS (M+H): 462.22.

(26-2):(E)-8-(4-methoxybenzylamino)-7-((naphthalen-l-yloxy)methyl)-8-oxo-6-octene acid

The procedure of Example (1-2) was repeated except for using the compound obtained in Example (26-1) as the starting material, to obtain 454 mg of the title compound (yield: 86%).

(26-3):(E)-Nl-(4-methoxybenzyl)-2-((naphthalen-l-yloxy)methyl)-N8-(tetrahydro-2H-pyran-2-yloxy)-2-octenediamide

The procedure of Example (4-3) was repeated except for using the compound obtained in Example (26-2) as the starting material, to obtain 378 mg of the title compound (yield: 85%).

\[ \text{H NMR} \ (200 \text{ MHz, } \text{CDCl}_3) \delta 1.52-1.95 (m, 10H), 2.07 (m, 2H), 2.29 (q, J = 7.2 Hz, 2H), 3.75 (s, 3H), 3.91 (m, 1H), 4.43 (d, J = 5.8 Hz, 2H), 4.90 (m, 1H), 4.92 (s, 2H), 6.79 (m, 3H), 6.87 (d, J = 7.6 Hz, 2H), 7.14 (d, J = 8.4 Hz, 1H). \]
2H), 7.47 (m, 4H), 7.77 (d, J = 8.0 Hz, IH), 7.98 (d, J = 7.8 Hz, IH), 8.65 (br, IH).
LC/MS (M+H): 547.27.

(26-4): (E)-N8-hydroxy-Nl-(4-methoxybenzyl)-2-((naphthalen-l-yloxy)methylI)-2-octenediamide

The procedure of Example (4-4) was repeated except for using the compound obtained in Example (26-3) as the starting material, to obtain 142 mg of the title compound (yield: 80%).

HPLC purification: 81mg (purity: 92%)

1H NMR (200 MHz, MeOH-d₄) δ 1.52 (m, 2H), 1.58 (m, 2H), 2.08 (t, J = 7.4 Hz, 2H), 2.34 (q, J = 7.6 Hz, 2H), 3.37 (s, 3H), 3.74 (s, IH), 5.03 (s, 2H), 6.59 (t, J = 7.4 Hz, IH), 6.74 (d, J = 8.2 Hz, 2H), 6.96 (d, J = 6.6 Hz, IH), 7.16 (d, J = 8.4 Hz, 2H), 7.42 (m, 4H), 7.77 (d, J = 7.8 Hz, IH), 8.06 (d, J = 7.4 Hz, IH).
LC/MS (M+H): 463.22.

Example 27: (E)-Nl-(4-fluorophenetyl)-N8-hydroxy-2-((naphthalen-l-yloxy)methylI)-2-octenediamide

(27-I): (E)-8-(4-fluorophenethylamino)-7-((naphthalen-l-yloxy)methylI)-8-oxo-6-octene acid methylester

The procedure of Example (1-1) was repeated except for using 4-fluorophenethylamine instead of dimethylaminehydrochloride as the amine to obtain 463 mg of the title compound (yield: 93%).

1H NMR (200 MHz, CDCl₃) δ 1.52 (m, 2H), 1.62 (m, 2H), 2.28 (m, 4H), 2.76 (t, J = 6.8 Hz, 2H), 3.54 (q, J = 5.6 Hz, 2H), 3.61 (s, 3H), 4.82 (s, 2H), 6.66 (br, IH), 6.70 (m, 2H), 6.86 (m, 2H), 6.96 (m, 2H), 7.48 (m, 4H), 7.80 (d, J = 7.4 Hz, IH), 7.99 (d, J = 7.0 Hz, IH).
LC/MS (M+H): 464.21.

(27-2):(E)-8-(4-fluorophenethylamino)-7-((naphthalen-1-yloxy)methyl)-8-oxo-6-octene acid

The procedure of Example (1-2) was repeated except for using the compound obtained in Example (27-1) as the starting material, to obtain 434 mg of the title compound (yield: 86%).

(27-3):(E)-N1-(4-fluorophenetyl)-N8-(tetrahydro-2H-pyran-2-yloxy)-2-octenediamide

The procedure of Example (4-3) was repeated except for using the compound obtained in Example (27-2) as the starting material, to obtain 362 mg of the title compound (yield: 65%).

$^1$H NMR (200 MHz, CDCl$_3$) $\delta$ 1.48-1.89 (m, 10H), 2.16 (m, 2H), 2.28 (q, $J = 7.2$ Hz, 2H), 2.75 (t, $J = 6.8$ Hz, 2H), 3.53 (q, $J = 5.8$ Hz, 2H), 3.60 (m, IH), 3.91 (m, IH), 4.81 (s, 2H), 4.90 (m, IH), 6.49 (m, IH), 6.70 (m, 2H), 6.85 (m, 2H), 6.96 (m, 2H), 7.42 (m, 4H), 7.81 (d, $J = 7.4$ Hz, IH), 7.98 (d, $J = 7.6$ Hz, IH), 8.56 (br, IH).

LC/MS (M+H): 549.27.

(27-4):(E)-N1-(4-fluorophenetyl)-N8-hydroxy-2-((naphthalen-1-yloxy)methyl)-2-octenediamide

The procedure of Example (4-4) was repeated except for using the compound obtained in Example (27-3) as the starting material, to obtain 83 mg of the title compound (yield: 76%).

HPLC purification: 36mg (purity: 92%)

$^1$H NMR (200 MHz, MeOH-$d_4$) $\delta$ 1.49 (m, 2H), 1.69 (m, 2H), 2.09 (t, $J = 6.8$ Hz, 2H), 2.34 (q, $J = 7.2$ Hz, 2H), 2.80 (t, $J = 6.8$ Hz, 2H), 3.48 (m, 2H), 4.97
(s, 2H), 6.55 (t, J = 7.8 Hz, IH), 6.86 (m, 2H), 6.97 (d, J = 7.6 Hz, IH), 7.14 (m, 2H), 7.45 (m, 4H), 7.79 (d, J = 7.8 Hz, IH), 8.10 (d, J = 8.0 Hz, IH).  
LC/MS (M+H): 465.21.

Example 28: (E)-N8-hydroxy-2-((naphthalen-1-yloxy)methyl)-N1-(tetrahydropyran-2-yl)methyl)-2-octenediamide

(28-1):(E)-7-(((naphthalen-1-yloxy)methyl)-8-oxo-8-((tetrahydropyran-2-yl)methylamino)-6-octene acid methylester

The procedure of Example (1-1) was repeated except for using tetrahydropyran-2-yl)methylamine instead of dimethylaminehydrochloride as the amine to obtain 426 mg of the title compound (yield: 87%).

1H NMR (200 MHz, CDCl3) δ 1.45-1.99 (m, 8H), 2.28 (m, 4H), 3.26 (m, IH), 3.78 (m, 3H), 3.61 (s, 3H), 3.97 (m, IH), 4.93 (s, 2H), 6.79 (m, IH) 6.90 (m, 2H), 7.47 (m, 4H), 7.78 (m, IH), 8.20 (m, IH).  
LC/MS (M+H): 426.22.

(28-2):(E)-7-(((naphthalen-1-yloxy)methyl)-8-oxo-8-((tetrahydropyran-2-yl)methylamino)-6-octene acid

The procedure of Example (1-2) was repeated except for using the compound obtained in Example (28-1) as the starting material, to obtain 370 mg of the title compound (yield: 90%).

(28-3):(E)-2-((naphthalen-1-yloxy)methyl)-N8-(tetrahydro-2H-pyran-2-yloxy)-N1-(tetrahydropyran-2-yl)-2-octenediamide

The procedure of Example (4-3) was repeated except for using the compound obtained in Example (28-2) as the starting material, to obtain 323 mg of the title compound (yield: 65%).
1H NMR (200 MHz, CDCl₃) δ 1.42-1.95 (m, 14H), 2.08 (m, 2H), 2.25 (q, J = 7.6 Hz, 2H), 3.28 (m, 1H), 3.59 (m, 3H), 3.89 (m, 2H), 4.88 (s, 2H), 4.90 (m, 1H), 6.77 (m, 2H), 6.85 (d, J = 7.2 Hz, 1H), 7.40 (m, 4H), 7.77 (m, 1H), 8.14 (m, 1H), 8.68 (br, 1H).

LC/MS (M+H): 511.27.

(28-4):(E)-N8-hydroxy-2-((naphthalen-1-yloxy)methyl)-Nl-(tetrahydropyran-2-yl)methyl)-2-octenediamide

The procedure of Example (4-4) was repeated except for using the compound obtained in Example (28-3) as the starting material, to obtain 85 mg of the title compound (yield: 85%).

HPLC purification: 32mg (purity: 95%)

1H NMR (200 MHz, MeOH-d₄) δ 1.60 (m, 6H), 1.81 (m, 2H), 2.09 (t, J = 7.2 Hz, 2H), 2.37 (q, J = 7.4 Hz, 2H), 3.35 (m, 2H), 3.68 (m, 2H), 4.00 (m, 1H), 5.02 (s, 2H), 6.65 (t, J = 7.8 Hz, 1H), 7.01 (d, J = 6.8 Hz, 1H), 7.44 (m, 4H), 7.78 (d, J = 8.6 Hz, 1H), 8.15 (d, J = 9.4 Hz, 1H).

LC/MS (M+H): 427.22.

Example 29: (E)-Nl-(2-cyclohexenylethyl)-N8-hydroxy-2-((naphthalen-1-yloxy)methyl)-2-octenediamide

(29-1):(E)-8-(2-cyclohexenylethylamino)-7-((naphthalen-1-yloxy)methyl)-8-oxo-6-octene acid methylester

The procedure of Example (1-1) was repeated except for using 2-cyclohexenylethylamine instead of dimethylaminehydrochloride as the amine to obtain 449 mg of the title compound (yield: 89%).

1HNMR (200 MHz, CDCl₃) δ 1.25 (m, 2H), 1.30-1.71 (m, 8H), 1.79 (m, 2H), 2.09 (t, J = 7.4 Hz, 2H), 2.28 (m, 4H), 3.39 (q, J = 5.4 Hz, 2H), 3.60 (s, 3H), 4.86 (s, 2H), 5.28 (br, 1H), 6.41 (br, 1H), 6.89 (t, J = 7.6 Hz, 2H), 7.46 (m,
4H), 7.79 (m, IH), 8.14 (m, IH).

(29-2): (E)-8-(2-cyclohexenylethlamino)-7-((naphthalen-l-yloxy)methyl)-8-oxo-6-octene acid

The procedure of Example (1-2) was repeated except for using the compound obtained in Example (29-1) as the starting material, to obtain 401 mg of the title compound (yield: 95%).


The procedure of Example (4-43) was repeated except for using the compound obtained in Example (29-2) as the starting material, to obtain 370 mg of the title compound (yield: 82%).

1H NMR (200 MHz, CDCl3) δ 1.27 (m, 2H), 1.35-2.02 (m, 16H), 2.10 (m, 4H), 2.30 (q, J = 6.8 Hz, 2H), 3.40 (q, J = 5.8 Hz, 2H), 3.63 (m, IH), 3.96 (m, IH), 4.87 (s, 2H), 4.92 (m, IH), 5.18 (br, IH), 6.44 (br, IH), 6.90 (t, J = 7.6 Hz, 2H), 7.44 (m, 4H), 7.80 (m, IH), 8.15 (m, IH), 8.80 (br, IH).
LC/MS (M+H): 535.31.

(29-4): (E)-N1-(2-cyclohexenylethyl)-N8-hydroxy-2-((naphthalen-l-yloxy)methyl)-2-octenediamide

The procedure of Example (4-4) was repeated except for using the compound obtained in Example (29-3) as the starting material, to obtain 112 mg of the title compound (yield: 91%).

HPLC purification: 62 mg (purity: 92%)
1H NMR (200 MHz, MeOH-d4) δ 1.36-1.82 (m, 10H), 1.91 (m, 2H), 2.09 (m, 4H), 2.36 (q, J = 7.4 Hz, 2H), 3.34 (m, 2H), 4.99 (s, 2H), 5.34 (br, IH), 6.63
Example 30: (E)-N8-hydroxy-2-((naphthalen-l-yloxy)methyl)-Nl-(3-(2-oxopyrrolidin-l-yl)propyl)-2-octenediamide

(30-1):(E)-7-((naphthalen-l-yloxy)methyl)-8-oxo-8-(3-(2-oxopyrrolidin-l-yl)propylamino)-6-octene acid methylester

The procedure of Example (1-1) was repeated except for using 3-(2-oxopyrrolidin-l-yl)proplylamine instead of dimethylaminehydrochloride as the amine to obtain 466 mg of the title compound (yield: 79%).

1H NMR (200 MHz, CDCl₃) δ 1.44 (m, 2H), 1.63 (m, 4H), 1.95 (m, 2H), 2.26 (m, 6H), 3.21 (m, 6H), 3.56 (s, 3H), 4.93 (s, 2H), 6.72 (t, J = 7.6 Hz, IH), 6.88 (d, J = 7.6 Hz, IH), 7.23 (m, IH), 7.39 (m, IH), 7.74 (m, IH), 8.12 (m, IH).
LC/MS (M+H): 467.25.

