

DESCRIPTION

NOVEL REBAMIPIDE PRODRUGS, PREPARATION METHOD AND USE THEREOF

Technical Field

The present invention relates to a novel rebamipide prodrug, a method for preparing the same, and the use thereof. More particularly, the present invention relates to a novel rebamipide prodrug which retains the same pharmaceutical efficacy as rebamipide, but is improved in bioavailability, and a method for preparing the same, which is a simple method.

Background Art

Rebamipide, systemically named 2-(4-chlorobenzoylamino)-3-[2(1H)-quinolon-4-yl]propionic acid, is an excellent therapeutic for digestive ulcer, including gastric ulcer, acute gastritis, and gastric mucosal lesion induced by the acute exacerbation of chronic gastritis. This drug performs a gastroprotective function by stimulating the biosynthesis of PGE2 in gastric mucosa and by promoting the proliferation of endothelial cells. Particularly, the drug is prescribed to patients with *Helicobacter pylori*-induced gastritis because it prevents the bacteria from adhering to and penetrating gastric mucosal cells.

As for the gastroprotective mechanism of rebamipide, it

is based on the dual action of defensive factor enhancement and inflammation suppression. Rebamipide stimulates the biosynthesis of prostaglandin to enhance defensive factors, and, among defensive factor enhancers, acts as the only antioxidant to protect against *Helicobacter*-induced inflammation. Therefore, rebamipide is very effectively applied to patients with ulcer or gastritis with a great reduction in relapse rate and treatment duration. A previous experiment in rats with acetic acid-induced gastric ulcers demonstrated that rebamipide reduces sizes and relapse rates of the ulcer while improving the cure rate.

There are many methods that are disclosed as for synthesizing rebamipide or producing rebamipide at high purity. For example, Korean Patent No. 10-0669823 discloses a process for preparing 2-(4-chlorobenzoylamino)-3-[2(1*H*)-quinolinon-4-yl]propionic acid and an intermediate thereof, and Korean Patent No. 10-1032600 provides a process for preparing highly pure rebamipide in which purification is performed while carrying out reactions so that rebamipide can be produced at high yield and low production cost with a purity of 99.95 %.

In addition to gastric ulcer, acute gastritis and chronic gastritis, rebamipide is known to have prophylactic and therapeutic effects on xerophthalmia, cancer, osteoarthritis, and rheumatoid arthritis. Moreover, rebamipide has aroused

keen interest as an anti-obesity agent as recent studies have revealed the suppressive effect of rebamipide on obesity. Like this, various pharmaceutical compositions based on rebamipide have been developed.

Rebamipide is freely soluble in dimethylformamide, slightly soluble in methanol and ethanol, but almost insoluble in ether and water. The aqueous solubility of rebamipide is reported to be approximately 0.0001 % (w/v) at pH 3 and approximately 0.013 % (w/v) at pH 7. According to the Biopharmaceutics Classification System (BCS), rebamipide is classified as Class IV due to its low solubility and low intestinal permeability. With extremely poor absorption to the circulation system, rebamipide is reported to have a bioavailability of around 5 %. Due to such poor absorption and bioavailability, pharmaceutical compositions having, as described above, various efficacies contain a relatively great amount of rebamipide, thus causing the patients to suffer from inconvenience upon administration, and lowering the relative efficiency to the dose. A variety of attempts have been made to increase the oral bioavailability, particularly attempts directed toward the use of absorption enhancers and auxiliary agents, or toward preparation into various salt forms. Korean Patent Laid-Open Publication No. 10-2004-0104020 suggests rebamipide lysinate, rebamipide arginate and pharmaceutical

preparations containing the same active substances as a pharmaceutical formulation, but their absorption in the body is still in doubt. Other techniques for effectively increasing the bioavailability of rebamipide have not yet been noticeably detected.

In the present invention, rebamipide, which is very poor in absorption rate despite being therapeutically effective in the treatment of various above-mentioned symptoms, is provided as a rebamipide prodrug which is increased 25-fold in absorption rate compared to rebamipide itself, and a method for preparing the same, and the uses of the rebamipide prodrug are also disclosed.

Disclosure

Technical Problem

It is an object of the present invention to provide a novel rebamipid prodrug which is improved in absorption rate.

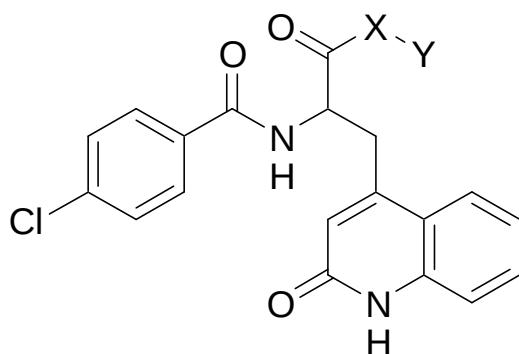
It is another object of the present invention to provide a method for preparing a rebamipide prodrug improved in absorption rate, and the use of the rebamipide prodrug.

Technical Solution

In accordance with an aspect thereof, the present invention provides a compound represented by the following

Chemical Formula 1, or a pharmaceutically acceptable salt, isomer, hydrate or solvate thereof:

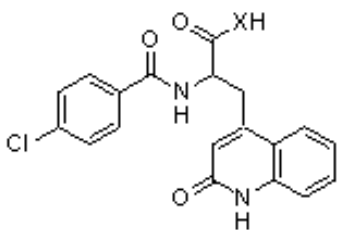
[Chemical Formula I]



wherein, X and Y are as defined below.

In accordance with another aspect thereof, the present invention provides a method for preparing the compound of Chemical Formula 1, comprising reacting a compound of the following Chemical Formula II with a compound of the following Chemical Formula III:

[Chemical Formula II]



[Chemical Formula III]

Y-Z

wherein,

X and Y are as defined below, and Z is a hydroxy group,

an amino group, an amine group, a halogen atom, or a leaving group.

In accordance with a further aspect thereof, the present invention provides a pharmaceutical composition for the prophylaxis or therapy of gastric ulcer, acute gastritis, chronic gastritis, xerophthalmia, cancer, osteoarthritis, rheumatoid arthritis, hyperlipidemia, hypertriglyceridemia, diabetes, irritable bowel syndrome, and obesity, comprising the rebamipide prodrug as an active ingredient, comprising the rebamipide prodrug as an active ingredient.

Advantageous Effects

As described hitherto, novel rebamipide prodrugs according to the present invention are greatly improved in body absorption performance. Also, the present invention provides a method for the preparation of the novel rebamipide prodrugs, and the use of the novel rebamipide prodrugs.

Particularly, when in the form of salts, the novel rebamipide prodrugs of the present invention are remarkably increased in body absorption performance, compared to free acid forms. Thus, even a small amount of salts of the novel rebamipide prodrugs are effective for preventing or treating various diseases including gastric ulcer, acute gastritis, chronic gastritis, xerophthalmia, cancer, osteoarthritis, rheumatoid arthritis, obesity, hyperlipidemia,

hypertriglyceridemia, diabetes, and irritable bowel syndrome.

Description of Drawings

FIG. 1 is a graph in which conversion of the rebamipide prodrug of Example 47 into rebamipide (acting drug) in whole rat blood is monitored with time.

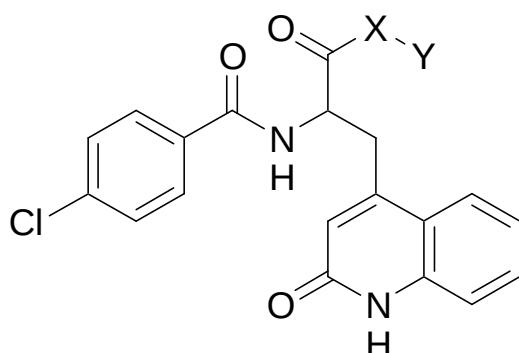
Mode for Invention

A detailed description will be given of the present invention, below.

In accordance with an aspect thereof, the present invention addresses a prodrug of rebamipide, which is known as a therapeutic for gastric ulcer, acute gastritis, chronic gastritis, xerophthalmia, cancer, osteoarthritis, and rheumatoid arthritis.

In one embodiment thereof, the present invention provides a compound represented by the following Chemical Formula 1, or a pharmaceutically acceptable salt, isomer, hydrate, or solvate thereof:

[Chemical Formula I]



wherein,

X is an oxygen atom, a nitrogen atom, or a sulfur atom;

and

Y is a radical selected from the group consisting of C₁-C₆ alkyl, C₁-C₆ haloalkyl, (C₁-C₃ alkyloxy)C₁-C₆ alkyl, (C₂-C₆ alkenyloxy)C₁-C₆ alkyl, (C₁-C₆ alkylcarbonyloxy)C₁-C₆ alkyl, (C₁-C₆ alkylsufanyl)C₁-C₆ alkyl, (arylsufanyl)C₁-C₆ alkyl, (arylsulfonyl)C₁-C₆ alkyl, (C₁-C₆ alkylamino)C₁-C₆ alkyl, [(C₁-C₆ alkyl)(C₁-C₆ alkyl)amino]C₁-C₆ alkyl, [(C₁-C₃ alkyl)(aryl)amino]C₁-C₆ alkyl, {[(C₁-C₃ alkyl)(aryl)C₁-C₃ alkyl]amino}C₁-C₆ alkyl, [(C₁-C₃ alkyl)(heteroaryl)amino]C₁-C₆ alkyl, (arylcarbonylamino)C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₂-C₆ oxoalkyl, C₃-C₈ cycloalkyl, (C₃-C₈ cycloalkyl)C₁-C₆ alkyl, (C₃-C₈ cycloalkenyl)C₁-C₆ alkyl, (C₃-C₈ heterocycloalkyl)C₁-C₆ alkyl, [(C₁-C₃ alkyl)C₃-C₈ heterocycloalkyl]C₁-C₆ alkyl, {[(aryl)C₁-C₃ alkyl]C₃-C₈ heterocycloalkyl}C₁-C₆ alkyl, [(C₁-C₆ alkyloxycarbonyl)C₃-C₈ heterocycloalkyl]C₁-C₆ alkyl, [(C₁-C₃ alkyloxycarbonyl)C₃-C₈ heterocycloalkyl]C₁-C₆ alkyl, (C₃-C₈ heterocycloalkyl)C₁-C₆

alkenyl, [(C₁-C₃ alkyl)C₃-C₈ heterocycloalkenyl]C₁-C₆ alkyl,
 (aryl)C₁-C₆ alkyl, [(C₁-C₃ alkyl)aryl]C₁-C₆ alkyl, [(C₁-C₃
 alkyloxy)aryl]C₁-C₆ alkyl, [(aryloxy)aryl]C₁-C₆ alkyl, [(C₁-C₃
 alkylsufanyl)aryl]C₁-C₆ alkyl, [(C₁-C₃ alkyloxycarbonyl)aryl]C₁-
 C₆ alkyl, [(aryloxycarbonyl)aryl]C₁-C₆ alkyl, (aryl)C₃-C₆
 alkenyl, (heteroaryl)C₁-C₆ alkyl,
 [(alkyloxycarbonyl)heteroaryl]C₁-C₆ alkyl, [(C₁-C₃ alkyl)C₃-C₈
 heteroaryl]C₁-C₆ alkyl, [(C₃-C₈ cycloalkyl)heteroaryl]C₁-C₆
 alkyl, [(aryl)heteroaryl]C₁-C₆ alkyl, [(C₁-C₃
 alkyl)heteroaryl]C₁-C₆ alkyl, {[(aryl)C₁-C₃ alkyl]heteroaryl}C₁-
 C₆ alkyl, (C₁-C₆ alkyloxycarbonyl)C₁-C₆ alkyl, [(C₃-C₈
 heterocycloalkyl)C₁-C₆ alkyloxycarbonyl]C₁-C₆ alkyl, (C₃-C₈
 heterocycloalkylcarbonyl)C₁-C₆ alkyl, [(C₁-C₃ alkyl)C₃-C₈
 heterocycloalkylcarbonyl]C₁-C₆ alkyl, [(C₁-C₃ alkyl)C₃-C₈
 heterocycloalkylcarbonyl]C₁-C₆ alkyl, [(C₃-C₈
 cycloalkyl)oxycarbonyloxy]C₁-C₆ alkyl, [(C₃-C₈
 heterocycloalkyl)oxycarbonyloxy]C₁-C₆ alkyl, (ureido)C₁-C₆
 alkyl, (ary lureido)C₁-C₆ alkyl, [(aryl)(C₁-C₃ alkylureido)C₁-C₆
 alkyl, (C₁-C₆ alkylaminocarbonyl)C₁-C₆ alkyl, [(C₃-C₈
 heterocycloalkyl)aminocarbonyl]C₁-C₆ alkyl, {[(C₁-C₃ alkyl)C₃-C₈
 heterocycloalkyl]aminocarbonyl}C₁-C₆ alkyl, [(C₁-C₃ alkyl)(C₁-C₃
 alkyloxy)aminocarbonyl]C₁-C₆ alkyl and (oxoC₃-C₈
 heterocycloalkyl)C₁-C₆ alkyl,

with a proviso that the C₁-C₆ alkyl radical, the C₂-C₆
 alkenyl radical, the C₂-C₆ alkynyl radical, the C₂-C₆ oxoalkyl

radical, the C₃-C₈ cycloalkyl radical, the C₃-C₈ cycloalkenyl radical, the C₃-C₈ heterocycloalkenyl radical, the aryl radical or the heteroaryl radical may be substituted with at least one substituent selected from the group consisting of C₁-C₃ alkyl, fluoro, chloro, bromo, hydroxy, oxo, nitro, and cyano.

As used herein, the term "heterocycloalkyl" refers to a non-aromatic, cyclic moiety having one or more heteroatoms, such as N, O and S, as constituent elements of the ring(s) at one, two or three sequential or discontinuous positions in the ring(s). As used herein, the term "heterocycloalkenyl" refers to a non-aromatic, cyclic moiety having one or more heteroatoms, such as N, O and S, as constituent elements of the ring(s) at one, two or three sequential or discontinuous positions in the ring(s), and having at least one double bond in the ring(s). Examples of heterocycloalkyl or heterocycloalkenyl radicals include aziridine, oxirane, azetidine, oxetane, pyrrolidine, pyrroline, pyrazolidine, pyrazoline, imidazolidine, imidazoline, triazolidine, oxazolidine, tetrahydrofuran, tetrahydrothiophene, thiazolidine, dioxolane, dioxole, oxathiolane, morpholine, thiomorpholine, dithiane, piperidine, piperazine, pyran, dioxane, and azepane, but are not limited thereto.