(30-2):(E)-7-((naphthalen-l-yloxy)methyl)-8-oxo-8-(3-(2-oxopyrrolidin-l-yl)propylamino)-6-octene acid

The procedure of Example (1-2) was repeated except for using the compound obtained in Example (30-1) as the starting material, to obtain 370 mg of the title compound (yield: 88%).

(30-3):(E)-2-((naphthalen-l-yloxy)methyl)-Nl-(3-(2-oxopyrrolidin-l-yl)propyl)-N8-(tetrahydro-2H-pyran-2-yloxy)-2-octenediamide

The procedure of Example (4-3) was repeated except for using the compound obtained in Example (30-2) as the starting material, to obtain 316 mg of the title compound (yield: 80%).
H NMR (200 MHz, CDCl₃) δ 1.42-1.90 (m, 12H), 2.04 (m, 4H), 2.39 (m, 4H), 3.27 (m, 6H), 3.59 (m, IH), 3.95 (m, IH), 4.94 (m, IH), 4.99 (s, 2H), 6.73 (t, J = 7.6 Hz, IH), 6.91 (d, J = 7.4 Hz, IH), 7.25 (br, 4H), 7.45 (m, 4H), 7.78 (d, J = 7.8 Hz, IH), 8.13 (d, J = 7.8 Hz, IH), 9.25 (br, IH).

LC/MS (M+H): 552.30.

(30-4): (E)-N₈-hydroxy-2-((naphthalen-1-yloxy)methyl)-N₁-(3-(2-oxopyrrolidin-1-yl)propyl)-2-octenediamide

The procedure of Example (4-4) was repeated except for using the compound obtained in Example (30-3) as the starting material, to obtain 166 mg of the title compound (yield: 82%).

HPLC purification: 49 mg (purity: 97%)

H NMR (200 MHz, MeOH-d₄) δ 1.53 (m, 2H), 1.74 (m, 4H), 2.06 (m, 4H), 2.36 (m, 4H), 3.33 (m, 6H), 4.86 (s, 2H), 6.61 (t, J = 7.4 Hz, IH), 7.00 (d, J = 6.8 Hz, IH), 7.43 (m, 4H), 7.78 (d, J = 7.4 Hz, IH), 8.14 (d, J = 7.4 Hz, IH).

LC/MS (M+H): 468.24.

Example 31: (E)-N₁-(furan-2-yl)-N₈-hydroxy-2-((naphthalen-1-yloxy)methyl)-2-octenediamide

(31-1): (E)-8-(furan-2-yIamino)-7-((naphthalen-1-yloxy)methyl)-8-oxo-6-octene acid methylester

The procedure of Example (1-1) was repeated except for using furan-2-ylamine instead of dimethylaminehydrochloride as the amine to obtain 421 mg of the title compound (yield: 83%).

H NMR (200 MHz, CDCl₃) δ 1.48 (m, 2H), 1.60 (m, 2H), 2.27 (m, 4H), 3.61 (s, 3H), 4.51 (d, J = 5.4 Hz), 2.93 (s, 2H), 6.20 (dd, J = 10.6 Hz, 3.2 Hz, 2H), 6.90 (m, 3H), 7.45 (m, 4H), 7.78 (d, J = 7.6 Hz, IH), 8.07 (d, J = 7.6 Hz,
IH).
LC/MS (M+H): 408.17.

(31-2):(E)-8-(furan-2-ylamino)-7-((naphthalen-1-yloxy)methyl)-8-oxo-6-octene acid

The procedure of Example (1-2) was repeated except for using the compound obtained in Example (31-1) as the starting material, to obtain 353 mg of the title compound (yield: 90%).

(31-3):(E)-Nl-(furan-2-yl)-2-((naphthalen-1-yloxy)methyl)-N8-(tetrahydro-2H-pyran-2-yl oxy)-2-octenediamide

The procedure of Example (4-3) was repeated except for using the compound obtained in Example (31-2) as the starting material, to obtain 306 mg of the title compound (yield: 55%).

\[
\begin{align*}
1^1H \text{ NMR} & (200 \text{ MHz, CDCl}_3) \delta 1.55-1.98 (m, 10H), 2.17 (m, 2H), 2.41 (q, J = 7.4 \text{ Hz, 2H}), 3.66 (m, 1H), 3.97 (m, 1H), 4.61 (d, J = 5.4 \text{ Hz, 2H}), 4.88 (m, 1H), 4.90 (s, 2H), 6.31 (d, J = 11.2 \text{ Hz, 2H}), 6.96 (m, 3H), 7.52 (m, 4H), 7.89 (d, J = 6.8 \text{ Hz, 1H}), 7.17 (d, J = 6.6 \text{ Hz, 1H}), 8.45 (br, 1H). \\
\text{LC/MS} & (M+H): 493.23
\end{align*}
\]

(31-4):(E)-Nl-(furan-2-y1)-N8-hydroxy-2-((naphthalen-1-yloxy)methyl)-2-octenediamide

The procedure of Example (4-4) was repeated except for using the compound obtained in Example (31-3) as the starting material, to obtain 156 mg of the title compound (yield: 79%).

HPLC purification: 68 mg (purity: 92%)

\[
\begin{align*}
1^1H \text{ NMR} & (200 \text{ MHz, MeOH-d}_4) \delta 1.50 (m, 2H), 1.62 (m, 2H), 2.08 (t, J = 6.8 \text{ Hz, 2H}), 2.37 (q, J = 7.4 \text{ Hz, 2H}), 4.47 (s, 2H), 5.03 (s, 2H), 6.24 (dd, J =
\end{align*}
\]
14.6 Hz, 3.0 Hz, 2H), 6.62 (t, J = 7.4 Hz, IH), 6.99 (d, J = 7.2 Hz, IH), 7.43 (m, 4H), 7.78 (d, J = 9.0 Hz, IH), 8.08 (d, J = 8.2 Hz, IH).

LC/MS (M+H): 409.17.

Example 32: (E)-N1-(4-(dimethylamino)benzyI)-N8-hydroxy-2-((naphthalen-1-yl oxy)methyl)-2-octenediamide

(32-1): (E)-8-(4-(dimethylamino)benzylamino)-7-((naphthalen-1-yl oxy) methyl)-8-oxo-6-octene acid methylester

The procedure of Example (1-1) was repeated except for using 4-(dimethylamino)benzylamine instead of dimethylaminehydrochloride as the amine to obtain 547 mg of the title compound (yield: 72%).

1H NMR (200 MHz, CDCl₃) δ 1.45-1.75 (m, 4H), 2.31 (m, 4H), 2.93 (s, 6H), 3.64 (s, 3H), 4.44 (d, J = 5.4 Hz, 2H), 4.96 (s, 2H), 6.62 (m, 3H), 6.91 (m, 2H), 7.14 (d, J = 8.4 Hz, 2H), 7.40 (m, 4H), 7.84 (d, J = 7.4 Hz, IH), 8.05 (d, J = 7.8 Hz, IH).

LC/MS (M+H): 475.

(32-2): (E)-8-(4-(dimethylamino)benzylamino)-7-((naphthalen-1-yl oxy)methyl)-8-oxo-6-octene acid

The procedure of Example (1-2) was repeated except for using the compound obtained in Example (32-1) as the starting material, to obtain 397 mg of the title compound (yield: 99%).

(32-3): (E)-N1-(4-dimethylamino)benzyl)-2-((naphthalen-1-yloxy)methyl)-N8-(tetrahydro-2H-pyran-2- yloxy)-2-octenediamide

The procedure of Example (4-3) was repeated except for using the compound obtained in Example (32-2) as the starting material, to obtain 380 mg of the title compound (yield: 96%).
\[ ^1H \text{NMR} \ (200 \text{ MHz, CDCl}_3) \ \delta \ 1.50-1.92 \ (m, 10H), \ 2.05 \ (m, 2H), \ 2.30 \ (q, J=IAHz, 2H), \ 2.92 \ (s, 2H), \ 2.96 \ (m, IH), \ 3.57 \ (m, IH), \ 3.92 \ (m, IH), \ 4.41 \ (d, J = 5.2 \text{ Hz}, 2H), \ 4.81 \ (m, IH), \ 4.94 \ (s, 2H), \ 6.60 \ (m, 3H), \ 6.89 \ (m, 2H), \ 7.12 \ (d, J = 8.4 \text{ Hz}, 2H), \ 7.41 \ (m, 4H), \ 7.78 \ (d, J = 8.0 \text{ Hz}, IH), \ 8.02 \ (d, J = 8.2 \text{ Hz}, IH), \ 8.37 \ (br, IH). \]

LC/MS (M+H): 560.

\((32-4):(E)-Nl-(4-(dimethylamino)benzyl)-N8-hydroxy-2-((naphthalen-1-yloxy)methyl)-2-octenediamide\)

The procedure of Example (4-4) was repeated except for using the compound obtained in Example (32-3) as the starting material, to obtain 305 mg of the title compound (yield: 92%).

HPLC purification: 287 mg (purity: 98%)

\[ ^1H \text{NMR} \ (300 \text{ MHz, MeOH-d}_4) \ \delta \ 1.44 \ (m, 2H), \ 1.59 \ (m, 2H), \ 2.00 \ (t, J = 7.2 \text{ Hz}, 2H), \ 2.28 \ (q, J = 7.2 \text{ Hz}, 2H), \ 3.04 \ (s, 6H), \ 4.38 \ (s, 2H), \ 5.01 \ (s, 2H), \ 6.54 \ (t, J = 7.5 \text{ Hz}, IH), \ 6.88 \ (d, J = 7.2 \text{ Hz}, IH), \ 7.17 \ (d, J = 8.4 \text{ Hz}, 2H), \ 7.33 \ (m, 6H), \ 7.70 \ (d, J = 8.1 \text{ Hz}, IH), \ 8.01 \ (d, J = 8.1 \text{ Hz}, IH). \]

LC/MS (M+H): 476.25.

Example 33: (E)-N8-hydroxy-Nl-(2-methoxyethyl)-2-((naphthalen-1-yloxy)methyl)-2-octenediamide

\((33-I):(E)-8-(2-methoxyethylamino)-7-((naphthalen-1-yloxy)methyl)-8-oxo-6-octene acid methylester\)

The procedure of Example (1-1) was repeated except for using 2-methoxyethylamine instead of dimethylaminehydrochloride as the amine to obtain 399 mg of the title compound (yield: 85%).

\[ ^1H \text{NMR} \ (200 \text{ MHz, CDCl}_3) \ \delta \ 1.44-1.79 \ (m, 4H), \ 2.31 \ (m, 4H), \ 3.19 \ (s, IH), \]
3.49 (m, 4H), 3.64 (s, 3H), 4.95 (s, 2H), 6.92 (m, 3H), 7.48 (m, 4H), 7.81 (m, IH), 7.81 (m, IH), 8.20 (m, IH).

LC/MS (M+H): 400.20.

**(33-2): (E)-8-(2-methoxyethylamino)-7-((naphthalen-1-yloxy)methyl)-8-oxo-6-octene acid**

The procedure of Example (1-2) was repeated except for using the compound obtained in Example (33-1) as the starting material, to obtain 339 mg of the title compound (yield: 95%).


The procedure of Example (4-3) was repeated except for using the compound obtained in Example (33-2) as the starting material, to obtain 313 mg of the title compound (yield: 70%).

$^1$H NMR (200 MHz, CDCl$_3$) $\delta$ 1.41-1.97 (m, 10H), 2.07 (m, 2H), 2.30 (q, $J =$ 7.4 Hz, 2H), 3.17(s, 3H), 3.46 (m, 5H), 3.92 (m, IH), 4.90 (m, IH), 4.92 (s, 2H), 6.85 (m, 3H), 7.46 (m, 4H), 7.81 (m, IH), 8.17 (m, IH), 8.67 (m, IH).


**(33-4): (E)-N8-hydroxy-N1-(2-methoxyethyl)-2-((naphthalen-1-yloxy)methyl)-2-octenediamide**

The procedure of Example (4-4) was repeated except for using the compound obtained in Example (33-3) as the starting material, to obtain 87 mg of the title compound (yield: 68%).

HPLC purification: 42 mg (purity: 98%)

$^1$H NMR (300 MHz, MeOH-d$_4$) $\delta$ 1.44 (m, 2H), 1.57 (m, 2H), 2.02 (t, $J =$ 7.2 Hz, 2H), 2.30 (q, $J =$ 7.2 Hz, 2H), 3.19 (s, 3H), 3.40 (s, 4H), 4.95 (s, 2H),
6.57 (t, J = 7.5 Hz, IH), 6.96 (d, J = 6.3 Hz, IH), 7.38 (m, 4H), 7.73 (d, J = 6.9 Hz, IH), 8.09 (d, J = 7.2 Hz, IH).

LC/MS (M+H): 401.20.

Example 34: (E)-N1-cyclohexyl-N8-hydroxy-2-((naphthalen-1-yloxy)methyl)-2-octenediamide

(34-1):(E)-8-(cyclohexylamino)-7-((naphthalen-1-yloxy)methyl)-8-oxo-6-octene acid methylester

The procedure of Example (1-1) was repeated except for using cyclohexylamine instead of dimethylaminehydrochloride as the amine to obtain 423 mg of the title compound (yield: 94%).

1H NMR (200 MHz, CDCl₃) δ 1.13 (m, 2H), 1.33 (m, 2H), 1.42-1.79 (m, 8H), 1.88 (m, 2H), 2.29 (m, 4H), 3.62 (s, 3H), 3.82 (m, 1H), 4.92 (s, 2H), 6.34 (d, J = 7.4 Hz, IH), 6.84 (t, J = 7.8 Hz, IH), 6.91 (d, J = 7.2 Hz, IH), 7.47 (m, 4H), 7.81 (m, IH), 8.15 (m, IH).


(34-2):(E)-8-(cyclohexylamino)-7-((naphthalen-1-yloxy)methyl)-8-oxo-6-octene acid

The procedure of Example (1-2) was repeated except for using the compound obtained in Example (34-1) as the starting material, to obtain 397 mg of the title compound (yield: 67%).

(34-3):(E)-N1-cyclohexyl-2-((naphthalen-1-yloxy)methyl)-N8-(tetrahydro-2H-pyran-2-yloxy)-2-octenediamide

The procedure of Example (4-3) was repeated except for using the compound obtained in Example (34-2) as the starting material, to obtain 257 mg of the title compound (yield: 95%).
The procedure of Example (4-4) was repeated except for using the compound obtained in Example (34-3) as the starting material, to obtain 122 mg of the title compound (yield: 83%).

HPLC purification: 78 mg (purity: 93%)

Example 35: (E)-N8-hydroxy-2-((naphthalen-1-yloxy)methyl)-Nl-(thiophen-2-ylmethyl)-2-octenediamide

The procedure of Example (1-1) was repeated except for using thiophen-2-ylmethylamine instead of dimethylaminehydrochloride as the amine to obtain 438 mg of the title compound (yield: 100%).
4.68 (d, J = 5.8 Hz, 2H), 4.90 (s, 2H), 6.93 (m, 5H), 7.18 (d, J = 4.8 Hz, IH), 7.46 (m, 4H), 7.78 (d, J = 8.0 Hz, IH), 8.04 (d, J = 8.0 Hz, 5H).

LC/MS (M+H): 438.17.

(35-2):(E)-7-((naphthalen-1-yl oxy)methyl)-8-oxo-8-(thiophen-2-ylmethylammino)-6-octene acid

The procedure of Example (1-2) was repeated except for using the compound obtained in Example (35-1) as the starting material, to obtain 438 mg of the title compound (yield: 92%).

(35-3):(E)-2-((naphthalen-1-yl oxy)methyl)-N8-(tetrahydro-2H-pyran-2-yloxy)-N1-(thiophen-2-ylmethyl)-2-octenediamide

The procedure of Example (4-3) was repeated except for using the compound obtained in Example (35-2) as the starting material, to obtain 390 mg of the title compound (yield: 66%).

\[ ^1H \text{NMR (200 MHz, CDCl}_3 \] \( \delta \) 1.46-1.94 (m, 10H), 2.10 (m, 2H), 2.32 (q, J = 7.0 Hz, 2H), 3.64 (m, IH), 3.93 (m, IH), 4.70 (d, J = 5.2 Hz, 2H), 4.90 (m, 5H), 4.95 (s, IH), 6.91 (m, 5H), 7.19 (d, J = 4.8 Hz, IH), 7.47 (m, 4H), 7.80 (d, J = 8.8 Hz, IH), 8.09 (d, J = 10.0 Hz, IH), 8.41 (br, IH).

LC/MS (M+H): 523.22.

(35-4):(E)-N8-hydroxy-2-((naphthalen-1-yl oxy)methyl)-N1-(thiophen-2-ylmethyl)-2-octenediamide

The procedure of Example (4-4) was repeated except for using the compound obtained in Example (35-3) as the starting material, to obtain 168 mg of the title compound (yield: 87%).

HPLC purification: 55 mg (purity: 95%)
\[ ^1H \text{NMR (300 MHz, MeOH-d}_4 \] \( \delta \) 1.34 (m, 2H), 1.58 (m, 2H), 2.10 (m, 2H), 2.10 (m, 2H),
2.32 (m, 2H), 4.58 (s, 2H), 4.96 (s, 2H), 6.55 (m, 1H), 6.86 (m, 3H), 7.19 (d, J = 4.8 Hz, 1H), 7.36 (m, 4H), 7.71 (d, J = 7.8 Hz, 1H), 8.01 (d, J = 7.8 Hz, 1H). LC/MS (M+H): 439.16.

Example 36: (E)-N8-hydroxy-Nl-(4-methoxyphenetyl)-2-((naphthalen-1-yloxy)methyl)-2-octenediamide

(36-l):(E)-8-(4-methoxyphenetylamino)-7-((naphthalen-1-yloxy)methyl)-8-oxo-6-octene acid methylester

The procedure of Example (1-1) was repeated except for using 4-methoxyphenetylamine instead of dimethylaminehydrochloride as the amine to obtain 476 mg of the title compound (yield: 100%).

1H NMR (200 MHz, CDCl₃) δ 1.45-1.73 (m, 4H), 2.30 (m, 4H), 2.75 (t, J = 6.4 Hz, 2H), 3.56 (q, J = 6.6 Hz, 2H), 3.63 (s, 3H), 3.66 (s, 3H), 4.84 (s, 2H), 6.46 (m, 1H), 6.56 (d, J = 8.6 Hz, 2H), 6.88 (m, 2H), 6.95 (d, J = 8.6 Hz, 2H), 7.50 (m, 4H), 7.82 (d, J = 8.4 Hz, 1H), 8.05 (d, J = 8.1 Hz, 1H). LC/MS (M+H): 476.24.

(36-2):(E)-8-(4-methoxyphenetylamino)-7-((naphthalen-1-yloxy)methyl)-8-oxo-6-octene acid

The procedure of Example (1-2) was repeated except for using the compound obtained in Example (36-1) as the starting material, to obtain 476 mg of the title compound (yield: 90%).

(36-3):(E)-Nl-(4-methoxyphenetyl)-2-((naphthalen-1-yloxy)methyl)-N8-(tetrahydro-2H-pyran-2-yloxy)-2-octenediamide

The procedure of Example (4-3) was repeated except for using the compound obtained in Example (36-2) as the starting material, to obtain 121 mg of the title compound (yield: 93%).
1H NMR (200 MHz, CDCl$_3$) $\delta$ 1.50-1.90 (m, 10H), 2.19 (m, 2H), 2.30 (m, 2H), 2.86 (m, 2H), 3.67 (m, 3H), 3.81 (s, 3H), 3.92 (m, IH), 4.85 (s, 2H), 4.92 (m, IH), 6.61 (m, IH), 6.87 (m, 2H), 7.15 (m, 4H), 7.46 (m, 4H), 7.82 (d, J = 8.0 Hz, IH), 8.09 (d, J = 8.0 Hz, IH), 8.39 (br, IH).

LC/MS (M+H): 561.29.

(36-4): (E)-N$_8$-hydroxy-N$1$-(4-methoxyphenetyl)-2-((naphthalen-1-yloxy)methyl)-2-octenediamide

The procedure of Example (4-4) was repeated except for using the compound obtained in Example (36-3) as the starting material, to obtain 155 mg of the title compound (yield: 84%).

HPLC purification: 50 mg (purity: 95%)

1H NMR (300 MHz, MeOH-d$_4$) $\delta$ 1.44 (m, 2H), 1.57 (m, 2H), 2.03 (t, J = 6.9 Hz, 2H), 2.28 (q, J = 6.9 Hz, 2H), 2.70 (t, J = 6.9 Hz, 2H), 3.41 (t, J = 7.2 Hz, 2H), 3.61 (s, 3H), 4.91 (s, 2H), 6.50 (t, J = 7.2 Hz, IH), 6.61 (d, J = 8.1 Hz, 2H), 6.92 (d, J = 7.2 Hz, IH), 6.98 (d, J = 8.1 Hz, 2H), 7.39 (m, 4H), 7.74 (d, J = 7.8 Hz, IH), 8.05 (d, J = 7.8 Hz, IH).

LC/MS (M+H): 478.23.

Example 37: (E)-N$_8$-hydroxy-2-((naphthalen-1-yloxy)methyl)-N$1$-(4-(trifluoromethoxy)benzyl)-2-octenediamide

(37-1): (E)-7-((naphthalen-1-yloxy)methyl)-8-oxo-8-(4-trifluoromethoxy)benzylamino)-6-octene acid methylester

The procedure of Example (1-1) was repeated except for using 4-(trifluoromethoxy)benzylamine instead of dimethylaminehydrochloride as the amine to obtain 515 mg of the title compound (yield: 57%).
4.52 (d, J = 5.6 Hz, 2H), 4.96 (s, 2H), 6.82 (br, 1H), 6.94 (m, 2H), 7.10 (d, J = 8.2 Hz, 2H), 7.38 (m, 2H), 7.48 (m, 2H), 7.82 (d, J = 8.2 Hz, 1H), 8.02 (d, J = 8.2 Hz, 1H).

LC/MS (M+H): 516.19.

(37-2): (E)-7-((naphthalen-1-yloxy)methyl)-8-oxo-8-(4-trifluoromethoxy)benzylamino)-6-octene acid

The procedure of Example (1-2) was repeated except for using the compound obtained in Example (37-1) as the starting material, to obtain 293 mg of the title compound (yield: 95%).

(37-3): (E)-2-((naphthalen-1-yloxy)methyl)-N8-(tetrahydro-2H-pyran-2-yloxy)-N1-(4-(trifluoromethoxy)benzyl)-2-octenediamide

The procedure of Example (4-3) was repeated except for using the compound obtained in Example (37-2) as the starting material, to obtain 291 mg of the title compound (yield: 60%).

1H NMR (200 MHz, CDCl3) δ 0.86 (m, 2H), 1.28 (m, 2H), 1.44-1.79 (m, 8H), 2.34 (m, 2H), 3.64 (br, 1H), 3.92 (br, 1H), 4.52 (d, J = 5.8 Hz, 2H), 4.90 (m, IH), 4.98 (s, 2H), 6.92 (m, 3H), 7.10 (m, 2H), 7.32 (m, 2H), 7.42 (m, 2H), 7.82 (d, J = 8.2 Hz, IH), 8.02 (d, J = 8.2 Hz, IH), 8.29 (br, IH).


(37-4): (E)-N8-hydroxy-2-((naphthalen-1-yloxy)methyl)-N1-(4-(trifluoromethoxy)benzyl)-2-octenediamide

The procedure of Example (4-4) was repeated except for using the compound obtained in Example (37-3) as the starting material, to obtain 74 mg of the title compound (yield: 52%).

HPLC purification: 15 mg (purity: 95%)
H NMR (300 MHz, MeOH-d4) δ 1.30 (m, 2H), 1.57 (m, 2H), 1.63 (m, 2H), 2.07 (t, J = 8.2 Hz, 2H), 2.38 (q, J = 7.4 Hz, 2H), 4.46 (s, 2H), 5.05 (s, 2H), 5.47 (s, 2H), 6.61 (t, J = 7.6 Hz, IH), 6.97 (d, J = 7.4 Hz, IH), 7.06 (d, J = 8.6 Hz, IH), 7.38 (m, 6H), 7.77 (d, J = 8.0 Hz, IH), 8.07 (d, J = 8.2 Hz, IH).

Example 38: (E)-Nl-(l-(cyclohexylmethyl)pyrrolidin-3-yl)-N8-hydroxy-2-((naphthalen-1-yl oxy)methyl)-2-octenediamide

The procedure of Example (1-1) was repeated except for using 1-(cyclohexylmethyl)pyrrolidin-3-ylamine instead of dimethylaminehydrochloride as the amine to obtain 506 mg of the title compound (yield: 26%).

1H NMR (200 MHz, CDCl3) δ 0.86 (m, 4H), 1.05-1.33 (m, 8H), 1.42-1.87 (m, 4H), 2.09 (m, 2H), 2.17-2.34 (m, 4H), 2.57 (m, 2H), 2.84 (m, IH), 3.62 (s, 3H), 4.53 (br, IH), 4.93 (s, 2H), 5.30 (s, 2H), 6.84 (m, 2H), 7.47 (m, 4H), 7.78 (m, IH), 8.15 (m, IH).

LC/MS (M+H): 507.31.

(38-2):(E)-8-(l-(cyclohexylmethyl)pyrrolidin-3-ylamino)-7-((naphthalen-1-yl oxy)methyl)-8-oxo-6-octene acid

The procedure of Example (1-2) was repeated except for using the compound obtained in Example (38-1) as the starting material, to obtain 135 mg of the title compound (yield: 89%).