The term "aryl," as used in the context of the present

invention, is intended to encompass benzene, naphthalene, anthracene, or phenanthrene, but is not limited thereto.

As used herein, the term "heteroaryl" refers to a moiety having at least one aromatic ring in which at least one heteroatom, such as N, O and S, as an element atom, is present at one, two or three sequential or discontinuous positions. Examples of heteroaryl moieties include pyrrole, imidazole, pyrazole, triazole, furan, thiophene, oxazole, isoxazole, thiazole, isothiazole, oxadiazole, thiadiazole, pyridine, pyrimidine, pyrazine, pyridazine, triazine, azepine, indole, benzimidazole, indazole, benzoxazole, benzoisoxazole, benzothiazole, benzotriazole, benzofuran, benzothiophene, quinoline, isoquinoline, quinoxaline, quinazoline, cinnoline, naphthyridine, phthalazine, benzopyran, benzoxazine, benzotriazine, chromane, chromene, benzodioxane, atridine, phenothiazine, phenoxazine, and carbazole, but are not limited thereto.

In the present invention, X-Y represents an amino acid or an amino acid (C₁-C₃ alkyl)ester. The amino acid includes glycine, leucine, methionine, valine, alanine, isoleucine, proline, tryptophan, phenylalanine, serine, threonine, asparagine, glutamic acid, lysine, histidine, and tyrosine.

Illustrative, non-limiting, concrete examples of the

compound of Chemical Formula 1 include:

- 1) methyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;
- 2) ethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;
- 3) 3-methylbutyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;
- 4) hexyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;
- 5) 2-bromoethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;
- 6) 2-hydroxyethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;
- 7) methoxymethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;
- 8) 2-methoxyethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;
- 9) 2-vinyloxyethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;
- 10) 2-acetoxyethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;
- 11) 2-methylsulfanylethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;
- 12) 2-phenylsulfanylethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;

13) 2-methylaminoethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;

14) 2-dimethylaminoethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;

15) 2-dimethylamino-1-methyl-ethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;

16) 2-diethylaminoethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;

17) 2-diisopropylaminoethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;

18) 3-dimethylaminopropyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;

19) 2-(methyl phenyl amino)ethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;

20) 2-(benzyl ethyl amino)ethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;

21) 2-(benzoxazol-2-ylmethyl amino)ethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;

22) 2-benzoylaminoethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;

23) allyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;

- 24) but-2-enyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;
- 25) 3-methylbut-2-enyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;
- 26) 3-prop-2-ynyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate
- 27) 2-oxopropyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;
- 28) 2-oxobutyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;
- 29) cyclopentyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;
- 30) cyclohexyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;
- 31) cyclopropylmethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;
- 32) cyclobutylmethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;
- 33) cyclohexylmethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;
- 34) cyclopent-3-enylmethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;
- 35) oxiranylmethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;
- 36) 3-methyloxetan-3-ylmethyl 2-(4-chlorobenzoylamino)-3-

- (2-oxo-1,2-dihydroquinolin-4-yl)propionate;
- 37) 2-(1-methylpyrrolidin-2-yl)ethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;
- 38) 2-pyrrolidin-1-yl-ethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;
- 39) tetrahydrofuran-2-ylmethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;
- 40) [1,3]dioxolan-2-ylmethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;
- 41) 2-[1,3]-dioxolan-2-ylethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;
- 42) 1-methylpiperidin-2-ylmethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;
- 43) 1-methylpiperidin-3-ylmethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;
- 44) 2-piperidin-1-ylethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;
- 45) tetrahydropyran 2-ylmethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;
- 46) 2-[1,3]dioxan-2-ylethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;
- 47) 2-morpholin-4-ylethyl 2-(4-chlorobenzoylamino)-3-(2-

oxo-1,2-dihydroquinolin-4-yl)propionate;

48) 3-morpholin-4-ylpropyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;

49) 4-morpholin-4-ylbutyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;

50) 6-morpholin-4-ylhexyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;

51) (4-methylpiperazin-1-yl)methyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;

52) 2-(4-benzylpiperazin-1-yl)ethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;

53) 4-[4-(3-chlorophenyl)piperazin-1-yl]butyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;

54) (4-*tert*-butyloxycarbonylpiperazin-1-yl)ethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;

55) 2-azepan-1-ylethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;

56) 2-(2-oxopyrrolidin-1-yl)ethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;

57) (2-oxooxazolidin-5-yl)methyl 2-(4-

chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;

58) 4-morpholin-4-yl- *cis*-but-2-enyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;

59) 4-morpholin-4-yl- *trans*-but-2-enyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;

60) 5-methyl-2-oxo-[1,3]dioxol-4-ylmethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;

61) benzyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;

62) phenethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;

63) 2-methylbenzyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;

64) 3-methylbenzyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;

65) 3,4-dimethylbenzyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;

66) 3,5-dimethylbenzyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;

67) 3-fluorobenzyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;

- 68) 2,5-difluorobenzyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;
- 69) 3-cyanobenzyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;
- 70) 3-nitrobenzyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;
- 71) 4-methoxybenzyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;
- 72) 3-phenoxybenzyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;
- 73) 4-methylsulfanylbenzyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;
- 74) (4-methyloxycarbonyl)benzyl 4-[2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate];
- 75) (3-phenyloxycarbonyl)benzyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;
- 76) naphthalen-2-ylmethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;
- 77) anthracen-9-ylmethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;
- 78) 2-pyrrol-1-ylethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;
- 79) (2-ethoxycarbonyl)furan-4-ylmethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-

yl)propionate;

80) 2-thiophen-2-ylethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;

81) 2-thiophen-3-ylethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;

82) 2-imidazol-1-ylethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;

83) 5-cyclopropyl-2-methyl-2H-pyrazol-3-ylmethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;

84) 3,5-dimethylisoxazol-4-ylmethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;

85) 2-(5-methyl-4-phenyloxazol-2-yl)ethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;

86) 2-methylthiazol-4-ylmethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;

87) 2-(4-methylthiazol-5-yl)ethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;

88) pyrimidin-2-ylmethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;

89) pyrimidin-3-ylmethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;

- 90) pyrimidin-4-ylmethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;
- 91) 2-(pyrimidin-2-yl)ethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;
- 92) quinolin-2-ylmethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;
- 93) quinolin-3-ylmethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;
- 94) 2-(1-methyl-1H-indol-3-yl)ethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;
- 95) benzothiazol-2-ylmethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;
- 96) 2,3-dihydrobenzo[1,4]dioxin-2-ylmethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;
- 97) carbazol-9-ylmethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;
- 98) methylcarbamoylmethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;
- 99) 2-(4-methylpiperazin-1-yl)-2-oxoethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;
- 100) 1-(4-methylpiperazine-1-carbonyl)propyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-

yl)propionate;

101) 2-morpholin-4-yl-2-oxoethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;

102) (methoxymethylcarbamoyl)methyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;

103) 2-ethoxycarbonylethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;

104) 2-ethoxycarbonylethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;

105) 2-morpholin-4-yl-ethoxycarbonylmethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;

106) 2-morpholin-4-ylethyl 2-[2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionyloxy]butyrate;

107) 2-(1,3-dioxo-1,3-dihydroisoindol-2-yl)ethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;

108) cyclohexyloxycarbonyloxymethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;

109) 2-morpholin-4-yl-ethoxycarbonyloxymethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;

- 110) 2-ureidoethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;
- 111) 2-(3-phenyl-ureido)ethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;
- 112) 2-(3-benzyl-ureido)ethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;
- 113) 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionic acid;
- 114) S-methyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate;
- 115) S-ethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate;
- 116) S-propyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate;
- 117) S-butyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate;
- 118) S-(3-methylbutyl)2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate;
- 119) S-hexyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate;
- 120) S-(2-dimethylamino)ethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate;
- 121) S-(2-diethylamino)ethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate;
- 122) S-(2-diisopropylamino)ethyl 2-(4-

chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate;

123) S-(2-dimethylamino)propyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate;

124) S-(2-benzoylamino)ethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate oxalate;

125) S-methoxymethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate;

126) S-(2-benzoyloxy)ethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate;

127) S-(2-methylsufanyl)ethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate;

128) S-(2-phenylsufanyl)ethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;

129) S-(2-benzenesulfonyl)ethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;

130) S-(2-oxobutyl) 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate;

131) S-(2-ureido)ethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate;

132) N,N-dimethyl S-[2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)]thiocarbamate;

133) S-allyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate;

134) S-but-2-enyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-

dihydroquinolin-4-yl)thiopropionate;

135) *S*-prop-2-ynyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate;

136) *S*-cyclopentyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate;

137) *S*-cyclohexyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate;

138) *S*-cyclopropylmethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate;

139) *S*-cyclobutylmethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate;

140) *S*-cyclohexylmethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate;

141) *S*-(cyclopent-3-enyl)methyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate;

142) *S*-oxiranylmethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate;

143) *S*-(tetrahydrofuran-2-yl)methyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate;

144) *S*-(2-pyrrolidin-1-yl)ethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate;

145) *S*-[2-(1-methylpyrrolidin-2-yl)]ethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate;

- 146) S-([1,3]dioxolan-2-yl)methyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate;
- 147) S-(2-[1,3]dioxolan-2-yl)ethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate;
- 148) S-(2-piperidin-1-yl)ethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate;
- 149) S-(1-methylpiperidin-2-yl)methyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate;
- 150) S-{4-[4-(4-chlorophenyl)piperazin-1-yl]-butyl} 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;
- 151) S-(2-morpholin-4-yl)ethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;
- 152) S-(tetrahydropyran 2-yl)methyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate;
- 153) S-(2-[1,3]-dioxan-2-yl)ethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate;
- 154) S-(2-azepan-1-yl)ethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate;
- 155) S-(5-methyl-2-oxo-[1,3]dioxol-4-yl)methyl 2-(4-

chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate;

156) S-benzyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate;

157) S-phenethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate;

158) S-(2-methylbenzyl) 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate;

159) S-(3-methylbenzyl) 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate;

160) S-(3,4-dimethylbenzyl) 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate;

161) S-(4-fluorobenzyl) 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate;

162) S-(2,5-difluorobenzyl) 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate;

163) S-(3-chlorobenzyl) 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate;

164) S-(3,5-dibromobenzyl) 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate;

165) S-(3-cyanobenzyl) 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate;

166) S-(4-cyanobenzyl) 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate;

167) S-(3-methoxybenzyl) 2-(4-chlorobenzoylamino)-3-(2-

oxo-1,2-dihydroquinolin-4-yl)thiopropionate;

168) S-(4-methoxybenzyl) 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate;

169) S-(3-phenoxybenzyl) 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate;

170) S-(3-methoxycarbonyl)benzyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate;

171) S-(3-phenyloxycarbonyl)benzyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;

172) S-[2-(4-methylthiazol-5yl)ethyl] 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate;

173) S-(pyrimidin-2-yl)methyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate;

174) S-(pyrimidin-3-yl)methyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate;

175) S-(3-phenylallyl) 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate;

176) S-ethoxy-3-oxopropyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate;

177) ethyl [2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionylamino]acetate;

178) [2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-

dihydroquinolin-4-yl)propionylamino]acetic acid;

179) ethyl 4-[2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionylamino]butyrate;

180) ethyl 2-[2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionylamino]-4-methyl pentanoate;

181) ethyl 2-[2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionylamino]-3-phenyl propionate;

182) ethyl 2-[2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionylamino]-3-(1H-indol-3-yl)propionate;

183) diethyl 2-[2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionylamino]pentane-1,5-dioate;

184) diethyl 2-[2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionylamino]pentane-1,5-dioic acid;

185) 4-chloro-N-[1-[2-(3H-imidazol-4-yl)ethylcarbamoyl]-2-(2-oxo-1,2-dihydroquinolin-4-yl)ethyl]benzamide;

186) 4-chloro-N-[2-(2-oxo-1,2-dihydroquinolin-4-yl)-1-(2-pyrrolidin-1-yl-ethylcarbamoyl)ethyl]benzamide; and

187) 4-chloro-N-[1-(2-morpholin-4-yl-ethylcarbamoyl)-2-(2-oxo-1,2-dihydroquinolin-4-yl)ethyl]benzamide.

The rebamipide prodrugs according to the present invention may be in the form of salts, and preferably, pharmaceutically acceptable salts. The salt most useful in the present invention is an acid addition salt formed with a

pharmaceutically acceptable free acid. The free acid may be an inorganic acid or an organic acid. Examples of the organic acids include, but are not limited to, citric acid, acetic acid, lactic acid, tartaric acid, maleic acid, fumaric acid, formic acid, propionic acid, oxalic acid, trifluoroacetic acid, benzoic acid, gluconic acid, methanesulfonic acid, glycolic acid, succinic acid, 4-toluenesulfonic acid, camphorsulfonic acid, glutamic acid, asparatic acid, salicylic acid, malonic acid, malic acid, and benzosulfonic acid. Among the inorganic acids may be hydrochloric acid, bromic acid, sulfuric acid and phosphoric acid, without limitation thereto.

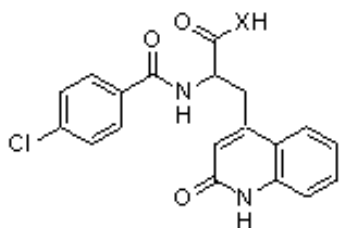
Also, isomers of the compounds of Chemical Formula 1 fall within the scope of the present invention. For example, the compounds of Chemical Formula 1 may have an asymmetric carbon atom (chiral center), and thus may exist as enantiomers taking R or S configuration, racemates, diastereomers, diastereomic racemates, or meso-forms. These and other optical isomers, and mixtures thereof, fall within the scope of the present invention.

In addition, the compound of Chemical Formula 1 may take a form of a solvate or a hydrate, which is also within the scope of the present invention.