(38-3):(E)-Nl-(l-(cyclohexylmethyl)pyrrolidin-3-yl)-2-((naphthalen-1-yl oxy)methyl)-N8-(tetrahydro-2H-pyran-2-yl oxy)methyl)-2-octenediamide
The procedure of Example (4-3) was repeated except for using the compound obtained in Example (38-2) as the starting material, to obtain 117 mg of the title compound (yield: 53%).

\[ ^1H \text{NMR (200 MHz, CDCl}_3) \delta 0.83 \text{ (m, 4H), 1.07 (m, 2H), 1.28 (m, 4H), 1.42 (m, IH), 1.57-1.78 (m, 12H), 2.17 (m, 2H), 2.31 (m, 6H), 2.61-2.89 (m, 3H), 3.60 (m, IH), 3.92 (m, IH), 4.57 (m, IH), 4.93 (s, 2H), 6.82 (t, J = 7.4 Hz, IH), 6.91 (d, J = 7.2 Hz, IH), 7.46 (m, 4H), 7.78 (d, J = 7.2 Hz, IH), 8.16 (d, J = 7.4 Hz, IH), 8.43 (br, IH). } \]

LC/MS (M+H): 592.37.

(38-4):(E)-Nl-(l-(cyclohexylmethyI)pyrrolidin-3-yl)-N8-hydroxy-2-((naphthalen-1-yloxy)methyl)-2-octenediamide

The procedure of Example (4-4) was repeated except for using the compound obtained in Example (38-3) as the starting material, to obtain 58 mg of the title compound (yield: 77%).

PHLC purification: 24 mg (purity: 95%)

\[ ^1H \text{NMR (300 MHz, MeOH-}d_4 \delta 0.92 \text{ (m, 2H), 1.15 (m, 4H), 1.46 (m, 2H), 1.50-1.70 (m, 8H), 2.04 (m, 3H), 2.36 (q, J = 7.2 Hz, 2H), 2.50 (m, IH), 2.96 (m, 3H), 3.56 (m, IH), 3.79 (m, IH), 4.34 (br, IH), 4.97 (s, 2H), 6.53 (t, J = 7.0 Hz, IH), 6.94 (d, J = 7.2 Hz, IH), 7.38 (m, 4H), 7.73 (d, J = 7.6 Hz, IH), 8.06 (d, J = 7.6 Hz, IH). } \]

LC/MS (M+H): 508.31.

Example 39: (E)-Nl-(l-cyclopentylpiperidin-4-yl)-N8-hydroxy-2-((naphthalen-1-yloxy)methyl)-2-octenediamide

(39-l):(E)-8-(l-cyclopentylpiperidin-4-ylamino)-7-((naphthalen-1-yloxy)methyl)-8-oxo-6-octene acid methylester
The procedure of Example (1-1) was repeated except for using 1-cyclopentylpiperidin-4-ylamine instead of dimethylaminehydrochloride as the amine to obtain 492 mg of the title compound (yield: 55%).

\[ ^1\text{HNMR} \ (200 \text{ MHz, CDCl}_3 \ \delta \ 0.83-1.04 \ (m, 4H), 1.28 \ (m, 6H), 1.42-1.70 \ (m, 8H), 1.92-2.59 \ (m, 6H), 2.85 \ (m, IH), 3.62 \ (s, 3H), 3.94 \ (m, IH), 4.92 \ (s, 2H), 6.39 \ (d, J = 7.8 \text{ Hz}, IH), 6.84 \ (m, 2H), 7.48 \ (m, 4H), 7.79 \ (m, IH), 8.17 \ (m, IH). \]

LC/MS (M+H): 493.30.

(39-2):(E)-8-(1-cyclopentylpiperidin-4-ylamino)-7-((naphthalen-l-yloxy) methyl)-8-oxo-6-octene acid

The procedure of Example (1-2) was repeated except for using the compound obtained in Example (39-1) as the starting material, to obtain 274 mg of the title compound (yield: 96%).

(39-3):(E)-Nl-(1-cyclopentylpiperidin-4-yl)-2-((naphthalen-l-yloxy) methyl)-N8-(tetrahydro-2H-pyran-2-yloxy)-2-octenediamide

The procedure of Example (4-3) was repeated except for using the compound obtained in Example (39-2) as the starting material, to obtain 257 mg of the title compound (yield: 48%).

\[ ^1\text{H NMR} \ (200 \text{ MHz, CDCl}_3 \ \delta \ 0.82 \ (m, 2H), 1.25-1.77 \ (m, 22H), 1.93-2.37 \ (m, 6H), 2.49 \ (m, IH), 2.90 \ (m, 2H), 3.61 \ (br, IH), 3.91 \ (br, IH), 4.91 \ (s, 2H), 6.52 \ (br, IH), 6.89 \ (m, 2H), 7.50 \ (m, 4H), 7.79 \ (m, IH), 8.16 \ (m, IH), 8.52 \ (br, IH). \]

LC/MS (M+H): 578.35.

(39-4):(E)-Nl-(1-cyclopentylpiperidin-4-yl)-N8-hydroxy-2-((naphthalen-l-yloxy)methyl)-2-octenediamide
The procedure of Example (4-4) was repeated except for using the compound obtained in Example (39-3) as the starting material, to obtain 122 mg of the title compound (yield: 70%).

HPLC purification: 42 mg (purity: 95%)

\[ ^1\text{H} \text{NMR (300 MHz, MeOH-d4)} \delta 1.46 (m, 2H), 1.54-1.78 (m, 12H), 1.99-2.11 (m, 6H), 2.32 (q, J = 7.4 Hz, 2H), 2.98 (t, J = 12.6 Hz, 2H), 3.39 (m, IH), 3.57 (d, J = 12.4 Hz, 2H), 3.94 (m, IH), 4.96 (s, 2H), 6.47 (t, J = 7.2 Hz, IH), 6.92 (d, J = 7.2 Hz, IH), 7.34 (m, 4H), 7.74 (d, J = 8.0 Hz, IH), 7.82 (s, IH) \]

LC/MS (M+H): 494.29.

Example 40: (E)-Nl-(1-benzyIpyrrolidin-3-yl)-N8-hydroxy-2-((naphthalen-1-yloxy)methyl)-2-octenediamide

(40-1):(E)-8-(1-benzylpyrrolidin-3-ylamino)-7-((naphthalen-1-yloxy)methyl)-8-oxo-6-octene acid methylester

The procedure of Example (1-1) was repeated except for using 1-benzylpyrrolidin-3-ylamine instead of dimethylaminehydrochloride as the amine to obtain 501 mg of the title compound (yield: 70%).

\[ ^1\text{H} \text{NMR (200 MHz, CDCl}_3\text{)} \delta 0.84 (m, 2H), 1.29 (m, 2H), 1.62 (m, 4H), 2.30 (m, 6H), 2.55 (m, 2H), 3.48 (m, 3H), 3.63 (s, 3H), 4.94 (s, 2H), 6.86 (m, 2H), 7.14 (m, 2H), 7.18 (m, 2H), 7.46 (m, 4H), 7.81 (d, J = 7.8 Hz, IH), 8.19 (d, J = 7.4 Hz, IH).

LC/MS (M+H): 501.27.

(40-2):(E)-8-(1-benzylpyrrolidin-3-ylamino)-7-((naphthalen-1-yloxy)methyl)-8-oxo-6-octene acid

The procedure of Example (1-2) was repeated except for using the compound obtained in Example (40-1) as the starting material, to obtain 352
mg of the title compound (yield: 55%).

(40-3): (E)-Nl-(l-benzylpyrrolidin-3-yl)-2-((naphthalen-1-yloxy)methyl)-N8-(tetrahydro-2H-pyran-2-yloxy)-2-octenediamide

The procedure of Example (4-3) was repeated except for using the compound obtained in Example (40-2) as the starting material, to obtain 188 mg of the title compound (yield: 67%).

1H NMR (200 MHz, CDCl₃) δ 0.86 (m, 2H), 1.28 (m, 2H), 1.42-1.77 (m, 8H), 2.08-2.37 (m, 6H), 2.54 (m, 2H), 2.75 (m, 1H), 3.48 (m, 3H), 3.91 (br, 1H), 4.53 (br, 1H), 4.85 (m, 2H), 4.92 (s, 2H), 6.94 (m, 3H), 7.16 (m, 4H), 7.40 (m, 4H), 7.84 (d, J = 7.0 Hz, 1H), 8.21 (d, J = 9.6 Hz, 1H), 8.60 (br, 1H).

LC/MS (M+H): 586.32.

(40-4): (E)-Nl-(l-benzylpyrrolidin-3-yl)-N8-hydroxy-2-((naphthalen-1-yloxy)methyl)-2-octenediamide

The procedure of Example (4-4) was repeated except for using the compound obtained in Example (40-3) as the starting material, to obtain 64 mg of the title compound (yield: 68%).

HPLC purification: 23 mg (purity: 95%)

1H NMR (300 MHz, MeOH-d₄) δ 1.30 (m, 2H), 1.52 (m, 2H), 1.64 (m, 2H), 2.07 (t, J = 7.0 Hz, 2H), 2.39 (q, J = 7.2 Hz, 2H), 4.32 (m, 3H), 4.94 (m, 3H), 5.47 (s, 2H), 6.57 (t, J = 7.4 Hz, 1H), 7.0 2(d, J = 7.2 Hz, 1H), 7.36-7.44 (m, 8H), 7.77 (d, J = 8.4 Hz, 1H), 7.86 (m, 1H), 8.08 (d, J = 6.4 Hz, 1H), 8.75 (br, 1H).


Example 41: (E)-N8-hydroxy-Nl-(l-isopropylpyrrolidin-3-yl)-2-((naphthalen-1-yloxy)methyl)-2-octenediamide
(41-1): (E)-8-(l-isopropylpyrrolidin-3-ylamino)-7-((naphthalen-l-yloxy) methyl)-8-oxo-6-octene acid methylester

The procedure of Example (1-1) was repeated except for using 1-isopropylpyrrolidin-3-ylamine instead of dimethylaminehydrochloride as the amine to obtain 452 mg of the title compound (yield: 41%).

$^1$H NMR (200 MHz, CDCl$_3$) $\delta$ 0.84 (m, 2H), 1.02 (m, 4H), 1.26 (m, 3H), 1.61 (m, 4H), 2.18 (m, 2H), 2.30 (m, 5H), 2.70 (t, $J = 6.6$ Hz, 2H), 3.63 (s, 3H), 4.95 (s, 2H), 6.86 (m, 3H), 7.46 (m, 4H), 7.79 (d, $J = 8.2$ Hz, IH), 8.17 (d, $J = 8.6$ Hz, IH).
LC/MS (M+H): 453.27.

(41-2): (E)-8-(l-isopropylpyrrolidin-3-ylamino)-7-((naphthalen-l-yloxy) methyl)-8-oxo-6-octene acid

The procedure of Example (1-2) was repeated except for using the compound obtained in Example (41-1) as the starting material, to obtain 184 mg of the title compound (yield: 83%).

(41-3): (E)-N1-(l-isopropylpyrroli din-3-yl)-2-((naphthalen-l-yloxy) methyl)-N8-(tetrahydro-2H-pyran-2-yloxy)-2-octenediamide

The procedure of Example (4-3) was repeated except for using the compound obtained in Example (41-1) as the starting material, to obtain 122 mg of the title compound (yield: 69%).

$^1$H NMR (200 MHz, CDCl$_3$) $\delta$ 0.83 (m, 4H), 1.05 (m, 6H), 1.25 (m, 4H), 1.59 (m, 6H), 2.09 (m, 2H), 2.34 (m, 4H), 2.76 (d, $J = 5.4$ Hz, 2H), 3.62 (m, IH), 3.92 (m, IH), 4.94 (s, 2H), 6.79 (t, $J = 7.8$ Hz, IH), 6.94 (d, $J = 7.4$ Hz, IH), 7.14 (m, IH), 7.44 (m, 4H), 7.77 (m, IH), 8.16 (m, IH).
LC/MS (M+H): 538.32.
(41-4):(E)-N8-hydroxy-NI-(l-isopropylpyrrolidin-3-yl)-2-((naphthalen-l-yloxy)methyl)-2-octenediamide

The procedure of Example (4-4) was repeated except for using the compound obtained in Example (41-3) as the starting material, to obtain 101 mg of the title compound (yield: 82%).

HPLC purification: 39 mg (purity: 96%)

$^1$H NMR (300 MHz, MeOH-d$_4$) $\delta$ 1.26 (m, 6H), 1.47 (q, J=7.2Hz, 2H), 1.62 (q, J=7.2Hz, 2H), 2.04 (t, J = 7.0 Hz, 3H), 2.34 (q, J = 7.2 Hz, 3H), 3.25-3.53 (m, 4H), 3.69 (m, IH), 4.43 (m, IH), 4.97 (m, 2H), 6.58 (m, IH), 6.95 (d, J = 7.2 Hz, IH), 7.34 (m, 4H), 7.74 (d, J = 7.6 Hz, IH), 8.06 (d, J = 8.0 Hz, IH).