In accordance with another aspect thereof, the present invention addresses a method for preparing the compound of

Chemical Formula 1, comprising reacting a compound represented by the following Chemical Formula II with a compound represented by the following Chemical Formula III:

[Chemical Formula II]



[Chemical Formula III]

Y-Z

wherein,

X and Y are as defined above, and Z is a hydroxy group, an amino group, an amine group, a halogen atom, or a leaving group.

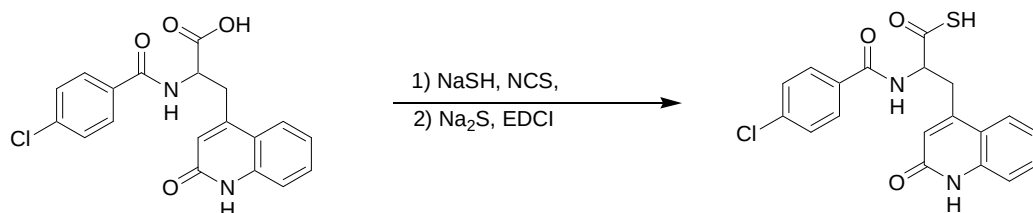
In one embodiment of the present invention, Z is hydroxy, -NH₂, Cl, Br, alkylsulfonyl or arylsulfonyl.

In detail, the compound of the present invention may be prepared as illustrated by the following Reaction Scheme 1, but without limitation thereto.

[Reaction Scheme 1]

In Reaction Scheme 1, when X is sulfur, the compound of Chemical Formula II may be synthesized according to the following Reaction Scheme 2:

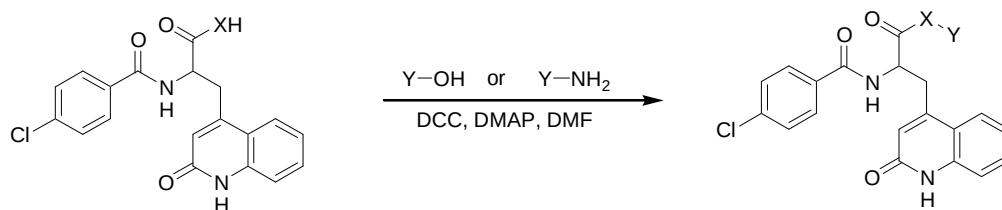
[Reaction Scheme 2]



In Reaction Scheme 2, sodium hydrosulfide is used in an amount of from 1 to 10 equivalents, and preferably in an amount of from 4 to 5 equivalents, while sodium sulfide is used in an amount of from 1 to 5 equivalents and preferably in an amount of 2 to 5 equivalents. This reaction may be carried out at 10 to 100°C for 1 to 24 hrs, with dimethylformamide, dimethylsulfoxide or acetonitrile serving as a solvent. In the reaction scheme, NCS stands for N-chlorosuccinimide.

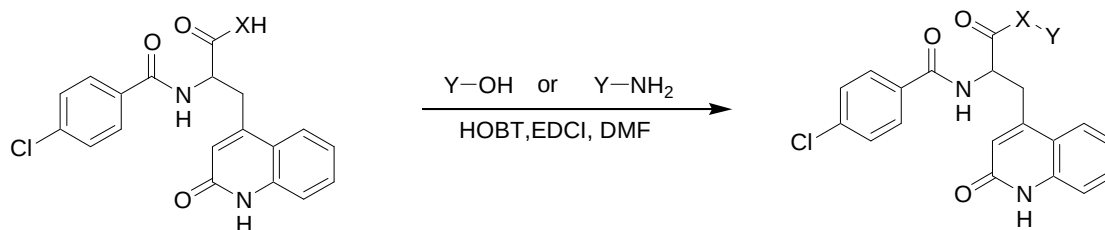
In detail, the compound of the present invention may be prepared according to the general experiment protocols set forth below.

Experiment Protocol A



A compound of Chemical Formula II is dissolved at an elevated temperature in DMF (dimethylformamide, 8~10 volumes of the compound of Chemical Formula II), and quenched to 0°C. To this mixture are added DCC (dicyclohexylcarbodiimide, 1~1.5 equivalents) and DMAP (dimethylaminopyridine, 0.1~0.3 equivalents). When the internal temperature becomes stable, an alcohol or amine (1~1.2 equivalents) is slowly added. The resulting mixture is stirred at room temperature for 4 to 24 hrs. The product thus formed is obtained by filtration, followed by removing DMF in a vacuum. Subsequently, the residue is subjected to column chromatography using methylene chloride: methanol (9:1, v/v) to afford the compound of Chemical Formula I as a solid. If necessary, recrystallization is carried out.

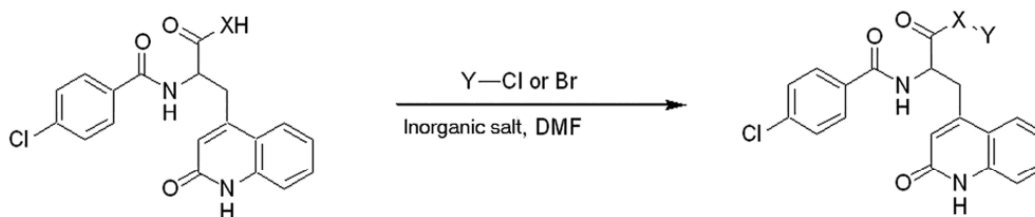
Experiment Protocol B



The compound of Chemical Formula II is dissolved at an

elevated temperature in DMF (dimethylformamide, 8~ 10 volumes of the compound of Chemical Formula II), and quenched to 0°C. To this mixture are added EDCI (1-ethyl-3-(3-dimethylaminopropyl)carbodiimide HCl, 1~3 equivalents) and HOBT (1-hydroxybenzotriazole, 1~3 equivalents). When the internal temperature becomes stable, an alcohol or amine (1~1.5 equivalents) is slowly added. The resulting mixture is stirred at room temperature for 4 to 24 hrs. The product thus formed is obtained by filtration, followed by removing DMF in a vacuum. Subsequently, the residue is subjected to column chromatography using methylene chloride: methanol (9:1, v/v) to afford the compound of Chemical Formula I as a solid. If necessary, recrystallization is carried out.

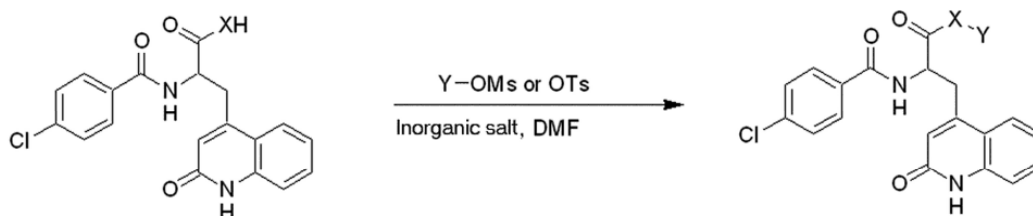
Experiment Protocol C



To a compound of Chemical Formula II are sequentially added DMF (dimethylformamide, 8~10 volumes of the compound of Chemical Formula II), a halogen compound (1~1.5 equivalents), and an inorganic salt (1~2 equivalents), and the resulting mixture is allowed to react at 20~80°C for 1~24 hrs. After completion of the reaction, the product is obtained by

filtration, followed by removing DMF in a vacuum. The residue is subjected to column chromatography using methylene chloride: methanol (9:1, v/v) to afford the compound of Chemical Formula 1 as a solid. If necessary, recrystallization is carried out.

Experiment Protocol D



To a compound of Chemical Formula II are sequentially added DMF (dimethylformamide, 8~10 volumes of the compound of Chemical Formula II), a sulfonate compound (1~1.5 equivalents), and an inorganic salt (1~2 equivalents), and the resulting mixture is allowed to react at 20~80°C for 1~24 hrs. After completion of the reaction, the product is obtained by filtration, followed by removing DMF in a vacuum. The residue is subjected to column chromatography using methylene chloride: methanol (9:1, v/v) to afford the compound of Chemical Formula 1 as a solid. If necessary, recrystallization is carried out.

In greater detail, the compound of Example 113, 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)-

thiopropionic acid, can be prepared according to Experiment Protocol A or B as follows:

Experiment Protocol A

In 400 mL of DMF (dimethylformamide) is dissolved 50 g (134.8 mmol) of rebamipide at an elevated temperature, and the solution is quenched to room temperature. The solution is stirred, together with 28.1 g (1.0 eq, 134.8 mmol) of DCC (dicyclohexylcarbodiimide) for 30 min, and then, together with 16.0 g (1.0 eq, 134.8 mmol) of NaSH (sodium hydrosulfide) at room temperature for 15 hrs. After the reaction is completed, the reaction mixture is added with 800 mL of water, and then extracted three times with 800 mL of ethyl acetate. The organic phase is dried over anhydrous magnesium sulfate, filtered, and concentrated. To the residue is added 800 mL of ethyl acetate, followed by stirring at room temperature. The precipitate thus formed is filtered, and dried to obtain the title compound as a yellowish solid (42.0 g).

Experiment Protocol B

In 80 mL of DMF (dimethylformamide) is dissolved 10 g (26.97 mmol) of rebamipide at an elevated temperature, and the solution is quenched to 0°C. The solution is mixed with 5.69 g (1.1 eq, 29.67 mmol) of EDCI (1-ethyl-3-(3-dimethylaminopropyl)carbodiimide HCl) and 13.6 g (3.0 eq, 80.9

stirred to afford the compound of Chemical Formula III as a solid.

Being superior in body absorption rate to rebamipide in the free acid state, the compound of Chemical Formula I according to the present invention can be usefully applied, instead of rebamipide, to the prophylaxis or therapy of gastric ulcer, acute gastritis, chronic gastritis, xerophthalmia, cancer, osteoarthritis, rheumatoid arthritis, or obesity. Because these diseases are known or are regarded as being treatable or curable with rebamipide, the rebamipide prodrugs of the present invention are more likely to effectively treat the diseases. Thus, according to a further aspect thereof, the present invention envisages a pharmaceutical composition for the prophylaxis or therapy of gastric ulcer, acute gastritis, chronic gastritis, xerophthalmia, cancer, osteoarthritis, rheumatoid arthritis, or obesity, comprising the compound of Chemical Formula I or a pharmaceutically acceptable salt thereof as an active ingredient.

The pharmaceutically effective daily dosage is about 0.5 mg/kg body weight to 100 mg/kg body, and preferably about 1 mg/kg body weight to 30 mg/kg body weight of the rebamipide or its pharmaceutically acceptable salt thereof. However, the

pharmaceutically effective dose may vary depending on various factors including the severity of disease, the patient's age, weight, health condition, and sex, the route of administration, and the time of administration.

In addition, the pharmaceutical composition of the present invention may further comprise a pharmaceutically acceptable additive. The term "pharmaceutically acceptable," as used herein, refers to pertaining to being physiologically compatible and not causing a gastrointestinal disorder, an allergic response such as dizziness, or analogous responses after administration to humans. The additive may be any one of a carrier, an excipient, and a diluent, as typified by lactose, dextrose, sucrose, sorbitol, mannitol, xylitol, erythritol, maltitol, starch, acacia gum, alginate, gelatin, calcium phosphate, calcium silicate, cellulose, methyl cellulose, polyvinylpyrrolidone, water, methylhydroxybenzoate, propylhydroxybenzoate, talc, magnesium stearate, and mineral oil. A filler, an anti-coagulant, a lubricant, a humectants, a flavoring agent, an emulsifier, and a preservative may be used in the pharmaceutical composition of the present invention.

Moreover, the pharmaceutical composition of the present invention may be formulated into a preparation suitable for use in releasing the active ingredient in an immediate,

sustained or delayed manner. The preparation may be in such a form as a powder, a granule, a tablet, an emulsion, a syrup, an aerosol, a soft or hard gelatin capsule, a sterile injection, or a sterile powder.

The pharmaceutical composition according to the present invention can be administered via various routes including oral, transdermal, subcutaneous, intravenous, and intramuscular routes. The dose of the active ingredient may be determined depending on various factors such as the route of administration, the patient's age, sex, and weight, the severity of disease to be treated, etc. The pharmaceutical composition may be administered in combination with a compound known to be prophylactic or therapeutic of the disease of interest.

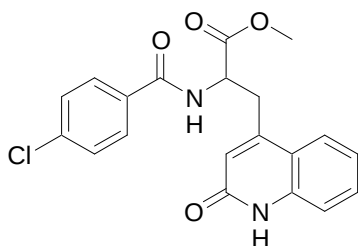
Also, contemplated in accordance with still another aspect of the present invention is a method for preventing or treating a disease, comprising administering the compound of Chemical Formula I to a subject in need thereof, said disease being selected from the group consisting of gastric ulcer, acute gastritis, chronic gastritis, xerophthalmia, cancer, osteoarthritis, rheumatoid arthritis, and obesity.

In accordance with a still further aspect thereof, the present invention addresses the use of the compound of

Chemical Formula I in preventing or treating gastric ulcer, acute gastritis, chronic gastritis, xerophthalmia, cancer, osteoarthritis, rheumatoid arthritis, or obesity.

A better understanding of the present invention may be obtained through the following examples which are set forth to illustrate, but are not to be construed as limiting the present invention.

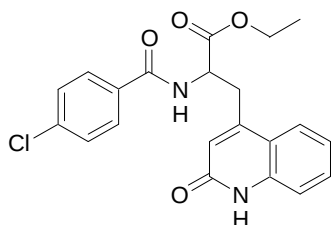
EXAMPLE 1: Preparation of Methyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate



According to Experiment Prototocol C, 1.0 g (2.69 mmol) of rebamipide and 0.36 g (1.5 eq, 0.40 mmol) of methyl iodide were reacted to afford the title compound as a white solid (0.8 g).

^1H NMR (400MHz, DMSO- d_6): δ 11.69(s, 1H), 9.06(d, 1H), 7.83(t, 3H), 7.55(d, 2H), 7.31(d, 1H), 7.24(dd, 1H), 6.44(s, 1H), 4.79(m, 1H), 3.69(s, 3H), 3.47(dd, 1H), 3.27(q, 1H)

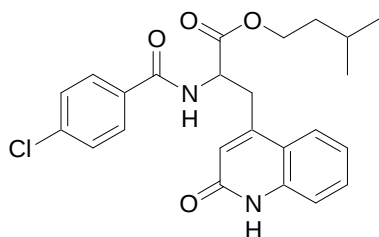
EXAMPLE 2: Preparation of Ethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate



According to Experiment Prototocol C, 1.0 g (2.69 mmol) of rebamipide and 0.62 g (1.5 eq, 4.03 mmol) of iodoethane were reacted to afford the title compound as a white solid (1.0 g).