Example 42: (E)-Nl-(l-(cyclohexanecarbonyl)pyrrolidin-3-yl)-N8-hydroxy-2-((naphthalen-l-yloxy)methyl)-2-octenediamide

(42-1):(E)-8-(l-(cyclohexanecarbonyl)pyrrolidin-3-ylamino)-7-((naphthalen-l-y!oxy)methyl)-8-oxo-6-octene acid methyl ester

The procedure of Example (1-1) was repeated except for using 1-(cyclohexanecarbonyl)pyrrolidin-3-ylamine instead of dimethylaminehydrochloride as the amine to obtain 520 mg of the title compound (yield: 66%).

$^1$H NMR (200 MHz, CDCl$_3$) $\delta$ 1.17-1.76 (m, 14H), 2.16-2.35 (m, 7H), 3.46 (m, 2H), 3.62 (s, 3H), 3.83 (m, 2H)$_2$ 4.54 (m, IH), 4.93 (s, 2H), 6.60 (m, IH), 6.88 (m, IH), 7.47 (m, 4H), 7.80 (d, J = 7.2 Hz, IH), 8.12 (d, J = 6.8 Hz, IH).

LC/MS (M+H): 521.29.

(42-2):(E)-8-(l-(cyclohexanecarbonyl)pyrrolidin-3-ylamino)-7-((naphthalen-l-y!oxy)methyl)-8-oxo-6-octene acid
The procedure of Example (1-2) was repeated except for using the compound obtained in Example (42-1) as the starting material, to obtain 342 mg of the title compound (yield: 78%).

(42-3): (E)-Nl-(l-cyclohexanecarbonyl)pyrrolidin-3-yl)-2-((naphthalen-1-yloxy)methyl)-N8-(tetrahydro-2H-pyran-2-yloxy)-2-octenediamide

The procedure of Example (4-3) was repeated except for using the compound obtained in Example (42-2) as the starting material, to obtain 262 mg of the title compound (yield: 40%).

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 1.20 (m, 4H), 1.42-1.77 (m, 16H), 2.1 1 (m, 4H), 2.32 (m, 3H), 3.37 (m, 2H), 3.44 (m, IH), 3.60 (m, 2H), 3.86 (m, IH), 4.53 (q, J = 5.6 Hz, IH), 4.93 (s, 2H), 6.89 (m, 3H), 7.45 (m, 4H), 7.80 (d, J = 7.4 Hz, IH), 8.10 (d, J = 7.6 Hz, IH), 8.41 (br, IH).

LC/MS (M+H): 606.35.

(42-4): (E)-Nl-(l-cyclohexanecarbonyl)pyrrolidin-3-yl)-N8-hydroxy-2-((naphthalen-1-yloxy)methyl)-2-octenediamide

The procedure of Example (4-4) was repeated except for using the compound obtained in Example (42-3) as the starting material, to obtain 154 mg of the title compound (yield: 80%).

HPLC purification: 67 mg (purity: 96%)

$^1$HNMR (300 MHz, MeOH-d$_4$) $\delta$ 1.18-1.69 (m, 14H), 2.03 (m, 4H), 2.32 (q, J = 7.0 Hz, 3H), 3.49 (m, 2H), 3.80 (m, IH), 3.93 (s, IH), 4.40 (m, IH), 4.98 (s, 2H), 6.48 (t, J = 7.8 Hz, IH), 6.94 (d, J = 5.4 Hz, IH), 7.37 (m, 4H), 7.73 (d, J = 7.8 Hz, IH), 8.08 (d, J = 8.8 Hz, IH).

LC/MS (M+H): 522.29.

Example 43: (E)-3-(8-(hydroxyamino)-2-((naphthalen-1-yloxy)methyl)-8-oxo-2-octeneamido)pyrrolidin-l-carboxylic acid t-butylerster
The procedure of Example (1-1) was repeated except for using 3-aminopyrrolidin-1-carboxylic acid t-butylester instead of dimethylaminehydrochloride as the amine to obtain 510 mg of the title compound (yield: 83%).

\[
\text{\textsuperscript{1}H NMR (300 MHz, CDCl}_{3} \text{) } \delta 1.33 (m, 2H), 1.39 (s, 9H), 1.60 (m, 2H), 2.15 (m, 2H), 2.31 (m, 4H), 3.36 (m, 4H), 3.62 (s, 3H), 4.93 (s, 2H), 6.66 (br, IH), 6.90 (m, 2H), 7.38 (t, J = 7.8 Hz, 2H), 7.49 (m, 2H), 7.80 (m, IH), 8.10 (m, IH).
\]

LC/MS (M+H): 511.27.

The procedure of Example (1-2) was repeated except for using the compound obtained in Example (43-1) as the starting material, to obtain 423 mg of the title compound (yield: 77%).

The procedure of Example (4-3) was repeated except for using the compound obtained in Example (43-2) as the starting material, to obtain 320 mg of the title compound (yield: 72%).

\[
\text{\textsuperscript{1}H NMR (300 MHz, CDCl}_{3} \text{) } \delta 1.25 (m, 2H), 1.39 (s, 9H), 1.45 (m, 2H), 1.50-1.77 (m, 6H), 1.92 (m, IH), 2.04 (m, 4H), 2.30 (q, J = 7.2 Hz, 2H), 3.36 (m, 4H), 3.60 (br, IH), 3.92 (br, IH), 4.92 (s, 2H), 6.74 (br, IH), 6.83 (t, J = 7.6 Hz, 2H).
\]
Hz, 6.92 (d, J = 7.4 Hz, IH), 7.46 (m, 4H), 7.80 (m, IH), 8.10 (m, IH), 8.71 (br, IH).
LC/MS (M+H): 596.33.

5 (43-4): (E)-3-(8-(hydroxyamino)-2-((naphthalen-1-yloxy)methyl)-8-oxo-2-octeneamido)pyrrolidin-1-carboxylic acid t-butylester

The procedure of Example (4-4) was repeated except for using the compound obtained in Example (43-3) as the starting material, to obtain 255 mg of the title compound (yield: 95%).

HPLC purification: 5 mg (purity: 96%)

1H NMR (300 MHz, MeOH-d₄) δ 1.29 (m, 2H), 1.42 (s, 9H), 1.62 (m, 2H), 1.89-2.09 (m, 4H), 2.33 (m, 2H), 3.20 (m, 2H), 3.57 (m, 2H), 4.41 (t, J = 5.4 Hz, IH), 5.48 (s, 2H), 6.52 (t, J = 7.4 Hz, IH), 7.00 (d, J = 7.2 Hz, 2H), 7.40 (m, 4H), 7.79 (d, J = 8.4 Hz, IH), 8.10 (d, J = 7.4 Hz, IH).
LC/MS (M+H): 512.27.

Example 44: (E)-N8-hydroxy-2-((naphthalen-1-yloxy)methyl)-N1-(pyrrolidin-3-yl)2-octenediamide

5 (44-1): (E)-3-(8-methoxy-2-((naphthalen-1-yloxy)methyl)-8-oxo-2-octeneamido)pyrrolidin-1-carboxylic acid t-butylester

The procedure of Example (1-1) was repeated except for using 3-aminopyrrolidin-1-carboxylic acid t-butylester instead of dimethylaminehydrochloride as the amine to obtain 510 mg of the title compound (yield: 83%).

1H NMR (300 MHz, CDCl₃) δ 1.33 (m, 2H), 1.39 (s, 9H), 1.60 (m, 2H), 2.15 (m, 2H), 2.31 (m, 4H), 3.36 (m, 4H), 3.62 (s, 3H), 4.93 (s, 2H), 6.66 (br, IH), 6.90 (m, 2H), 7.38 (t, J = 7.8 Hz, 2H), 7.49 (m, 2H), 7.80 (m, IH), 8.10 (m, IH).
LC/MS (M+H): 511.27.

(44-2): (E)-8-(1-((t-butoxycarbonyl)pyrroloidin-3-ylamino)-7-((naphthalen-1-ylOxy)methyl)-8-oxo-6-octene acid

The procedure of Example (1-2) was repeated except for using the compound obtained in Example (44-1) as the starting material, to obtain 423 mg of the title compound (yield: 77%).

(44-3): (E)-3-((naphthalen-1-ylOxy)methyl)-8-oxo-8-(tetrahydro-2H-pyran-2-ylOxyamino)-2-octeneamido)pyrroloidin-1-carboxylic acid t-butylerster

The procedure of Example (4-3) was repeated except for using the compound obtained in Example (44-2) as the starting material, to obtain 320 mg of the title compound (yield: 72%).

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 1.25 (m, 2H), 1.39 (s, 9H), 1.45 (m, 2H), 1.50-1.77 (m, 6H), 1.92 (m, IH), 2.04 (m, 4H), 2.30 (q, J = 7.2 Hz, 2H), 3.36 (m, 4H), 3.60 (br, IH), 3.92 (br, IH), 4.92 (s, 2H), 6.74 (br, IH), 6.83 (t, J = 7.6 Hz, IH), 6.92 (d, J = 7.4 Hz, IH), 7.46 (m, 4H), 7.80 (m, IH), 8.10 (m, IH), 8.71 (br, IH).

LC/MS (M+H): 596.33.

(44-4): (E)-3-((8-(hydroxyamino)-2-((naphthalen-1-ylOxy)methyl)-8-oxo-2-octeneamido)pyrroloidin-1-carboxylic acid t-butylerster

The procedure of Example (4-4) was repeated except for using the compound obtained in Example (44-3) as the starting material, to obtain 255 mg of the title compound (yield: 95%).

HPLC purification: 5 mg (purity: 96%)

$^1$H NMR (300 MHz, MeOH-d$_4$) $\delta$ 1.29 (m, 2H), 1.42 (s, 9H), 1.62 (m, 2H),
1.89-2.09 (m, 4H), 2.33 (m, 2H), 3.20 (m, 2H) 5 3.57 (m, 2H) 5 4.41 (t, J = 5.4 Hz) 5 1H) 5 5.48 (s, 2H) 5 6.52 (t, J = 7.4 Hz) 5 7.00 (d, J = 7.2 Hz) 5 7.40 (m, 4H) 5 7.79 (d, J = 8.4 Hz) 5 8.10 (d, J = 7.4 Hz) 5 8.40 (m, 4H).

LC/MS (M+H): 512.27.

(44-5): (E)-N8-hydroxy-2-((naphthalen-1-yloxy)methyl)-Nl-(pyrrolidin-3-yl)2-octenediamide

The procedure of Example (4-4) was repeated except for using the compound obtained in Example (44-4) as the starting material, to obtain 172 mg of the title compound (yield: 92%).

HPLC purification: 58 mg (purity: 96%)

\[ ^1H \text{NMR (300 MHz$_5$MeOH-d$_4$)} \delta 1.46 (m, 2H), 1.58 (m, 2H), 2.04 (t, J = 7.0 Hz) 5 2.34 (m, 4H) 5 3.22 (m, 2H) 5 3.44 (m, 2H) 5 4.43 (m, IH) 5 4.97 (s, 2H) 5 6.55 (m, IH) 5 6.95 (d, J = 6.8 Hz) 5 7.38 (m, 4H), 7.73 (d, J = 7.4 Hz) 5 8.08 (d, J = 7.8 Hz) 5 8.40 (m, 4H).

LC/MS (M+H): 412.22.

Example 45: (E)-Nl-(1-cyclohexylpyrroliidin-3-yl)-N8-hydroxy-2-((naphthalen-2-yloxy)methyl)-2-octenediamide

(45-I): (E)-8-(1-cyclohexyIpyrrolidin-3-ylamino)-7-((naphthalen-2-yloxy)methyl)-8-oxo-6-octene acid methylester

The procedure of Example (1-1) was repeated except for using 1-cyclohexylpyrroldin-3-ylamine instead of dimethylaminehydrochloride as the amine to obtain 492 mg of the title compound (yield: 54%).

\[ ^1H \text{NMR (200 MHz$_5$CDCl$_3$)} \delta 1.08-1.42 (m, 4H), 1.51-1.78 (m, 10H), 1.94 (m, 2H) 5 2.29 (m, 6H), 2.64 (d, J = 5.4 Hz) 5 2.82 (m, IH), 3.63 (s, 3H) 5 4.53 (m, IH) 5 4.93 (s, 2H), 6.90 (m, 2H), 7.48 (m, 4H), 7.78 (m, IH), 8.17 (d, J = 7.2 Hz) 5 8.40 (m, 4H).
(45-2):(E)-8-(1-cyclohexylpyrrolidin-3-ylamino)-7-((naphthalen-2-yloxy)methyl)-8-oxo-6-octene acid

The procedure of Example (1-2) was repeated except for using the compound obtained in Example (45-1) as the starting material, to obtain 269 mg of the title compound (yield: 100%).

(45-3):(E)-N1-(1-cyclohexylpyrrolidin-3-yl)-2-((naphthalen-2-yloxy)methyl)-N8-(tetrahydro-2H-pyran-2-yloxy)-2-octenediamide

The procedure of Example (4-3) was repeated except for using the compound obtained in Example (45-2) as the starting material, to obtain 269 mg of the title compound (yield: 43%).

1H NMR 200 MHz CDCl3 δ 0.83 (m 4H), 1.13-1.42 (m, 6H), 1.56-1.89 (m, 12H), 2.16 (m, 6H), 2.32 (m, 2H), 2.77 (m, IH), 3.62 (br, IH), 3.94 (br, IH), 4.61 (m, IH), 4.80 (m, IH), 4.94 (s, 2H), 6.82 (t, J = 7.8 Hz, IH), 6.91 (d, J = 7.6 Hz, 2H), 7.44 (m, 4H), 7.82 (m, 4H), 8.16 (m, IH).

LC/MS (M+H): 578.35.

(45-4):(E)-N1-(1-cyclohexylpyrrolidin-3-yl)-N8-hydroxy-2-((naphthalen-2-yloxy)methyl)-2-octenediamide

The procedure of Example (4-4) was repeated except for using the compound obtained in Example (45-3) as the starting material, to obtain 140 mg of the title compound (yield: 88%).

1H NMR 300 MHz MeOH-d4 δ 1.24-1.34 (m, 8H), 1.47-1.65 (m, 6H), 1.77 (m, IH), 1.98 (m, 2H), 2.05 (t, J = 7.2 Hz, 2H), 2.11 (s, 2H), 2.34 (m, 2H), 2.76 (br, IH), 4.41 (m, IH), 4.99 (s, 2H), 6.59 (t, J = 7.4 Hz, 2H), 6.98 (d, J =
7.0 Hz, IH), 7.39 (m, 4H), 7.74 (d, J = 7.6 Hz, 5 IH), 8.07 (d, J = 8.2 Hz, IH). LC/MS (M+H): 494.29.

Example 46: (E)-Nl-(l-cyclopropylpyrrolidin-3-yl)-N8-hydroxy-2-((naphthalen-1-yloxy)methyl)-2-octenediamide

(46-1):(E)-8-(l-cyclopropylpyrrolidin-3-yIamino)-7-((naphthalen-2-yloxy)methyl)-8-oxo-6-octene acid methylester

The procedure of Example (1-1) was repeated except for using 1-cyclopropylpyrrolidin-3-ylamine instead of dimethylaminehydrochloride as the amine to obtain 450 mg of the title compound (yield: 78%).

\[^{1}\text{HNMR} (200 \text{ MHz}, \text{CDCl}_3) \delta 0.15 \text{ (m, 2H), 0.28 (m, 2H), 1.28-1.93 (m, 8H), 2.29 (m, 6H), 2.80 (m, 2H), 3.62 (s, 3H), 4.92 (s, 2H), 6.69 (d, J = 7.8 Hz, IH), 6.82 (m, IH), 7.47 (m, 4H), 7.82 (m, IH), 8.15 (m, IH). LC/MS (M+H): 451.25.

(46-2):(E)-8-(l-cyclopropylpyrrolidin-3-yIamino)-7-((naphthalen-2-yloxy)methyl)-8-oxo-6-octene acid

The procedure of Example (1-2) was repeated except for using the compound obtained in Example (46-1) as the starting material, to obtain 355 mg of the title compound (yield: 98%).

(46-3):(E)-Nl-(l-cyclopropylpyrrolidin-3-yl)-2-((naphthalen-1-yloxy)methyl)-N8-(tetrahydro-2H-pyran-2-yloxy)-2-octenediamide

The procedure of Example (4-3) was repeated except for using the compound obtained in Example (46-2) as the starting material, to obtain 334 mg of the title compound (yield: 61%).

\[^{1}\text{H NMR} (200 \text{ MHz}, \text{CDCl}_3) \delta 0.16 \text{ (m, 2H), 0.31 (m, 2H)\text{,} 1.47-1.83 (m,
12H), 2.15 (m, 2H), 2.17 (s, 2H), 2.30 (m, 2H), 2.37 (m, 2H), 2.81 (m, 2H), 3.62 (br, IH), 3.91 (br, IH), 4.90 (m, 2H), 6.80 (t, J = 7.8 Hz, IH), 6.90 (d, J = 7.6 Hz, IH), 7.46 (m, 4H), 7.80 (m, 4H), 8.14 (m, IH), 8.44 (br, IH).

LC/MS (M+H): 536.30.

(46-4):(E)-Nl-(l-cyclopropylpyrrolidin-3-yl)-N8-hydroxy-2-((naphthalen-l-yloxy)methyl)-2-octenediamide

The procedure of Example (4-4) was repeated except for using the compound obtained in Example (46-3) as the starting material, to obtain 154 mg of the title compound (yield: 89%).

HPLC purification: 65 mg (purity: 95%)

1H NMR (300 MHz, MeOH-d₄) δ 0.42 (m, 4H), 1.44 (q, J = 7.4 Hz, 2H), 1.59 (m, 3H), 1.82 (br, IH), 2.02 (t, J = 7.2 Hz, IH), 2.09 (s, IH), 2.27 (m, IH), 2.32 (q, J = 7.2 Hz, 2H), 2.71 (m, 2H), 3.01 (m, 2H), 4.94 (s, 2H), 6.53 (t, J = 7.4 Hz, IH), 6.92 (d, J = 7.2 Hz, IH), 7.36 (m, 4H), 7.74 (d, J = 7.8 Hz, IH), 7.81 (s, IH), 8.08 (d, J = 7.8 Hz, IH).

Example 47: (E)-Nl-(l-cyclopropypiperidin-4-yl)-N8-hydroxy-2-((naphthalen-l-yloxy)methyl)-2-octenediamide

(47-l):(E)-8-(l-cyclopropypiperidin-4-ylamino)-7-((naphthalen-l-yloxy)methyl)-8-oxo-6-octene acid methylester

The procedure of Example (1-1) was repeated except for using 1-cyclopropypiperidin-4-ylamine instead of dimethylaminehydrochloride as the amine to obtain 464 mg of the title compound (yield: 47%).

1H NMR (200 MHz, CDCl₃) δ 0.33-0.40 (m, 4H), 1.24-1.73 (m, 9H), 1.88 (m, 2H), 2.17 (m, IH), 2.29 (m, 6H), 3.62 (s, 3H), 3.92 (m, IH), 4.91 (s, 2H), 6.35 (d, J = 8.0 Hz, IH), 6.90 (m, 2H), 7.48 (m, 4H), 7.80 (m, IH), 8.12 (m, 2H), 8.44 (br, IH).
IH).
LC/MS (M+H): 465.27.

(47-2):(E)-8-(l-cyclopropylpiperidin-4-ylamino)-7-((naphthalen-1-yloxy) methyl)-8-oxo-6-octene acid

The procedure of Example (1-2) was repeated except for using the compound obtained in Example (47-1) as the starting material, to obtain 221 mg of the title compound (yield: 100%).

(47-3):(E)-Nl-(l-cyclopropylpiperidin-4-yl)-2-((naphthalen-1-yloxy) methyl)-N8-(tetrahydro-2H-pyran-2-yloxy)-2-octenediamide

The procedure of Example (4-3) was repeated except for using the compound obtained in Example (47-2) as the starting material, to obtain 221 mg of the title compound (yield: 51%).

1H NMR (200 MHz, CDCl₃) δ 0.38 (m, 4H), 1.28-1.94 (m, 18H), 2.10 (m, 2H), 2.32 (m, 4H), 3.64 (m, IH), 3.95 (m, IH), 4.88 (m, IH), 4.92 (s, 2H), 6.40 (d, J = 8.2 Hz, IH), 6.92 (m, 2H), 7.48 (m, 4H), 7.84 (m, IH), 8.14 (m, IH), 8.42 (br, IH).
LC/MS (M+H): 550.32.

(47-4):(E)-Nl-(l-cyclopropylpiperidin-4-yl)-N8-hydroxy-2-((naphthalen-1-yloxy)methyl)-2-octenediamide

The procedure of Example (4-4) was repeated except for using the compound obtained in Example (47-3) as the starting material, to obtain 150 mg of the title compound (yield: 90%).

HPLC purification: 107 mg (purity: 95%)
1H NMR (300 MHz, MeOH-d₄) δ 0.89 (m, 4H), 1.25 (m, 4H), 1.46 (m, 2H), 1.62 (m, 2H), 2.04 (t, J = 7.2 Hz, 2H), 2.10 (m, 2H), 2.33 (q, J = 7.4, 2H),
2.73 (m, IH), 3.59 (m, 2H), 3.99 (m, IH), 4.98 (s, 2H), 6.49 (m, IH), 6.94 (d, J = 7.2 Hz, IH), 7.36 (m, 4H), 7.73 (d, J = 7.8 Hz, IH), 8.06 (d, J = 7.8 Hz, IH).

Example 48: (E)-Nl-(l-ethylpiperidin-4-yl)-N8-hydroxy-2-((naphthalen-1-yloxy)methyl)-2-octenediamide

(48-1):(E)-8-(l-ethylpiperidin-4-ylamino)-7-((naphthalen-1-yloxy)methyl)-8-oxo-6-octene acid methylester

The procedure of Example (1-1) was repeated except for using 1-ethylpiperidin-4-ylamine instead of dimethylaminehydrochloride as the amine to obtain 452 mg of the title compound (yield: 62%).

1H NMR (200 MHz, CDCl₃) δ 1.02 (t, J = 7.4, 3H), 1.26-1.74 (m, 8H), 1.92-2.17 (m, 4H), 2.32 (m, 4H), 2.72 (m, 2H), 3.63 (s, 3H), 4.92 (s, 2H), 6.38 (d, J = 8.0 Hz, IH), 6.80 (t, J = 7.8 Hz, IH), 6.90 (d, J = 7.6 Hz, IH), 7.48 (m, 4H), 7.82 (m, IH), 8.14 (m, IH).
LC/MS (M+H): 453.27.

(48-2):(E)-8-(l-ethylpiperidin-4-ylamino)-7-((naphthalen-1-yloxy)methyl)-8-oxo-6-octene acid

The procedure of Example (1-2) was repeated except for using the compound obtained in Example (48-1) as the starting material, to obtain 279 mg of the title compound (yield: 100%).

(48-3):(E)-Nl-(l-ethylpiperidin-4-yl)-2-((naphthalen-1-yloxy)methyl)-N8-(tetrahydro-2H-pyran-2-yloxy)-2-octenediamide

The procedure of Example (4-3) was repeated except for using the compound obtained in Example (48-2) as the starting material, to obtain 279
mg of the title compound (yield: 80%).

$^1$H NMR (200 MHz, CDCl$_3$) $\delta$ 0.84 (m, 2H), 1.05 (t, J = 7.4 Hz, 3H), 1.27 (m, 2H), 1.44-1.79 (m, 10H), 1.94-2.26 (m, 4H), 2.35 (m, 4H), 2.90 (m, 2H), 3.62 (m, IH), 3.93 (m, IH), 4.94 (s, 2H), 4.97 (m, IH), 6.46 (d, J = 7.8 Hz, IH), 6.84 (t, J = 7.8 Hz, IH), 6.92 (d, J = 7.0 Hz, IH), 7.48 (m, 4H), 7.82 (m, IH), 8.14 (m, IH), 8.43 (br, IH).

LC/MS (M+H): 538.32.

(48-4):(E)-Nl-(1-ethylpiperidin-4-yl)-N8-hydroxy-2-((naphthalen-l-yloxy)methyl)-2-octenediamide

The procedure of Example (4-4) was repeated except for using the compound obtained in Example (48-3) as the starting material, to obtain 146 mg of the title compound (yield: 94%).

HPLC purification: 114 mg (purity: 95%)

$^1$HNMR (400 MHz, MeOH-d$_4$) $\delta$ 1.24 (t, J = 7.2 Hz, 3H), 1.45-1.81 (m, 7H), 1.93-2.10 (m, 5H), 2.32 (q, J = 7.2 Hz, 2H), 2.98 (m, 2H), 3.09 (q, J = 7.2 Hz, 2H), 3.51 (m, IH), 4.97 (s, 2H), 6.46 (t, J = 7.6 Hz, IH), 6.94 (d, J = 7.0 Hz, IH), 7.38 (m, 4H), 7.72 (d, J = 7.6 Hz, IH), 8.05 (d, J = 7.8 Hz, IH).


Example 49: (E)-Nl-(1-ethylpyrrolidin-3-yl)-N8-hydroxy-2-((naphthalen-l-yloxy)methyl)-2-octenediamide

(49-I):(E)-8-(1-ethylpyrrolidin-3-ylamino)-7-((naphthalen-l-yloxy)methyl)-8-oxo-6-octene acid methylester

The procedure of Example (1-1) was repeated except for using 1-ethylpyrrolidin-3-ylamine instead of dimethylaminehydrochloride as the amine to obtain 438 mg of the title compound (yield: 52%).
1H NMR (200 MHz, CDCl$_3$) $\delta$ 0.99 (t, $J = 7.2$ Hz, 3H), 1.26-1.73 (m, 6H), 2.16-2.47 (m, 8H), 2.60 (m, 2H), 2.80 (m, IH), 3.63 (s, 3H), 4.95 (s, 2H), 6.81 (t, $J = 7.6$ Hz, IH), 6.90 (d, $J = 7.4$ Hz, IH), 7.46 (m, 4H), 7.79 (m, IH), 8.16 (m, IH).