^1H NMR (400MHz, DMSO-d_6): δ 11.70 (s, 1H), 9.04 (d, 1H), 7.82 (m, 3H), 7.55 (d, 2H), 7.52 (t, 1H), 7.31 (d, 1H), 7.24 (t, 1H), 6.45 (s, 1H), 4.76 (m, 1H), 4.12 (q, 2H), 3.44 (dd, 1H), 3.28 (q, 1H), 1.17 (t, 3H)

EXAMPLE 3: Preparation of 3-Methylbutyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate

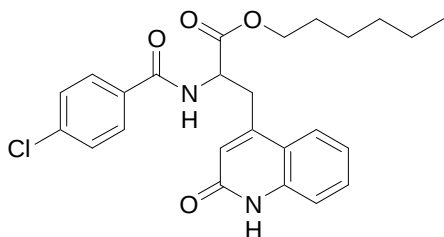


According to Experiment Prototocol C, 1.0 g (2.69 mmol) of rebamipide and 0.60 g (1.5 eq, 4.03 mmol) of 1-bromo-3-methylbutane were reacted to afford the title compound as a

white solid (0.7 g).

^1H NMR (700MHz, DMSO-d_6): δ 11.70 (s, 1H), 9.04 (d, 1H), 7.84-7.80 (m, 3H), 7.58-7.50 (m, 2H), 7.50 (t, 1H), 7.32 (dd, 1H), 7.24-7.21 (m, 1H), 6.44 (s, 1H), 4.77-4.74 (m, 1H), 4.09 (t, 2H), 3.43 (dd, 1H), 3.29 (q, 1H), 1.57-1.53 (m, 1H), 1.43-1.40 (m, 2H), 0.83 (q, 6H)

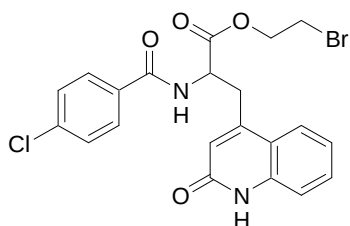
EXAMPLE 4: Preparation of Hexyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate



According to Experiment Prototocol C, 1.0 g(2.69 mmol) of rebamipide and 0.66 g(1.5 eq, 4.03 mmol) of 1-bromohexanewere reacted to afford the title compound as a white solid (1.1 g).

^1H NMR (400MHz, DMSO-d_6): δ 11.70 (s, 1H), 9.07 (d, 1H), 7.82 (q, 3H), 7.56 (d, 2H), 7.52 (t, 1H), 7.31 (d, 1H), 7.23 (t, 1H), 6.44 (s, 1H), 4.75 (m, 1H), 4.06 (t, 2H), 3.43 (dd, 1H), 3.29 (q, 1H), 1.51 (t, 3H), 1.19 (br-s, 6H), 0.81 (t, 3H)

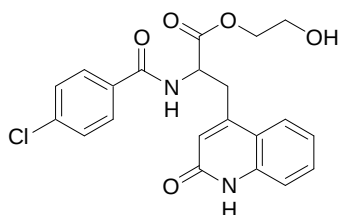
EXAMPLE 5: Preparation of 2-Bromoethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate



According to Experiment Prototocol A, 1.0 g(2.69 mmol) of rebamipide and 0.33 g(1.0 eq, 2.69 mmol) of 2-bromoethanol were reacted to afford the title compound as a white solid (0.4 g).

^1H NMR (400MHz, DMSO-d_6): δ 11.67(s, 1H), 9.11(d, 1H), 8.03(d, 1H), 7.85(m, 3H), 7.74(d, 1H), 7.55(m, 4H), 7.44(m, 1H), 7.31(d, 1H), 7.24(t, 1H), 6.47(s, 1H), 4.83(m, 3H), 4.52(m, 2H), 3.43(dd, 1H), 3.33(m, 1H)

EXAMPLE 6: Preparation of 2-Hydroxyethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate

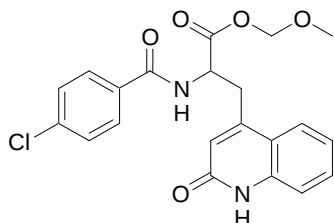


According to Experiment Prototocol C, 1.0 g(2.69 mmol) of rebamipide and 0.50 g(1.5 eq, 4.03 mmol) of 2-bromoethanol were reacted to afford the title compound as a white solid (0.7 g).

^1H NMR (700MHz, DMSO-d_6): δ 11.68(s, 1H), 9.03(d, 1H),

7.85-7.82(m, 3H), 7.57(s, 1H), 7.56(s, 1H), 7.52(t, 1H), 7.31(d, 1H), 7.24(t, 1H), 6.45(s, 1H), 4.88(t, 1H), 4.16-4.11(m, 2H), 3.61-3.58(m, 2H), 3.51(dd, 1H), 3.26(q, 1H)

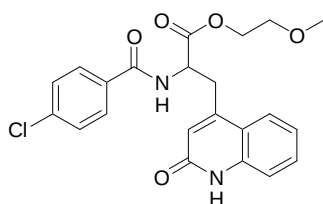
EXAMPLE 7: Preparation of Methoxymethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate



According to Experiment Prototocol C, 1.0 g(2.69 mmol) of rebamipide and 0.32 g(1.5 eq, 4.03 mmol) of chloromethyl methyl ether were reacted to afford the title compound as a white solid (0.6 g).

^1H NMR (400MHz, DMSO- d_6): δ 11.70(s, 1H), 9.11(d, 1H), 7.83(br-s, 3H), 7.59-7.51(m, 3H), 7.32(d, 1H), 7.25(t, 1H), 6.47(s, 1H), 5.29(s, 2H), 4.80(m, 1H), 3.56-3.49(m, 5H)

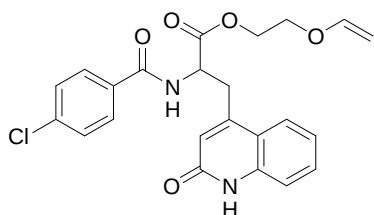
EXAMPLE 8: Preparation of 2-Methoxyethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate



According to Experiment Prototocol C, 1.0 g(2.69 mmol) of rebamipide and 0.38g(1.5 eq, 4.03 mmol) of 2-chloroethyl methyl ether were reacted to afford the title compound as a white solid (1.0 g).

^1H NMR (400MHz, DMSO-d_6): δ 11.70(s, 1H), 9.07(d, 1H), 7.82(t, 3H), 7.56(d, 2H), 7.52(t, 1H), 7.32(d, 1H), 7.24(t, 1H), 6.45(s, 1H), 4.76(m, 1H), 4.21(m, 2H), 3.56-3.49(m, 2H), 3.43(dd, 1H), 3.29(q, 1H), 3.24(s, 3H)

EXAMPLE 9: Preparation of 2-Vinyloxyethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate

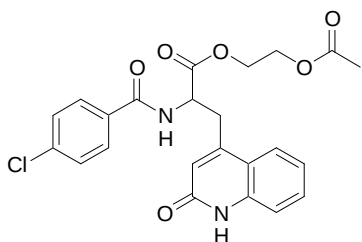


According to Experiment Prototocol C, 1.0 g(2.69 mmol) of rebamipide and 0.43 g(1.5 eq, 4.03 mmol) of 2-chloroethyl vinyl ether were reacted to afford the title compound as a white solid (0.7 g).

^1H NMR (400MHz, DMSO-d_6): δ 11.69(s, 1H), 9.07(d, 1H),

7.84-7.81(m, 3H), 7.57(t, 1H), 7.56(t, 1H), 7.52(m, 1H), 7.31(dd, 1H), 7.21(m, 1H), 6.49(q, 1H), 6.45(s, 1H), 4.78(m, 1H), 4.36-4.27(m, 2H), 4.19(dd, 1H), 3.97(dd, 1H), 3.94-3.84(m, 2H), 3.45(dd, 1H), 3.28(q, 1H)

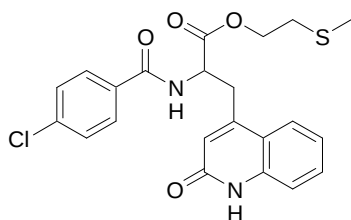
EXAMPLE 10: Preparation of 2-Acetoxyethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate



According to Experiment Prototocol C, 1.0 g(2.69 mmol) of rebamipide and 0.49 g(1.5 eq, 4.03 mmol) of 2-chloroethyl acetate were reacted to afford the title compound as a white solid (0.8 g).

^1H NMR (400MHz, DMSO-d_6): δ 11.70(s, 1H), 9.07(d, 1H), 7.82(t, 3H), 7.56(d, 2H), 7.52(t, 1H), 7.32(d, 1H), 7.24(t, 1H), 6.46(s, 1H), 4.76(m, 1H), 4.36-4.29(m, 2H), 4.22-4.18(m, 2H), 3.45(dd, 1H), 3.28(q, 1H), 1.99(s, 3H)

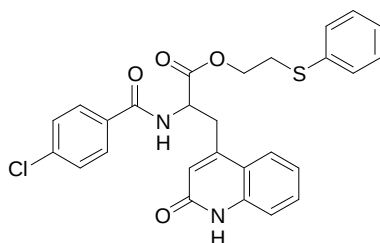
EXAMPLE 11: Preparation of 2-Methylsulfonyl ethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate



According to Experiment Prototocol C, 1.0 g(2.69 mmol) of rebamipide and 0.44 g(1.5 eq, 4.03 mmol) of 2-chloroethyl methyl sulfide were reacted to afford the title compound as a white solid (0.7 g).

^1H NMR (400MHz, DMSO-d_6): δ 11.70(s, 1H), 9.06(d, 1H), 7.84(t, 3H), 7.56(d, 2H), 7.52(t, 1H), 7.31(d, 1H), 7.24(t, 1H), 6.46(s, 1H), 4.78(m, 1H), 4.25(m, 2H), 3.48(dd, 1H), 3.29(q, 1H), 2.72(t, 2H), 2.07(s, 3H)

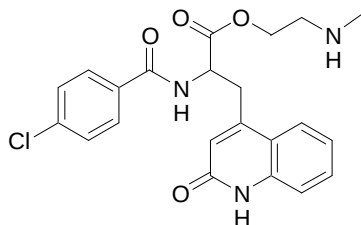
EXAMPLE 12: Preparation of 2-Phenylsulfanylethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate



According to Experiment Prototocol C, 1.0 g(2.69 mmol) of rebamipide and 0.69 g(1.5 eq, 4.03 mmol) of 2-chloroethyl phenyl sulfide were reacted to afford the title compound as a white solid (0.9 g).

¹H NMR (400MHz, DMSO-d₆): δ 11.71 (s, 1H), 9.06 (d, 1H), 7.82 (t, 3H), 7.58 (d, 2H), 7.52 (t, 1H), 7.39-7.30 (m, 5H), 7.25-7.18 (m, 2H), 6.45 (s, 1H), 4.75 (m, 1H), 4.25 (m, 2H), 3.43 (dd, 1H), 3.29-3.22 (m, 3H)

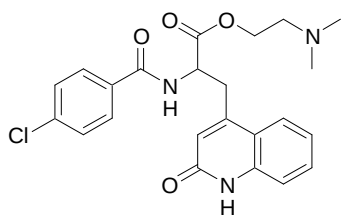
EXAMPLE 13: Preparation of 2-Methylaminoethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate



According to Experiment Prototocol B, 1.0 g (2.69 mmol) of rebamipide and 0.24 g (1.2 eq, 3.23 mmol) of (2-methylamino)ethanol were reacted to afford the title compound as a white solid (0.4 g).

¹H NMR (400MHz, DMSO-d₆): δ 11.61 (s, 1H), 8.84 (d, 1H), 8.17 (q, 1H), 7.91 (d, 1H), 7.86 (d, 2H), 7.55 (d, 2H), 7.48 (t, 1H), 7.30 (d, 1H), 7.23 (m, 1H), 6.46 (s, 1H), 4.79 (m, 1H), 3.44 (dd, 1H), 3.14 (q, 1H), 2.90 (d, 3H)

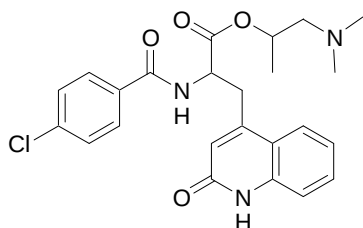
EXAMPLE 14: Preparation of 2-Dimethylaminoethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate



According to Experiment Prototocol C, 1.0 g(2.69 mmol) of rebamipide and 0.57 g(1.5 eq, 4.03 mmol) of (2-dimethylamino)ethylchloride HCl were reacted to afford the title compound as a white solid (0.7 g).

^1H NMR (400MHz, DMSO- d_6): δ 11.61(s, 1H), 9.06(d, 1H), 7.83(m, 3H), 7.56(d, 2H), 7.52(t, 1H), 7.32(d, 1H), 7.23(t, 1H), 6.46(s, 1H), 4.76(m, 1H), 4.15(m, 2H), 3.45(dd, 1H), 3.28(q, 1H), 2.43(m, 2H), 2.13(s, 6H)

EXAMPLE 15: Preparation of 2-Dimethylamino-1-methyl-ethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate

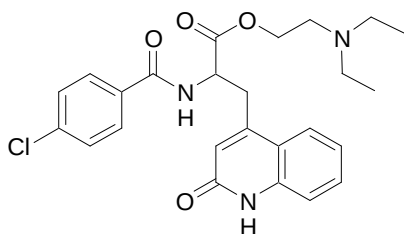


According to Experiment Prototocol B, 1.0 g(2.69 mmol) of rebamipide and 0.33 g(1.2 eq, 3.23 mmol) of 1-dimethylamino-2-propanol were reacted to afford the title compound as a white solid (0.7 g).