LC/MS (M+H): 469.30.

(49-2):(E)-8-(1-ethylpyrrolidin-3-ylamino)-7-((naphthalen-1-yloxy)methyl)-8-oxo-6-octene acid

The procedure of Example (1-2) was repeated except for using the compound obtained in Example (49-1) as the starting material, to obtain 224 mg of the title compound (yield: 100%).

(49-3):(E)-N1-(1-ethylpyrrolidin-3-yl)-2-((naphthalen-1-yloxy)methyl)-N8-(tetrahydro-2H-pyran-2-yloxy)-2-octenediamide

The procedure of Example (4-3) was repeated except for using the compound obtained in Example (49-2) as the starting material, to obtain 224 mg of the title compound (yield: 69%).

1H NMR (200 MHz, CDCl$_3$) $\delta$ 0.82 (m, 2H), 1.06 (t, $J = 7.4$ Hz, 3H), 1.24 (m, 4H), 1.41-2.20 (m, 8H), 2.31 (m, 4H), 2.51 (m, 3H), 2.57 (m, IH), 2.62 (m, IH), 3.61 (br, IH), 3.92 (br, IH), 4.91 (m, IH), 4.94 (s, 2H), 6.79 (t, $J = 7.8$ Hz, IH), 6.94 (d, $J = 7.0$ Hz, IH), 7.44 (m, 4H), 7.82 (m, IH), 8.20 (m, IH).

LC/MS (M+H): 524.30.

(49-4):(E)-N1-(1-ethylpyrrolidin-3-yl)-N8-hydroxy-2-((naphthalen-1-yloxy)methyl)-2-octenediamide

The procedure of Example (4-4) was repeated except for using the compound obtained in Example (49-3) as the starting material, to obtain 184 mg of the title compound (yield: 91%).
HPLC purification: 128 mg (purity: 96%)

\[ \text{\textsuperscript{1}H NMR (300 MHz, MeOH-d}_4\text{\textsuperscript{4})} \delta 1.22 (m, 4H), 1.46-1.62 (m, 6H), 1.79 (m, IH), 2.03 (m, 3H), 2.33 (m, 6H), 4.97 (s, 2H), 6.54 (m, IH), 6.94 (d, J = 6.4 Hz, IH), 7.38 (m, 4H), 7.73 (d, J = 7.8 Hz) 8.04 (d, J = 8.2 Hz) \]

LC/MS (M+H): 440.25.

It should be understood that Examples, while indicating preferred embodiments of the invention, are given by way of illustration only. From the above Examples, one skilled in the art can ascertain the essential characteristics of this invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usage and conditions.

**Test example 1**

HDAC activity was analyzed using BIOMOL Quantizyme™ Assay system which comprised two steps of 1) enzyme reaction between HDAC and a substrate and 2) determination of the level of HDAC inhibitory activity. In step 1) 42 \( \mu \text{L} \) of a buffer solution (25 mM Tris-HCl [pH 8.0], 137 mM NaCl, 2.7 mM KCl, 1 mM MgCl\(_2\)) and 5 \( \mu \text{L} \) of 250 \( \mu \text{M} \) Fluor de Lys™ substrate were added to each well of a 96-well plate, to which 2.5 \( \mu \text{L} \) of a test compound (compounds of Example 1 to 49) was added. 0.5 \( \mu \text{L} \) of HeLa nuclear extract(10 \( \mu \text{M} \) (a source of HDAC enzymes) was then added thereto to a final concentration of 100 nM. The enzyme reaction was carried out for 1 hr. Subsequently, in step 2), 2 \( \mu \text{M} \) tricostatin A was added to 50 \( \mu \text{L} \) of Flour de Lys™ developer, followed by allowing the mixture to react at room temperature for 15 minutes. The light excited at 355 nm and emitted at 460 nm from the fluorophore was measured with a fluorometric plate reader. The intensity of the fluorescence increases as the enzyme activity is higher. The HDAC inhibitory activity of each of the test compounds was determined and compared with that of the control. And suberoylanilide hydroxamic acid (SAHA) (Biomol) was used at the same level with the test compounds as a comparative control.
The HDAC inhibitory concentrations ($IC_{50}$) of the compounds according to the present invention are shown in Table 1.

<table>
<thead>
<tr>
<th>compound</th>
<th>$IC_{50}$ (µM/ml)</th>
<th>compound</th>
<th>$IC_{50}$ (µM/ml)</th>
<th>compound</th>
<th>$IC_{50}$ (µM/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Example 2</td>
<td>0.015</td>
<td>Example 26</td>
<td>0.005</td>
<td>Example 39</td>
<td>0.013</td>
</tr>
<tr>
<td>Example 4</td>
<td>0.014</td>
<td>Example 27</td>
<td>0.020</td>
<td>Example 40</td>
<td>0.007</td>
</tr>
<tr>
<td>Example 6</td>
<td>0.014</td>
<td>Example 28</td>
<td>0.014</td>
<td>Example 41</td>
<td>0.012</td>
</tr>
<tr>
<td>Example 7</td>
<td>0.012</td>
<td>Example 29</td>
<td>0.027</td>
<td>Example 42</td>
<td>0.022</td>
</tr>
<tr>
<td>Example 8</td>
<td>0.025</td>
<td>Example 30</td>
<td>0.016</td>
<td>Example 44</td>
<td>0.012</td>
</tr>
<tr>
<td>Example 10</td>
<td>0.020</td>
<td>Example 31</td>
<td>0.006</td>
<td>Example 45</td>
<td>0.010</td>
</tr>
<tr>
<td>Example 13</td>
<td>0.015</td>
<td>Example 32</td>
<td>0.006</td>
<td>Example 46</td>
<td>0.011</td>
</tr>
<tr>
<td>Example 21</td>
<td>0.023</td>
<td>Example 33</td>
<td>0.024</td>
<td>Example 47</td>
<td>0.016</td>
</tr>
<tr>
<td>Example 22</td>
<td>0.009</td>
<td>Example 35</td>
<td>0.008</td>
<td>Example 48</td>
<td>0.013</td>
</tr>
<tr>
<td>Example 23</td>
<td>0.021</td>
<td>Example 36</td>
<td>0.017</td>
<td>Example 49</td>
<td>0.010</td>
</tr>
<tr>
<td>Example 24</td>
<td>0.009</td>
<td>Example 37</td>
<td>0.007</td>
<td>SAHA</td>
<td>0.100</td>
</tr>
<tr>
<td>Example 25</td>
<td>0.017</td>
<td>Example 38</td>
<td>0.010</td>
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<td></td>
</tr>
</tbody>
</table>

As shown in Table 1, each of the inventive alkylcarbamoyl naphthalenylloxyoctenoyl hydroxyamide derivatives of formula (1) has a
markedly higher inhibitory activity against HDAC than SAHA which is known as a HDAC inhibitor.

**Test Example 2**

Inhibitory activities of the compounds synthesized in Examples against proliferation of cancer cells were examined by SRB (Sulforhodamine B) analysis using cervix adenocarcinoma HeLa (Korean Cell Line Bank, KCLB 10002) and colon cancer cells HCT116 (Korean Cell Line Bank, KCLB 10247) as followed:

Cancer cells were inoculated into a 96-well microplate at a concentration of 1x10^3~3x10^3 cells/well and incubated under the condition of 37°C, 5% CO₂ for 24 hrs. After the incubation was completed, 0.2, 1, 5, 25, or 100 μM of each of the compounds of Examples was added to the plate, and then the reactant was incubated again. After the substrate was stained, the anti-cancer activity was determined by comparing the amount of protein in the cells treated with compound of Examples with that of protein in non-treated cells.

Specifically, after the incubation was completed, the culture medium was removed from each well, and the cells were washed 3 times with PBS (pH7.4). Then, a solution of 50% trichloroacetic acid (TCA) was added to each well in an amount of 50 μL/well at 4°C for 1 hr to fix them. Then, the microplate was washed 5 times with distilled water and dried at room temperature.

50 μL of a staining solution prepared by dissolving 0.4% SRB in 1% acetic acid was added to the wells, and the microplate was kept at room temperature for 1 hr. The well plate was then washed 5 times with 1% acetic acid to remove unbound SRB and dried at room temperature.

The stained cells were treated with 150 μL/well of 10 mM Tris-HCl solution (pH 10.5) to elute SRB from the cells, and the absorbance of each well at 520 nm was measured.

The ED₅₀ value representing inhibition of the cancer cell growth by the extent of 50% was calculated from the measured absorbance, and the
results are shown in Table 2.

When cancer cells were treated with a HDAC inhibitor, histone deacetylation would be inhibited, leading to an increase in the amount of acetyl-histone. In this test, the increased amount of acetyl-histone in the cancer cells was determined by using Western blotting, after the treatment with each of the compounds of Examples.

HeLa cells were inoculated into a 6-well microplate at a concentration of 1.5x10^8 cells/well and incubated overnight under the condition of 37°C, 5% CO₂.

10 µM of each compound of Examples, and suberoylanilide hydroxamic acid (SAHA) as a control was added to the plate and the plate was incubated again for 24 hrs.

The cells were harvested in the presence of the test compound and were subjected to fractionation to separate the nuclei from the cells. The cells were allowed to swell in a hypotonic solution, lysed by several rounds of freezing-thawing cycles, and then centrifuged of 1,300 rpm for 5 min to collect the nuclei. The nuclei was lysed in a lysis buffer solution (20 mM HEPES (pH 7.9), 25% glycerol, 420 mM KCl, 1.5 mM MgCl₂, 0.2 mM EDTA) to obtain a protein extract.

The resulting protein extract was subjected to SDS-PAGE to separate the proteins by the size and transferred onto the nitrocellulose membrane according to the conventional method.

The amount of acetylated histon H4 was measured using anti-acetyl histone H4 antibody (Upstate, USA) and evaluated the HDAC inhibitory activity of the inventive compounds by comparing the degree of increase of acetylated histone H4 relative to the control (SAHA).

The results are shown in Table 2.
<table>
<thead>
<tr>
<th>Example</th>
<th>Inhibitory conc. against the cancer cell growth (EC&lt;sub&gt;50&lt;/sub&gt; µM)</th>
<th>Effect on increase of acetylated histon H4 compared with SAHA</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCT116</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Example 1</td>
<td>1.0</td>
<td>++</td>
</tr>
<tr>
<td>Example 2</td>
<td>0.3</td>
<td>++</td>
</tr>
<tr>
<td>Example 4</td>
<td>0.4</td>
<td>++</td>
</tr>
<tr>
<td>Example 5</td>
<td>0.6</td>
<td>++</td>
</tr>
<tr>
<td>Example 6</td>
<td>0.4</td>
<td>++</td>
</tr>
<tr>
<td>Example 7</td>
<td>0.2</td>
<td>++</td>
</tr>
<tr>
<td>Example 8</td>
<td>0.6</td>
<td>+</td>
</tr>
<tr>
<td>Example 13</td>
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<tr>
<td>Example 24</td>
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<tr>
<td>Example 25</td>
<td>1.3</td>
<td>+</td>
</tr>
<tr>
<td>Example 26</td>
<td>0.8</td>
<td>+</td>
</tr>
<tr>
<td>Example 27</td>
<td>1.2</td>
<td>+</td>
</tr>
<tr>
<td>Example 28</td>
<td>0.7</td>
<td>+</td>
</tr>
<tr>
<td>Example 31</td>
<td>0.6</td>
<td>+</td>
</tr>
<tr>
<td>Example 32</td>
<td>0.5</td>
<td>+</td>
</tr>
<tr>
<td>Example 33</td>
<td>0.6</td>
<td>+</td>
</tr>
<tr>
<td>Example 34</td>
<td>0.8</td>
<td>+</td>
</tr>
<tr>
<td>Example 35</td>
<td>0.4</td>
<td>+</td>
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<tr>
<td>Example 36</td>
<td>0.7</td>
<td>+</td>
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<tr>
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<td>+</td>
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<tr>
<td>Example 41</td>
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</tr>
<tr>
<td>Example 45</td>
<td>0.5</td>
<td>+</td>
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<tr>
<td>Example 46</td>
<td>&lt;0.2</td>
<td>+</td>
</tr>
<tr>
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As shown in Table 2, the inventive alkylcarbamoyl naphthalenyloxyoctenoyl hydroxyamide derivatives of formula (1) has a markedly enhanced inhibitory activity against HDAC, which leads to effective suppression of the cancer cell proliferation.
WHAT IS CLAIMED IS:

1. An alkylcarbamoyl naphthalenylxyoctenoyl hydroxyamide derivative of formula (1):

   \[
   R_1 \quad \text{(1)} \quad R_2
   \]

   wherein:
   
   - \( R_1 \) is hydrogen or \( C_{1-3} \) alkyl;
   
   - \( R_2 \) is \( C_{1-6} \) alkyl optionally having one or more substituents selected from the group consisting of di\( C_{1-3} \) alkylamino, oxopropyridinyl, pyrrolidinyl, morpholinyl, \( C_3 \) alkylpiperazinyl, cyano, hydroxy, imidazolyl, methoxy, tetrahydrofuran, \( C_{3-8} \) cycloalkenyl, and thiophenyl; \( C_1 \) alkyl substituted with hydroxyphenyl, fluorophenyl, di\( C_1 \) alkyl amino phenyl, methoxyphenyl and trifluoromethoxyphenyl; pyrrolidine substituted with \( C_1 \) alkyl, \( C_{3-8} \) cycloalkyl, \( C_{3-8} \) cycloalkyl \( C_{1-3} \) alkyl, benzyl or \( C_{3-8} \) cycloalkylcarbonyl; piperidine substituted with \( C_{3-8} \) cycloalkyl or \( C_{1-6} \) alkyl; furan; pyridine substituted with (di\( C_{1-3} \) alkyl amino) \( C_{1-3} \) alkyl amino, methoxy, di\( C_{1-3} \) alkyl amino, morpholino \( C_{1-3} \) alkylamino, or \( C_{1-3} \) alkylpiperazinyl; or \( C_{3-8} \) cycloalkyl; or
   
   - \( R_1 \) and \( R_2 \) may optionally form a morpholinyl, piperidinyl or piperazinyl ring together with the nitrogen atom to which they are bonded.