^1H NMR (400MHz, DMSO- d_6): δ 11.69(s, 1H), 9.05(d, 1H),

7.83(m, 3H), 7.56(m, 2H), 7.52(t, 1H), 7.32(d, 1H), 7.22(m, 1H), 6.46(t, 1H), 4.77(m, 1H), 4.18(m, 1H), 3.94(m, 1H), 3.46(dd, 1H), 3.30(m, 1H), 2.75(m, 1H), 2.15(dd, 6H), 1.16(m, 1H), 0.89(q, 2H)

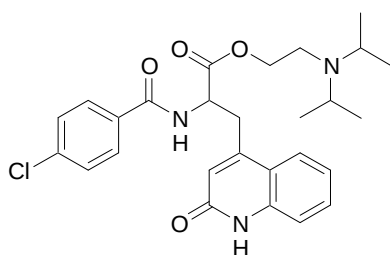
EXAMPLE 16: Preparation of 2-Diethylaminoethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate



According to Experiment Prototocol C, 1.0 g(2.69 mmol) of rebamipide and 0.69 g(1.5 eq, 4.03 mmol) of 2-(diethylamino)ethyl chloride HCl were reacted to afford the title compound as a white solid (0.6 g).

^1H NMR (400MHz, DMSO- d_6): δ 11.68(s, 1H), 9.03(d, 1H), 7.83(t, 3H), 7.56(d, 2H), 7.50(t, 1H), 7.32(d, 1H), 7.23(t, 1H), 6.46(s, 1H), 4.78(m, 1H), 4.11(m, 2H), 3.49(dd, 1H), 3.28(m, 1H), 2.60(m, 2H), 2.48(q, 4H), 0.90(t, 6H)

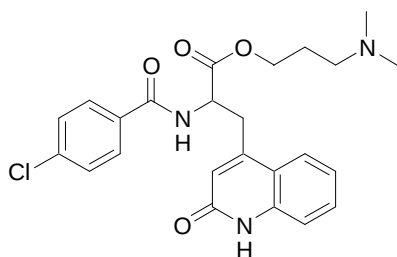
EXAMPLE 17: Preparation of 2-Diisopropylaminoethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate



According to Experiment Prototocol C, 1.0 g(2.69 mmol) of rebamipide and 0.80 g(1.5 eq, 4.03 mmol)of 2-(diisopropylamino)ethyl chloride HCl were reacted to afford the title compound as a white solid (0.6 g).

^1H NMR (400MHz, DMSO-d_6): δ 11.69(s, 1H), 9.02(d, 1H), 7.83(t, 3H), 7.56(d, 2H), 7.51(t, 1H), 7.32(d, 1H), 7.23(t, 1H), 6.45(s, 1H), 4.80(m, 1H), 3.98(m, 2H), 3.46(dd, 1H), 3.27(m, 1H), 2.93(m, 2H), 2.55(t, 2H), 0.93(s, 6H), 0.91(s, 6H)

EXAMPLE 18: Preparation of 3-dimethylaminopropyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate

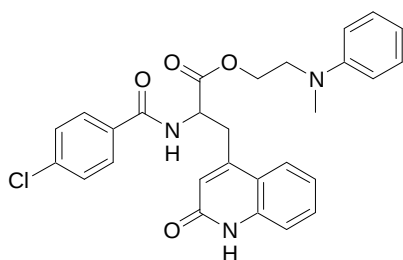


According to Experiment Prototocol B, 1.0 g(2.69 mmol) of rebamipide and 0.33 g(1.2 eq, 3.23 mmol) of 3-dimethylamino-1-propanol were reacted to afford the title compound as a white

solid (0.5 g).

¹H NMR (400MHz, DMSO-d₆): δ 11.69 (s, 1H), 9.03 (d, 1H), 7.83 (m, 3H), 7.54 (m, 3H), 7.32 (d, 1H), 7.23 (m, 1H), 6.45 (s, 1H), 4.76 (m, 1H), 4.09 (m, 1H), 3.46 (dd, 1H), 3.30 (m, 1H), 2.16 (t, 2H), 2.06 (s, 6H), 1.66 (m, 2H)

EXAMPLE 19: Preparation of 2-(Methyl phenyl amino)ethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate

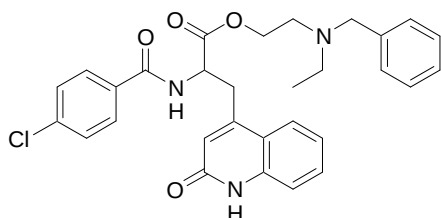


According to Experiment Prototocol B, 1.0 g (2.69 mmol) of rebamipide and 0.49 g (1.2 eq, 3.23 mmol) of 2-(methylphenylamino)ethanol were reacted to afford the title compound as a white solid (0.5 g).

¹H NMR (400MHz, DMSO-d₆): δ 11.70 (s, 1H), 9.03 (d, 1H), 7.80 (d, 2H), 7.73 (d, 1H), 7.55 (d, 2H), 7.51 (t, 1H), 7.30 (d, 1H), 7.21 (t, 1H), 7.13 (t, 2H), 6.70 (d, 2H), 6.59 (t, 1H), 6.43 (s, 1H), 4.76 (m, 1H), 4.25 (m, 2H), 3.66-3.54 (m, 2H), 3.38 (dd, 1H), 3.20 (q, 1H), 2.87 (s, 3H)

EXAMPLE 20: Preparation of 2-(Benzyl ethyl amino)ethyl 2-

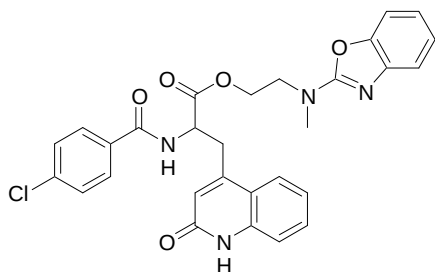
(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate



According to Experiment Prototocol C, 1.0 g(2.69 mmol) of rebamipide and 0.61 g(1.5 eq, 4.03 mmol) of 2-(benzyl ethylamino)ethyl chloride HCl were reacted to afford the title compound as a white solid (0.5 g).

¹H NMR (700MHz, DMSO-d₆): δ 11.71(s, 1H), 9.05(d, 1H), 7.83(d, 2H), 7.79(d, 1H), 7.55(d, 2H), 7.51(t, 1H), 7.33(d, 1H), 7.27-7.24(m, 4H), 7.20(q, 2H), 6.47(s, 1H), 4.83-4.79(m, 1H), 4.22-4.14(m, 2H), 3.56(s, 2H), 3.46(dd, 1H), 3.28(q, 1H), 2.69-2.64(m, 2H), 2.51-2.43(m, 2H), 0.92(t, 3H)

EXAMPLE 21: Preparation of 2-(Benzoxazol-2-ylmethyl amino)ethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate

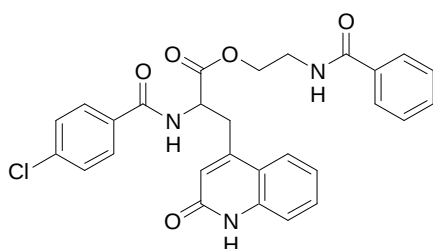


According to Experiment Prototocol C, 1.0 g(2.69 mmol) of

rebamipide and 0.85 g(1.5 eq, 4.03 mmol) of benzoxazol-2-yl-(2-chloroethyl)methyl amine were reacted to afford the title compound as a white solid (0.5 g).

¹H NMR (400MHz, DMSO-d₆):δ 11.64(s, 1H), 8.99(d, 1H), 7.96(s, 1H), 7.75(d, 2H), 7.63(d, 1H), 7.50(d, 2H), 7.46(t, 1H), 7.33(d, 1H), 7.27(d, 1H), 7.22(d, 1H), 7.09(t, 1H), 6.95(t, 1H), 6.38(s, 1H), 4.75(m, 1H), 4.41(m, 2H), 3.83(m, 2H), 3.38(dd, 1H), 3.17(dd, 1H), 3.14(s, 3H)

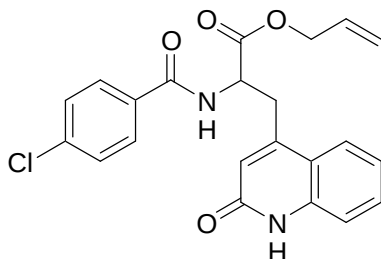
EXAMPLE 22: Preparation of 2-Benzoylaminoethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate



According to Experiment Prototocol C, 1.0 g(2.69 mmol) of rebamipide and 0.74 g(1.5 eq, 4.03 mmol) of 2-chloroethyl benzamide were reacted to afford the title compound as a white solid (0.4 g).

¹H NMR (400MHz, DMSO-d₆):δ 11.68(s, 1H), 8.67(d, 1H), 8.64(t, 1H), 7.84-7.77(m, 5H), 7.54-7.43(m, 6H), 7.29(d, 1H), 7.13(t, 1H), 6.43(s, 1H), 4.80(m, 1H), 4.38(m, 1H), 4.23(m, 1H), 3.61-3.50(m, 3H), 3.21(q, 1H)

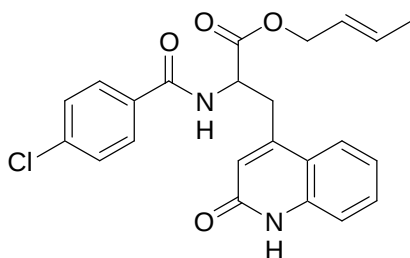
EXAMPLE 23: Preparation of Allyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate



According to Experiment Prototocol C, 1.0 g(2.69 mmol) of rebamipide and 0.48 g(1.5 eq, 4.03 mmol) of allylbromide were reacted to afford the title compound as a white solid (0.7 g).

^1H NMR (400MHz, DMSO-d_6): δ 11.68(s, 1H), 9.06(d, 1H), 7.84-7.81(m, 3H), 7.55(d, 2H), 7.51(t, 1H), 7.31(d, 1H), 7.23(t, 1H), 6.45(s, 1H), 5.94-5.84(m, 1H), 5.32-5.27(m, 1H), 5.22-5.19(dd, 1H), 4.85-4.80(m, 1H), 4.63-4.62(m, 2H), 3.47(dd, 1H), 3.30(q, 1H)

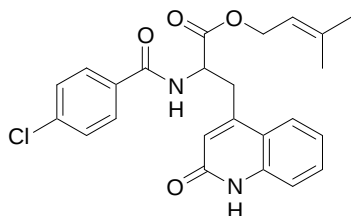
EXAMPLE 24: Preparation of But-2-enyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate



According to Experiment Prototocol C, 1.0 g(2.69 mmol) of rebamipide and 0.36 g(1.5 eq, 4.03 mmol) of 1-chloro-2-butene were reacted to afford the title compound as a white solid (0.6 g).

^1H NMR (400MHz, DMSO-d_6): δ 11.66(s, 1H), 9.02(d, 1H), 7.84-7.80(m, 3H), 7.57(t, 1H), 7.55(t, 1H), 7.53-7.49(m, 1H), 7.31(dd, 1H), 7.25-7.21(m, 1H), 6.43(s, 1H), 5.78-5.71(m, 1H), 5.55-5.48(m, 1H), 4.83-4.66(m, 1H), 4.54(d, 2H), 3.43(dd, 1H), 3.29(q, 1H), 1.65(t, 3H)

EXAMPLE 25: Preparation of 3-Methylbut-2-enyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate

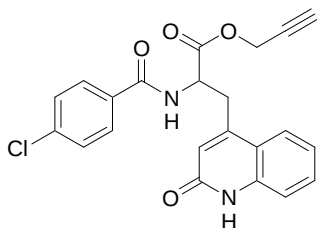


According to Experiment Prototocol C, 1.0 g(2.69 mmol) of rebamipide and 0.42 g(1.5 eq, 4.03 mmol) of 1-chloro-3-methyl-2-butene were reacted to afford the title compound as a white solid (0.7 g).

^1H NMR (700MHz, DMSO-d_6): δ 11.66(s, 1H), 9.00(d, 1H), 7.84-7.82(m, 2H), 7.79(d, 1H), 7.52-7.50(m, 2H), 7.49-7.46(m, 1H), 7.31(dd, 1H), 7.22-7.20(m, 1H), 6.44(s, 1H), 5.26-5.25(m, 1H), 4.80-4.77(m, 1H), 4.60-4.59(m, 2H), 3.42(dd, 1H), 3.27(q,

1H), 1.71(s, 3H), 1.65(s, 3H)

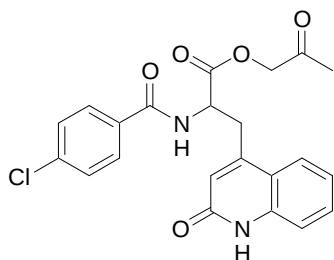
EXAMPLE 26: Preparation of 3-Prop-2-ynyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate



According to Experiment Prototocol D, 1.0 g(2.69 mmol) of rebamipide and 0.84 g(1.5 eq, 4.03 mmol) of propargyl tosylate were reacted to afford the title compound as a white solid (0.7 g).

^1H NMR (700MHz, DMSO-d_6): δ 11.66(s, 1H), 9.07(d, 1H), 7.84-7.80(m, 3H), 7.57(s, 1H), 7.55(s, 1H), 7.51(t, 1H), 7.31(d, 1H), 7.23(t, 1H), 6.45(s, 1H), 4.81-4.76(m, 2H), 3.50-4.3(m, 1H), 3.32-3.26(m, 3H)

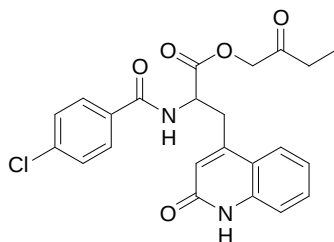
EXAMPLE 27: Preparation of 2-Oxopropyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate



According to Experiment Prototocol C, 1.0 g(2.69 mmol) of rebamipide and 0.37 g(1.5 eq, 4.03 mmol) of chloroacetone were reacted to afford the title compound as a white solid (1.0 g).

^1H NMR (700MHz, DMSO-d_6): δ 11.69(s, 1H), 9.11(d, 1H), 7.84(t, 1H), 7.83(t, 1H), 7.81(d, 1H), 7.57(t, 1H), 7.56(t, 1H), 7.53-7.51(m, 1H), 7.32(dd, 1H), 7.26-7.24(m, 1H), 6.50(s, 1H), 4.95-4.86(m, 3H), 3.58(dd, 1H), 3.31(q, 1H), 2.15(s, 3H)

EXAMPLE 28: Preparation of 2-oxobutyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate

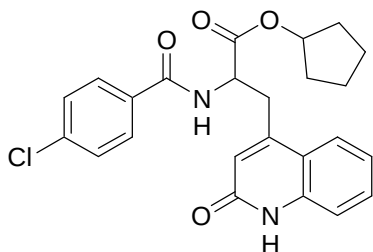


According to Experiment Prototocol C, 1.0 g(2.69 mmol) of rebamipide and 0.43 g(1.5 eq, 4.03 mmol) of 1-chloro-2-butanone were reacted to afford the title compound as a white solid (1.0 g).