2. The compound of claim 1, which is selected from the group consisting of:

   - \((E)-N_1, N_1\)-dimethyl-2-((naphthalen-1-ylxyloxy)methyl)octenediamide,
   - \((E)-N_1-(2-(dimethylamino)ethyl)-N_1\)-hydroxy-2-((naphthalen-1-ylxyloxy)methyl)octenediamide,
   - \((E)-N_1-(2-(dimethylamino)ethyl)-N_8\)-hydroxy-2-((naphthalen-1-ylxyloxy)methyl)octenediamide
((naphthalene-1-yloxy)methyl)octenediamide,
(E)-N1-(2-(diethylamino)ethyl)-N8-hydroxy-2-((naphthalen-1-yloxy)methyl)octenediamide,
(E)-N1-(2-(diethylamino)ethyl)-N8-hydroxy-Nl-methyl-2-
((naphthalene-1-yloxy)methyl)octenediamide,
(E)-N8-hydroxy-2-((naphthalen-1-yloxy)ethyl)octenediamide,
(E)-N8-hydroxy-2-((naphthalen-1-yloxy)methyl)-N1-(2-(pyrrolidin-1-yl)ethyl)octenediamide,
(E)-N8-hydroxy-2-((naphthalen-1-yloxy)methyl)-N1-(2-(piperidin-1-yl)ethyl)octenediamide,
(E)-N8-hydroxy-2-((naphthalen-1-yloxy)methyl)-N1-(2-morpholinoethyl)octenediamide,
(E)-N8-hydroxy-N1-(2-morpholinoethyl)-2-((naphthalen-1-yloxy)methyl)octenediamide,
(E)-N8-hydroxy-8-(4-methylpiperazin-1-yl)-7-((naphthalen-1-yloxy)methyl)-8-oxoocteneamide,
(E)-N8-hydroxy-N1-(2-(4-methylpiperazin-1-yl)ethyl)-2-((naphthalen-1-yloxy)methyl)octenediamide,
(E)-N8-hydroxy-N1-(2-hydroxyethyl)-N1-methyl-2-((naphthalen-1-yloxy)methyl)octenediamide,
(E)-N8-hydroxy-N1-(I-methylpyrrolidin-3-yl)-2-((naphthalen-1-yloxy)methyl)octenediamide,
(E)-N8-hydroxy-N1-(3-(dimethylamino)propyl)-N8-hydroxy-2-((naphthalen-1-yloxy)methyl)octenediamide,
(E)-N8-hydroxy-8-morpholino-7-((naphthalen-1-yloxy)methyl)-8-oxoocteneamide,
(E)-N8-hydroxy-N1-(6-(4-methylpiperazin-1-yl)pyridin-3-yl)-2-((naphthalen-1-yloxy)methyl)octenediamide,
(E)-N1-(6-(2-morpholinoethylamino)pyridin-3-yl)-N8-hydroxy-2-((naphthalen-1-yloxy)methyl)octenediamide,
(E)-N1-(6-(dimethylamino)pyridin-3-yl)-N8-hydroxy-2-((naphthalen-1-yloxy)methyl)octenediamide,
(E)-N1-(6-(2-(dimethylamino)ethylamino)pyridin-3-yl)-N8-hydroxy-2-((naphthalen-1-yloxy)methyl)octenediamide,
(E)-Nδ-hydroxy-Nl-(6-methoxypyridin-3-yl)-2-((naphthalen-1-yloxy)methyl)octenediamide,

(E)-N1-(3-(1H-imidazol-1-yl)propyl)-N8-hydroxy-2-((naphthalen-1-yloxy)methyl)octenediamide,

(E)-N8-hydroxy-N1-(4-hydroxyphenethyl)-2-((naphthalen-1-yloxy)methyl)-2-octenediamide,

(E)-N1-(3-(dimethylamino)-2-dimethylpropyl)-N8-hydroxy-2-((naphthalen-1-yloxy)methyl)octenediamide,

(E)-N1-(2-(diisopropylamino)ethyl)-N8-hydroxy-2-((naphthalen-1-yloxy)methyl)octenediamide,

(E)-Nδ-hydroxy-N1-(1-methoxypropan-2-yl)-2-((naphthalen-1-yloxy)methyl)-2-octenediamide,

(E)-Nδ-hydroxy-N1-(4-methoxybenzyl)-2-((naphthalen-1-yloxy)methyl)-2-octenediamide,

(E)-N1-(4-fluorophenethyl)-N8-hydroxy-2-((naphthalen-1-yloxy)methyl)-2-octenediamide,

(E)-N8-hydroxy-2-((naphthalen-1-yloxy)methyl)-N1-(tetrahydrofuran-2-yl)methyl)-2-octenediamide,

(E)-N1-(2-cyclohexenylethyl)-N8-hydroxy-2-((naphthalen-1-yloxy)methyl)-2-octenediamide,

(E)-N8-hydroxy-2-((naphthalen-1-yloxy)methyl)-N1-(3-(2-oxopyrrolidin-1-yl)propyl)-2-octenediamide,

(E)-N1-(furan-2-yl)-N8-hydroxy-2-((naphthalen-1-yloxy)methyl)-2-octenediamide,

(E)-N1-(4-(dimethylamino)benzyl)-N8-hydroxy-2-((naphthalen-1-yloxy)methyl)-2-octenediamide,

(E)-N8-hydroxy-N1-(2-methoxyethyl)-2-((naphthalen-1-yloxy)methyl)-2-octenediamide,

(E)-N1-cyclohexyl-N8-hydroxy-2-((naphthalen-1-yloxy)methyl)-2-octenediamide,

(E)-Nδ-hydroxy-2-((naphthalen-1-yloxy)methyl)-N1-(thiophen-2-ylmethyl)-2-octenediamide,

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(E)-N1-(1-cyclohexylmethyl)pyrrolidin-3-yl)-N8-hydroxy-2-((naphthalen-1-yloxy)methyl)-2-octenediamide,
(E)-N1-(1-cyclopentylpiperidin-4-yl)-N8-hydroxy-2-((naphthalen-1-yloxy)methyl)-2-octenediamide,
(E)-N1-(1-(cyclohexylmethy)pyrrolidin-3-yl)-N8-hydroxy-2-((naphthalen-1-yloxy)methyl)-2-octenediamide,
(E)-N1-(1-cyclopentylpiperidin-4-yl)-N8-hydroxy-2-((naphthalen-1-yloxy)methyl)-2-octenediamide,
(E)-N1-(1-cyclohexylpyrrolidin-3-yl)-N8-hydroxy-2-((naphthalen-1-yloxy)methyl)-2-octenediamide,
(E)-N1-(1-cyclopropylpiperidin-4-yl)-N8-hydroxy-2-((naphthalen-1-yloxy)methyl)-2-octenediamide,
(E)-N1-(1-cyclopropylpyrrolidin-3-yl)-N8-hydroxy-2-((naphthalen-1-yloxy)methyl)-2-octenediamide,
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(E)-N1-(1-cyclohexylpyrrolidin-3-yl)-N8-hydroxy-2-((naphthalen-1-yloxy)methyl)-2-octenediamide,
(E)-N1-(1-cyclohexylpyrrolidin-3-yl)-N8-hydroxy-2-((naphthalen-1-yloxy)methyl)-2-octenediamide,
in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) to obtain a compound of the formula (4);

3) subjecting the compound of formula (4) to a reaction with tribromophosphine (PBr₃) to obtain a compound of formula (5);

4) bringing the compound of formula (5) to react with 1-naphthol to obtain a compound of formula (6);

5) hydrolyzing the compound of formula (6) in the presence of an inorganic or organic acid to obtain a compound of formula (7);

6) acylating the compound of formula (7) with an amine (R|R₂NH or R₂NH₂) to obtain a compound of formula (8);

7) hydrolyzing the compound of formula (8) in the presence of an inorganic base to obtain a compound of formula (9);

8) acylating the compound of formula (9) with tetrahydropyranoyloxyamine (NH₂OTH) to obtain a compound of formula (10); and

9) removing the tetrahydropyranyl group from the compound of formula (10) by trifluoroacetic acid (TFA) treatment.

![Chemical structure 1](image1.png)

(1)

![Chemical structure 2](image2.png)

(2)

![Chemical structure 3](image3.png)

(3)
Wherein:

R₁ and R₂ have the same meanings as defined in formula (1) above, and

Y is C₁₄ alkyl.

4. The method of claim 3, wherein the alkyl acrylate in step 2) is selected from the group consisting of ethyl acrylate, isobutyl acrylate, and t-butyl acrylate.

5. The method of claim 3, wherein the reaction step 4) is carried out in acetone or acetonitrile in the presence of potassium carbonate, sodium bicarbonate, or sodium carbonate.

6. The method of claim 3, wherein the hydrolysis step 5) is carried out in the dichloromethane, tetrahydrofuran or N,N’-dimethylformamide.

7. The method of claim 3, wherein the inorganic acid used in step 5) is selected from the group consisting of hydrochloric acid, sulfuric acid and phosphoric acid, and the organic acid is trifluoroacetic acid (TFA).

8. The method of claim 3, wherein the acylation step 6) is carried out
using an acylation agent in an aprotic solvent.

9. The method of claim 8, wherein the aprotic solvent is selected from the group consisting of dimethylformamide, dimethylsulfoxide, tetrahydrofuran, and dichloromethane and the acylation agent is selected from the group consisting of N-Methanesulfonyloxy-6-trifluoromethylbenzotriazole (FMS), N-hydroxy-6-trifluorobenzotriazole (FOBT) and 1-(3-diethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC·HCl).

10. The method of claim 3, wherein the hydrolysis step 7) is carried out in aqueous alcohol or tetrahydrofuran.

11. The method of claim 3, wherein the inorganic base is lithium hydroxide (LiOH·H₂O) or sodium hydroxide.

12. The method of claim 3, wherein the acylation step 8) is carried out in the presence of N-hydroxy-6-trifluorobenzotriazole (FOBT) and 1-(3-diethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC·HCl).

13. The method of claim 3, wherein step 9) is carried out in methanol, ethanol, tetrahydrofuran, or dichloromethane.

14. An anti-cancer composition comprising the alkylcarbamoyl naphthalenloxyoctenoyl hydroxyamide derivative of formula (1) of claim 1 as an active ingredient and a pharmaceutically acceptable carrier.

15. An inhibitor for histone deacetylase comprising the alkylcarbamoyl naphthalenloxyoctenoyl hydroxyamide derivative of formula (1) of claim 1 as an active ingredient and a pharmaceutically acceptable carrier.
A. CLASSIFICATION OF SUBJECT MATTER

C07C 237/32(2006.01)i

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)

C07C, C07D, A61K.

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)

eKIPASS, PAJ, STN(CAS online)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<td>WO 2004/063146 A1 (Ital-Farmaco SPA) 29 July 2004 See the whole document (abstract, claims)</td>
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<td>WO 2003/076395 A1 (Janssen Pharmaceutica N V ) 18 September 2003 See the whole document (abstract, claims)</td>
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<td>WO 2004/065354 A1 (Topotarget UK Ltd ) 5 August 2004 See the whole document (abstract, claims)</td>
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* Further documents are listed in the continuation of Box C

See patent family annex

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

& document member of the same patent family

Date of the actual completion of the international search

07 FEBRUARY 2007 (07.02.2007)

Date of mailing of the international search report

07 FEBRUARY 2007 (07.02.2007)

Name and mailing address of the ISA/KR

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Facsimile No 82-42-472-7140

Authorized officer

HONG, SUNG RAN
Telephone No 82-42-481-8146

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