^1H NMR (400MHz, DMSO-d_6): δ 11.68(s, 1H), 9.08(d, 1H),

7.82(t, 3H), 7.57(s, 1H), 7.55(s, 1H), 7.52(t, 1H), 7.32(d, 1H), 7.25(t, 1H), 6.50(s, 1H), 4.97-4.85(m, 3H), 3.58(dd, 1H), 3.31(q, 1H), 2.47(q, 2H), 0.96(t, 3H)

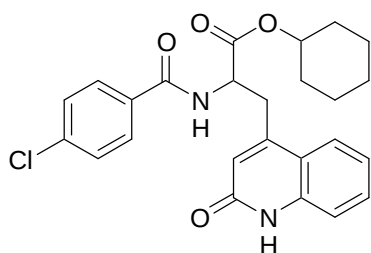
EXAMPLE 29: Preparation of Cyclopentyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate



According to Experiment Prototocol C, 1.0 g(2.69 mmol) of rebamipide and 0.42 g(1.5 eq, 4.03 mmol) of chlorocyclopentane were reacted to afford the title compound as a white solid (0.8g).

¹H NMR (700MHz, DMSO-d₆): δ 11.70(s, 1H), 9.02(d, 1H), 7.83(d, 2H), 7.81(d, 1H), 7.57(d, 2H), 7.52(t, 1H), 7.32(d, 1H), 7.24(t, 1H), 6.44(s, 1H), 5.11-5.10(m, 1H), 4.71-4.68(m, 1H), 3.40(dd, 1H), 3.29(q, 1H), 1.81-1.74(m, 2H), 1.65-1.62(m, 1H), 1.58-1.55(m, 5H)

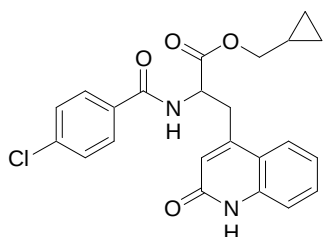
EXAMPLE 30: Preparation of Cyclohexyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate



According to Experiment Prototocol C, 1.0 g(2.69 mmol) of rebamipide and 0.47 g(1.5 eq, 4.03 mmol) of chlorocyclohexane were reacted to afford the title compound as a white solid (0.9 g).

^1H NMR (400MHz, DMSO-d_6): δ 11.68(s, 1H), 9.01(d, 1H), 7.85-7.81(m, 3H), 7.58(t, 1H), 7.55(t, 1H), 7.53-7.49(m, 1H), 7.31(dd, 1H), 7.25-7.21(m, 1H), 6.44(s, 1H), 4.75-4.70(m, 1H), 3.45-3.37(m, 2H), 3.28(q, 1H), 1.75-1.56(m, 4H), 1.44-1.27(m, 6H)

EXAMPLE 31: Preparation of Cyclopropylmethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate

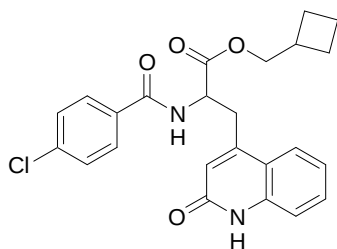


According to Experiment Prototocol C, 1.0 g(2.69 mmol) of rebamipide and 0.36 g(1.5 eq, 4.03 mmol) of (chloromethyl)cyclopropane were reacted to afford the title

compound as a white solid (0.8g).

¹H NMR (400MHz, DMSO-d₆): δ 11.70 (s, 1H), 9.06 (d, 1H), 7.86-7.80 (m, 3H), 7.58 (s, 1H), 7.56 (s, 1H), 7.52 (t, 1H), 7.32 (d, 1H), 7.24 (t, 1H), 6.45 (s, 1H), 4.78 (m, 1H), 3.93 (d, 2H), 3.44 (dd, 1H), 3.28 (q, 1H), 1.10-1.01 (m, 1H), 0.51-0.45 (m, 2H), 0.29-0.23 (m, 2H)

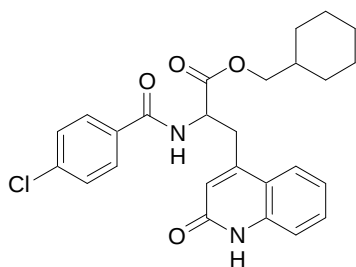
EXAMPLE 32: Preparation of Cyclobutylmethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate



According to Experiment Prototocol A, 1.0 g(2.69 mmol) of rebamipide and 0.28 g(1.2 eq, 3.23 mmol) of cyclobutanemethanol were reacted to afford the title compound as a white solid (0.5 g).

¹H NMR (700MHz, DMSO-d₆): δ 11.70 (s, 1H), 9.06 (d, 1H), 7.84 (t, 1H), 7.82 (t, 1H), 7.81 (d, 1H), 7.57 (t, 1H), 7.56 (t, 1H), 7.53-7.50 (m, 1H), 7.321 (dd, 1H), 7.24-7.22 (m, 1H), 6.45 (s, 1H), 4.77-4.75 (m, 1H), 4.05-4.02 (m, 2H), 3.44 (dd, 1H), 3.30 (q, 1H), 2.55-2.51 (m, 1H), 1.94-1.90 (m, 2H), 1.83-1.79 (m, 1H), 1.75-1.69 (m, 3H)

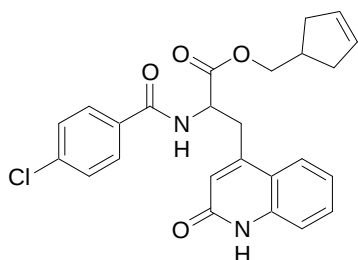
EXAMPLE 33: Preparation of Cyclohexylmethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate



According to Experiment Prototocol C, 1.0 g(2.69 mmol) of rebamipide and 0.37 g(1.2 eq, 3.23 mmol) of cyclohexanemethanol were reacted to afford the title compound as a white solid (0.7 g).

^1H NMR (700MHz, DMSO- d_6): δ 11.70(s, 1H), 9.05(d, 1H), 7.84(t, 1H), 7.83(t, 1H), 7.81(d, 1H), 7.58(t, 1H), 7.56(t, 1H), 7.53-7.50(m, 1H), 7.32(dd, 1H), 7.24-7.22(m, 1H), 6.44(s, 1H), 4.79-4.76(m, 1H), 3.87(d, 2H), 3.42(dd, 1H), 3.31(q, 1H), 1.63-1.55(m, 5H), 1.50-1.49(m, 1H), 1.18-1.12(m, 2H), 1.07-1.03(m, 1H), 0.89-0.85(m, 2H)

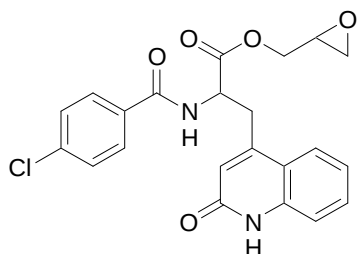
EXAMPLE 34: Preparation of Cyclopent-3-enylmethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate



According to Experiment Prototocol D, 1.0 g(2.69 mmol) of rebamipide and 1.02 g(1.5 eq, 4.03 mmol) of (cyclopent-3-enyl)methyl tosylate were reacted to afford the title compound as a white solid (0.8g).

^1H NMR (700MHz, DMSO-d_6): δ 11.70(s, 1H), 9.05(d, 1H), 7.84(t, 1H), 7.82(t, 1H), 7.80(d, 1H), 7.58(t, 1H), 7.56(t, 1H), 7.53-7.50(m, 1H), 7.32(dd, 1H), 7.25-7.22(m, 1H), 6.44(s, 1H), 5.64(s, 2H), 4.77-4.73(m, 1H), 4.02-3.97(m, 2H), 3.44(dd, 1H), 3.29(q, 1H), 2.53-2.51(m, 1H), 2.39-2.35(m, 2H), 2.05-2.01(m, 2H)

EXAMPLE 35: Preparation of Oxiranylmethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate

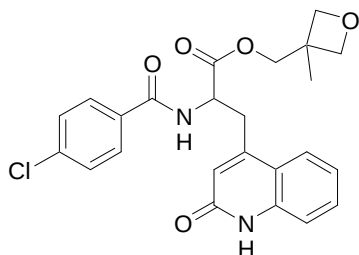


According to Experiment Prototocol C, 1.0 g(2.69 mmol) of rebamipide and 0.37 g(1.5 eq, 4.03 mmol) of 2-

(chloromethyl)oxirane were reacted to afford the title compound as a white solid (0.5 g).

¹H NMR (400MHz, DMSO-d₆): δ 11.70 (s, 1H), 9.09 (d, 1H), 7.81 (m, 3H), 7.57 (s, 1H), 7.56 (d, 1H), 7.52 (t, 1H), 7.31 (d, 1H), 7.22 (t, 1H), 6.44 (s, 1H), 5.09 (m, 1H), 4.80 (m, 1H), 4.60 (t, 1H), 4.47-4.31 (m, 3H), 4.22-4.18 (m, 2H), 3.47 (dd, 1H), 3.28 (q, 1H)

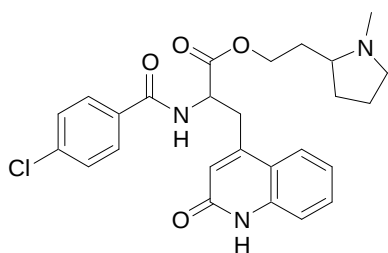
EXAMPLE 36: Preparation of 3-Methyloxetan-3-ylmethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate



According to Experiment Prototocol D, 1.0 g(2.69 mmol) of rebamipide and 0.72 g(1.5 eq, 4.03 mmol) of 3-methyl-3-oxetanemethyl methanesulfonate were reacted to afford the title compound as a white solid (0.5 g).

¹H NMR (400MHz, DMSO-d₆): δ 11.70 (s, 1H), 9.08 (d, 1H), 7.82 (d, 3H), 7.58-7.50 (m, 3H), 7.32 (d, 1H), 7.23 (t, 1H), 6.45 (s, 1H), 4.78 (m, 1H), 4.36 (t, 2H), 4.21 (t, 4H), 3.48 (dd, 1H), 3.36-3.30 (m, 1H)

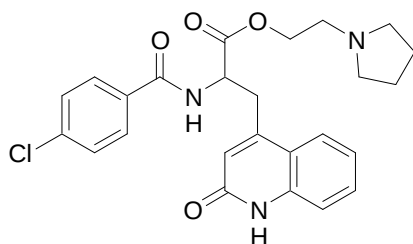
EXAMPLE 37: Preparation of 2-(1-Methylpyrrolidin-2-yl)ethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate



According to Experiment Prototocol D, rebamipide 1.0 g(2.69 mmol) and 0.83 g(1.5 eq, 4.03 mmol) of 1-methyl-2-pyrrolidine ethylmethanesulfonate were reacted to afford the title compound as a white solid (0.7 g).

^1H NMR (400MHz, DMSO-d_6): δ 11.69(s, 1H), 9.04(d, 1H), 7.83(t, 3H), 7.58(s, 1H), 7.56(s, 1H), 7.52(t, 1H), 7.32(d, 1H), 7.24(m, 1H), 6.44(s, 1H), 4.95(m, 1H), 4.70(m, 1H), 3.41(dd, 1H), 3.30(m, 2H), 2.51-2.36(m, 3H), 2.20(s, 3H), 1.99-1.81(m, 2H), 1.70-1.51(m, 4H)

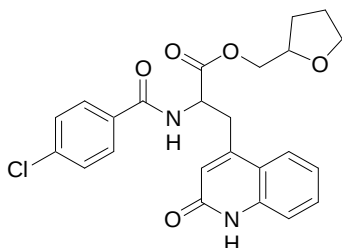
EXAMPLE 38: Preparation of 2-Pyrrolidin-1-yl-ethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate



According to Experiment Prototocol D, 1.0 g(2.69 mmol) of rebamipide and 0.78 g(1.5 eq, 4.03 mmol) of 2-pyrrolidine ethylmethanesulfonate were reacted to afford the title compound as a white solid (0.7 g).

¹H NMR (400MHz, DMSO-d₆):δ 11.69(s, 1H), 9.04(d, 1H), 7.83(t, 3H), 7.57(s, 1H), 7.55(s, 1H), 7.50(t, 1H), 7.32(d, 1H), 7.23(m, 1H), 6.46(s, 1H), 4.78(m, 1H), 4.18(m, 2H), 3.46(dd, 1H), 3.30(m, 2H), 2.60(m, 1H), 2.41(d, 4H), 1.59(m, 4H)

EXAMPLE 39: Preparation of Tetrahydrofuran-2-ylmethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate

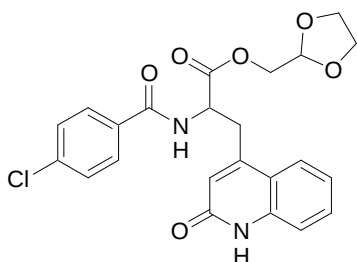


According to Experiment Prototocol C, 1.0 g(2.69 mmol) of rebamipide and 0.48 g(1.5 eq, 4.03 mmol) of 2-(chloromethyl)tetrahydrofuran were reacted to afford the title compound as a white solid (0.8g).

¹H NMR (400MHz, DMSO-d₆):δ 11.70(s, 1H), 9.06(d, 1H), 7.85-7.81(m, 3H), 7.58(s, 1H), 7.56(s, 1H), 7.52(t, 1H), 7.32(d, 1H), 7.23(t, 1H), 6.46(s, 1H), 4.79(m, 1H), 4.12-

3.98(m, 32H), 3.72-3.58(m, 2H), 3.45(dd, 1H), 3.32(q, 1H), 1.93-1.78(m, 1H), 1.77-1.72(m, 2H), 1.61-1.49(m, 1H)

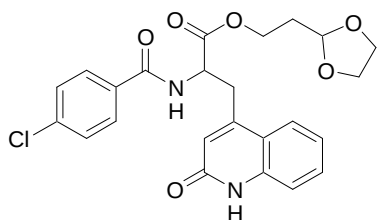
EXAMPLE 40: Preparation of [1,3]Dioxolan-2-ylmethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate



According to Experiment Prototocol C, 1.0 g(2.69 mmol) of rebamipide and 0.49 g(1.5 eq, 4.03 mmol) of 2-chloromethyl-1,3-dioxolane were reacted to afford the title compound as a white solid (0.5 g).

^1H NMR (700MHz, DMSO-d_6): δ 11.68(s, 1H), 9.06(d, 1H), 7.84-7.82(m, 2H), 7.79(d, 1H), 7.53-7.51(m, 2H), 7.50-7.47(m, 1H), 7.32(d, 1H), 7.23-7.21(m, 1H), 6.46(s, 1H), 5.07(t, 1H), 4.83-4.80(m, 1H), 4.17-4.10(m, 2H), 3.90-3.87(m, 2H), 3.84-3.80(m, 2H), 3.44(dd, 1H), 3.29(q, 1H)

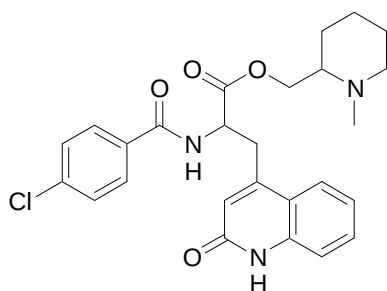
EXAMPLE 41: Preparation of 2-[1,3]-Dioxolan-2-ylethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate



According to Experiment Prototocol C, 1.0 g(2.69 mmol) of rebamipide and 0.73 g(1.5 eq, 4.03 mmol) of 2-(2-bromoethyl)-1,3-dioxolane were reacted to afford the title compound as a white solid (0.6 g).

^1H NMR (400MHz, DMSO-d_6): δ 11.70(s, 1H), 9.04(d, 1H), 7.82(d, 3H), 7.56(d, 2H), 7.52(t, 1H), 7.31(d, 1H), 7.24(t, 1H), 6.45(s, 1H), 4.83(t, 1H), 4.76(m, 1H), 4.19(m, 2H), 3.89-3.86(m, 2H), 3.76-3.72(m, 2H), 3.47(dd, 1H), 3.26(q, 1H), 1.88(q, 2H)

EXAMPLE 42: Preparation of 1-Methylpiperidin-2-ylmethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate

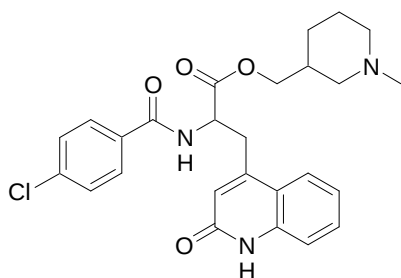


According to Experiment Prototocol D, 1.0 g(2.69 mmol) of rebamipide and 0.83 g(1.5 eq, 4.03 mmol) of 1-methyl-2-piperidinemethyl methanesulfonate were reacted to afford the

title compound as a white solid (0.4 g).

¹H NMR (400MHz, DMSO-d₆): δ 11.68(s, 1H), 9.04(d, 1H), 7.85-7.81(m, 3H), 7.57(s, 1H), 7.55(s, 1H), 7.51(t, 1H), 7.32(d, 1H), 7.22(t, 1H), 6.44(s, 1H), 4.77-4.69(m, 1H), 4.09-4.05(m, 1H), 3.45-3.40(m, 1H), 3.33-3.27(m, 4H), 2.73-2.67(m, 1H), 2.47-2.44(m, 2H), 1.99-1.91(m, 1H), 1.62-1.47(m, 4H), 1.41-1.38(m, 1H), 1.20-1.15(m, 1H)

EXAMPLE 43: Preparation of 1-Methylpiperidin-3-ylmethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate

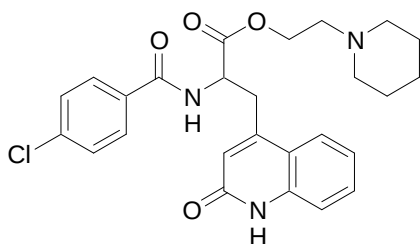


According to Experiment Prototocol C, 1.0 g(2.69 mmol) of rebamipide and 0.74 g(1.5 eq, 4.03 mmol) of 3-chloromethyl-1-methylpiperidine HCl were reacted to afford the title compound as a white solid (0.3 g).

¹H NMR (400MHz, DMSO-d₆): δ 11.71(s, 1H), 9.07(dd, 1H), 7.86-7.81(m, 3H), 7.59(s, 1H), 7.57(s, 1H), 7.52(t, 1H), 7.32(d, 1H), 7.23(m, 1H), 6.44(s, 1H), 4.75(m, 1H), 4.00-3.82(m, 2H), 3.47-3.40(m, 1H), 3.35-3.28(m, 1H), 2.58-2.50(m, 2H), 2.05(s, 3H), 1.77-1.72(m, 2H), 1.63-1.39(m, 4H), 0.92-

0.84(m, 1H)

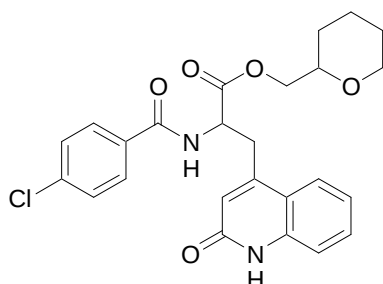
EXAMPLE 44: Preparation of 2-Piperidin-1-ylethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate



According to Experiment Prototocol C, 1.0 g(2.69 mmol) of rebamipide and 0.74 g(1.5 eq, 4.03 mmol) of 1-(2-chloroethyl)piperidine HCl were reacted to afford the title compound as a white solid (0.7 g).

^1H NMR (400MHz, DMSO- d_6): δ 11.69(s, 1H), 9.04(d, 1H), 7.83(m, 3H), 7.58(t, 1H), 7.56(t, 1H), 7.50(m, 1H), 7.32(dd, 1H), 7.23(m, 1H), 6.47(s, 1H), 4.76(m, 1H), 4.24(m, 1H), 4.12(m, 1H), 3.47(dd, 1H), 3.31(m, 2H), 2.48(m, 1H), 2.33(br-s, 4H), 1.40(m, 4H), 1.32(m, 2H)

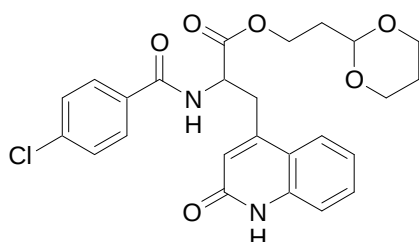
EXAMPLE 45: Preparation of Tetrahydropyran 2 ylmethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate



According to Experiment Prototocol C, 1.0 g(2.69 mmol) of rebamipide and 0.54 g(1.5 eq, 4.03 mmol) of 2-(chloromethyl)tetrahydro-2H-pyran were reacted to afford the title compound as a white solid (0.9 g).

^1H NMR (400MHz, DMSO-d_6): δ 11.70(s, 1H), 9.07(dd, 1H), 7.85-7.82(m, 3H), 7.58(t, 1H), 7.56(t, 1H), 7.52(m, 1H), 7.32(dd, 1H), 7.24(t, 1H), 6.45(s, 1H), 4.76(m, 1H), 4.09-3.98(m, 2H), 3.89-3.86(m, 2H), 3.82(d, 1H), 3.47-3.39(m, 2H), 3.34-3.27(m, 2H), 1.74(br-s, 1H), 1.50-1.36(m, 4H), 1.21-1.17(m, 1H)

EXAMPLE 46: Preparation of 2-[1,3]Dioxan-2-ylethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate

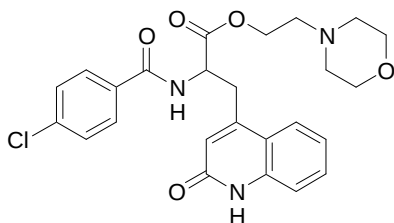


According to Experiment Prototocol C, 1.0 g(2.69 mmol) of rebamipide and 0.78 g(1.5 eq, 4.03 mmol) of 2-(2-bromoethyl)-

1,3-dioxane were reacted to afford the title compound as a white solid (0.8 g).

^1H NMR (400MHz, DMSO-d_6): δ 11.71(s, 1H), 9.05(d, 1H), 7.83(t, 3H), 7.57(d, 2H), 7.52(t, 1H), 7.32(d, 1H), 7.24(t, 1H), 6.45(s, 1H), 4.75(m, 1H), 4.54(t, 1H), 4.12(m, 2H), 3.95(dd, 2H), 3.62-3.56(m, 2H), 3.43(dd, 1H), 3.28(q, 1H), 1.89-1.74(m, 3H), 1.28(d, 1H)

EXAMPLE 47: Preparation of 2-Morpholin-4-ylethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate

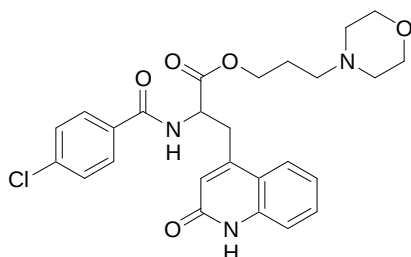


According to Experiment Prototocol C, 1.0 g(2.69 mmol) of rebamipide and 0.75 g(1.5 eq, 4.03 mmol) of 4-(2-chloroethyl)morpholine HCl were reacted to afford the title compound as a white solid (0.8 g).

^1H NMR (DMSO-d_6): δ 9.0(d, 1H), 7.82(t, 3H), 7.53(m, 4H), 7.31(d, 1H), 7.23(t, 1H), 6.44(s, 1H), 4.78-4.72(m, 1H), 4.26-4.14(m, 2H), 3.74(t, 1H), 3.66(t, 1H), 3.46(t, 6H), 3.30-3.24(m, 2H), 3.01-2.95(m, 2H)

EXAMPLE 48: Preparation of 3-Morpholin-4-ylpropyl 2-(4-

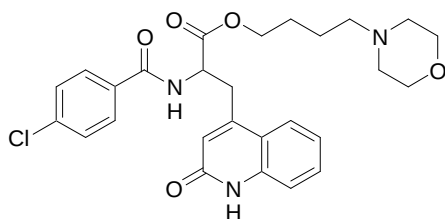
chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate



According to Experiment Prototocol D, 1.0 g(2.69 mmol) of rebamipide and 0.90 g(1.5 eq, 4.03 mmol) of 3-(morpholin-4-yl)propyl HClmethanesulfonate were reacted to afford the title compound as a white solid (0.7 g).

^1H NMR (400MHz, DMSO-d_6): δ 11.68(s, 1H), 9.04(d, 1H), 7.81(d, 3H), 7.57(s, 1H), 7.55(s, 1H), 7.52(t, 1H), 7.31(d, 1H), 7.23(t, 1H), 6.44(s, 1H), 4.77(m, 1H), 4.17(t, 2H), 4.05(t, 2H), 3.53(t, 4H), 3.46(dd, 1H), 3.38-3.26(m, 6H), 1.89(m, 2H)

EXAMPLE 49: Preparation of 4-Morpholin-4-ylbutyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate

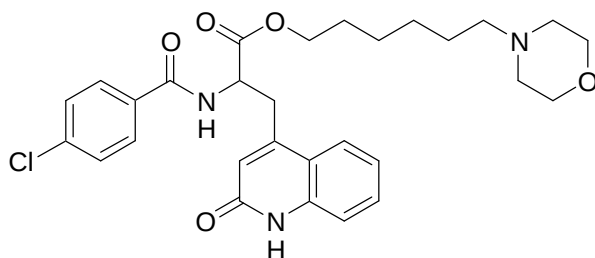


According to Experiment Prototocol C, 1.0 g(2.69 mmol) of

rebamipide and 0.89 g(1.5 eq, 4.03 mmol) of 4-(4-bromobutyl)morpholine were reacted to afford the title compound as a white solid (0.7 g).

^1H NMR (400MHz, DMSO-d_6): δ 11.71(s, 1H), 9.06(d, 1H), 7.83(d, 3H), 7.57(s, 1H), 7.55(s, 1H), 7.52(t, 1H), 7.31(d, 1H), 7.23(t, 1H), 6.44(s, 1H), 4.75(m, 1H), 4.13-4.08(m, 2H), 3.98(t, 2H), 3.52(m, 5H), 3.36-3.26(m, 5H), 1.61-1.54(m, 4H)

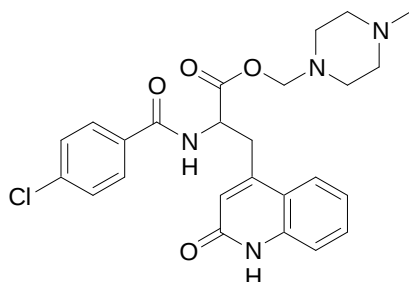
EXAMPLE 50: Preparation of 6-Morpholin-4-ylhexyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate



According to Experiment Prototocol C, 1.0 g(2.69 mmol) of rebamipide and 1.01 g(1.5 eq, 4.03 mmol) of 4-(6-bromohexyl)morpholine were reacted to afford the title compound as a white solid (0.6 g).

^1H NMR (400MHz, DMSO-d_6): δ 11.71(s, 1H), 9.05(d, 1H), 7.82(m, 3H), 7.58(s, 1H), 7.56(s, 1H), 7.52(t, 1H), 7.31(d, 1H), 7.23(t, 1H), 6.44(s, 1H), 4.75(m, 1H), 4.06(m, 2H), 3.54(t, 4H), 3.43(dd, 1H), 3.35-3.27(m, 2H), 2.27(br-s, 4H), 2.16(t, 2H), 1.52(m, 2H), 1.31(m, 2H), 1.21(s, 4H)

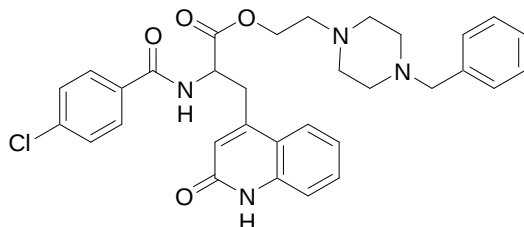
EXAMPLE 51: Preparation of (4-Methylpiperazin-1-yl)methyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate



According to Experiment Prototocol C, 1.0 g(2.69 mmol) of rebamipide and 0.60 g(1.5 eq, 4.03 mmol) of 1-chloromethyl-4-methylpiperazine were reacted to afford the title compound as a white solid (0.4 g).

^1H NMR (700MHz, DMSO-d_6): δ 11.70(s, 1H), 9.03(d, 1H), 7.85-7.82(m, 3H), 7.58-7.56(m, 2H), 7.52(t, 1H), 7.33(d, 1H), 7.24(t, 1H), 6.44(s, 1H), 4.75-4.72(m, 1H), 3.42(dd, 1H), 3.30(q, 1H), 1.76-1.57(m, 4H), 1.45-1.31(m, 6H)

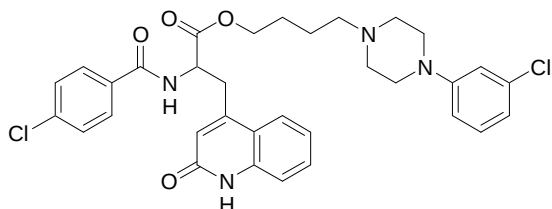
EXAMPLE 52: Preparation of 2-(4-Benzylpiperazin-1-yl)ethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate



According to Experiment Prototocol C, 1.0 g(2.69 mmol) of rebamipide and 0.96 g(1.5 eq, 4.03 mmol) of 1-benzyl-4-(2-chloroethyl)piperazine were reacted to afford the title compound as a white solid (0.6 g).

¹H NMR (700MHz, DMSO-d₆):δ 11.70(s, 1H), 9.06(d, 1H), 7.83-7.81(m, 3H), 7.55-7.53(m, 2H), 7.51(t, 1H), 7.33-7.30(m, 3H), 7.26-7.24(m, 3H), 7.21(t, 1H), 6.46(s, 1H), 4.77-4.74(m, 1H), 4.25-4.22(m, 1H), 4.17-4.13(m, 1H), 3.47(dd, 1H), 3.38(s, 2H), 3.28(q, 1H), 2.57-2.48(m, 4H), 2.41-2.26(m, 6H)

EXAMPLE 53: Preparation of 4-[4-(3-chlorophenyl)piperazin-1-yl]butyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate

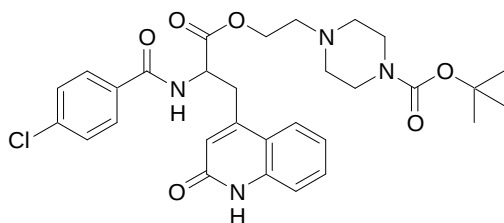


According to Experiment Prototocol D, 1.0 g(2.69 mmol) of rebamipide and 1.70 g(1.5 eq, 4.03 mmol) of 4-[4-(3-chlorophenyl)piperazin-1-yl]butyl toluenesulfonate were reacted to afford the title compound as a white solid (0.6 g).

¹H NMR (400MHz, DMSO-d₆):δ 11.71(s, 1H), 9.06(d, 1H), 7.84(m, 3H), 7.56(d, 2H), 7.52(t, 1H), 7.32(d, 1H), 7.22(m, 2H), 6.91(br-s, 1H), 6.86(dd, 1H), 6.77(dd, 1H), 6.46(s, 1H), 4.77(m, 1H), 4.11(m, 2H), 3.45(dd, 1H), 3.56-3.28(m, 3H),

3.12(t, 4H), 2.40(t, 4H), 2.28(t, 2H), 1.72(m, 2H)

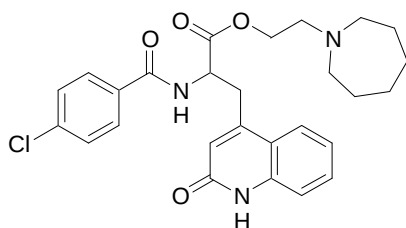
EXAMPLE 54: Preparation of (4- *tert*-Butyloxycarbonylpiperazin-1-yl)ethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate



According to Experiment Prototocol C, 1.0 g(2.69 mmol) of rebamipide and 1.18 g(1.5 eq, 4.03 mmol) of tert-butyl 4-(2-bromoethyl)piperazine-1-carboxylate were reacted to afford the title compound as a white solid (0.6 g).

¹H NMR (700MHz, DMSO-d₆): δ 11.70(s, 1H), 9.05(d, 1H), 7.85-7.81(m, 3H), 7.58-7.56(m, 2H), 7.52(t, 1H), 7.32(d, 1H), 7.22(t, 1H), 6.46(s, 1H), 4.77-4.74(m, 1H), 4.25-4.16(m, 2H), 3.47(dd, 1H), 3.29(q, 1H), 3.19(t, 4H), 2.74-2.50(m, 2H), 2.32(m, 4H), 1.38(s, 9H)

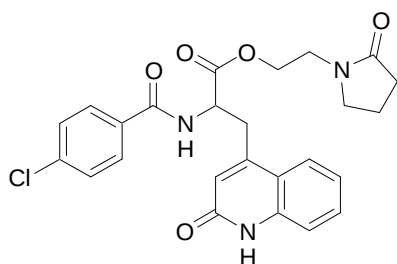
EXAMPLE 55: Preparation of 2-Azepan-1-ylethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate



According to Experiment Prototocol C, 1.0 g(2.69 mmol) of rebamipide and 0.80 g(1.5 eq, 4.03 mmol) of 2-(hexamethyleneimino)ethyl chloride HCl was reacted to afford the title compound as a white solid (0.8 g).

^1H NMR (400MHz, DMSO- d_6): δ 11.69(s, 1H), 9.03(d, 1H), 7.84(t, 3H), 7.58(s, 1H), 7.55(s, 1H), 7.52(t, 1H), 7.32(d, 1H), 7.23(m, 1H), 6.47(s, 1H), 4.77(m, 1H), 4.19(m, 1H), 4.11(m, 1H), 3.47(dd, 1H), 3.32(m, 1H), 2.57(m, 4H), 1.47(s, 8H)

EXAMPLE 56: Preparation of 2-(2-Oxopyrrolidin-1-yl)ethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate

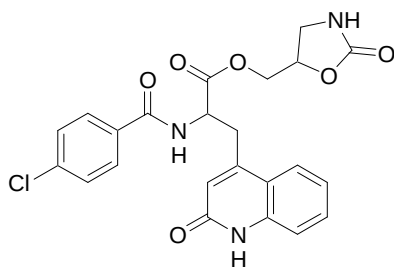


According to Experiment Prototocol C, 1.0 g(2.69 mmol) of rebamipide and 0.77 g(1.5 eq, 4.03 mmol) of 1-(2-bromoethyl)pyrrolidin-2-one were reacted to afford the title

compound as a white solid (0.3 g).

¹H NMR (400MHz, DMSO-d₆): δ 11.70 (s, 1H), 9.04 (d, 1H), 7.82 (t, 3H), 7.56 (d, 2H), 7.52 (t, 1H), 7.31 (d, 1H), 7.24 (m, 1H), 6.45 (s, 1H), 4.75 (m, 1H), 4.30-4.17 (m, 2H), 3.50-3.45 (m, 3H), 3.32 (t, 2H), 3.24 (q, 1H), 2.17-2.09 (m, 2H), 1.86-1.78 (m, 2H)

EXAMPLE 57: Preparation of (2-oxooxazolidin-5-yl)methyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate

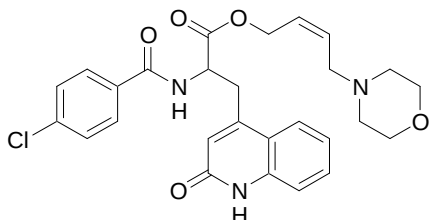


According to Experiment Prototocol C, 1.0 g(2.69 mmol) of rebamipide and 0.54 g(1.5 eq, 4.03 mmol) of 5-chloromethyl-2-oxazolidinone were reacted to afford the title compound as a white solid (0.4 g).

¹H NMR (400MHz, DMSO-d₆): δ 11.66 (s, 1H), 9.07 (d, 1H), 7.82 (d, 3H), 7.59-7.49 (m, 4H), 7.31 (d, 1H), 7.27-7.23 (m, 1H), 6.46 (s, 1H), 4.84-4.79 (m, 2H), 4.31 (d, 1H), 4.27 (q, 1H), 3.62-3.53 (m, 1H), 3.52(-3.47 (m, 1H), 3.30-3.25 (m, 2H)

EXAMPLE 58: Preparation of 4-Morpholin-4-yl- *cis*-but-2-

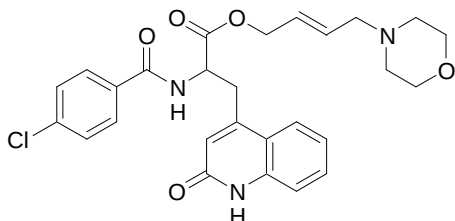
enyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate



According to Experiment Prototocol C, 1.0 g(2.69 mmol) of rebamipide and 0.88 g(1.5 eq, 4.03 mmol) of 4-(4-bromo- *cis*-but-2-enyl)morpholine were reacted to afford the title compound as a white solid (0.6 g).

¹H NMR (400MHz, DMSO-d₆):δ 11.70(s, 1H), 9.08(d, 1H), 7.82(t, 3H), 7.56(d, 2H), 7.52(t, 1H), 7.31(d, 1H), 7.23(t, 1H), 6.44(s, 1H), 5.76-5.62(m, 2H), 4.78(m, 1H), 4.60(m, 2H), 3.52(t, 4H), 3.44(dd, 1H), 3.30(m, 2H), 2.89(d, 2H), 2.28(s, 4H)

EXAMPLE 59: Preparation of 4-Morpholin-4-yl- *trans*-but-2-enyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate

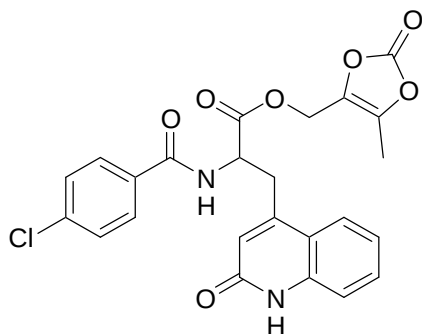


According to Experiment Prototocol C, 1.0 g(2.69 mmol) of rebamipide and 0.88 g(1.5 eq, 4.03 mmol) of 4-(4-bromo- *trans*-

but-2-enyl)morpholine were reacted to afford the title compound as a white solid (0.7 g).

¹H NMR (400MHz, DMSO-d₆): δ 11.70 (s, 1H), 9.07 (d, 1H), 7.82 (t, 3H), 7.56 (d, 2H), 7.50 (t, 1H), 7.31 (d, 1H), 7.23 (t, 1H), 6.44 (s, 1H), 5.75-5.63 (m, 2H), 4.60 (m, 2H), 3.52 (t, 3H), 3.44 (dd, 1H), 3.39-3.27 (m, 2H), 2.89 (d, 2H), 2.28 (s, 3H)

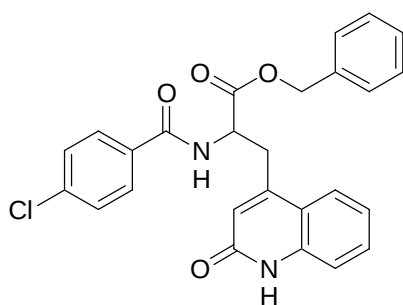
EXAMPLE 60: Preparation of 5-Methyl-2-oxo-[1,3]dioxol-4-ylmethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate



According to Experiment Prototocol C, 1.0 g(2.69 mmol) of rebamipide and 0.60 g(1.5 eq, 4.03 mmol) of 4-chloromethyl-5-methyl-1,3-dioxol-2-one were reacted to afford the title compound as a white solid (0.5 g).

¹H NMR (400MHz, DMSO-d₆): δ 11.68 (s, 1H), 9.10 (d, 1H), 7.82 (m, 3H), 7.56 (m, 2H), 7.51 (t, 1H), 7.33 (d, 1H), 7.20 (t, 1H), 6.51 (s, 1H), 5.05 (s, 2H), 4.80 (m, 1H), 3.47 (dd, 1H), 3.32 (m, 1H), 2.16 (s, 3H)

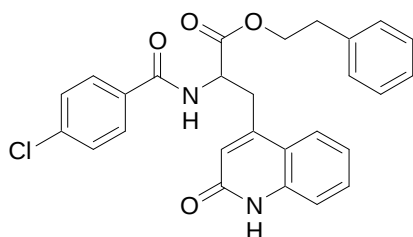
EXAMPLE 61: Preparation of Benzyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate



According to Experiment Prototocol C, 1.0 g(2.69 mmol) of rebamipide and 0.69 g(1.5 eq, 4.03 mmol) of benzyl bromide were reacted to afford the title compound as a white solid (1.0 g).

^1H NMR (700MHz, DMSO-d_6): δ 11.70(s, 1H), 9.10(d, 1H), 7.84-7.82(m, 3H), 7.58-7.56(m, 2H), 7.51(t, 1H), 7.37-7.32(m, 6H), 7.21(t, 1H), 6.47(s, 1H), 5.16(q, 2H), 4.87-4.84(m, 1H), 3.50(dd, 1H), 3.33(q, 1H)

EXAMPLE 62: Preparation of Phenethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate

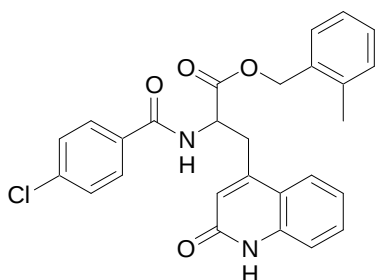


According to Experiment Prototocol C, 1.0 g(2.69 mmol) of

rebamipide and 0.74 g(1.5 eq, 4.03 mmol) of (1-bromoethyl)benzene were reacted to afford the title compound as a white solid (0.9 g).

^1H NMR (400MHz, DMSO-d_6): δ 11.69(s, 1H), 9.01(d, 1H), 7.83(t, 1H), 7.81(t, 1H), 7.72(d, 1H), 7.58(t, 1H), 7.56(t, 1H), 7.52(m, 1H), 7.31(dd, 1H), 7.25-7.19(m, 6H), 6.43(s, 1H), 4.72(m, 1H), 4.39-4.02(m, 2H), 3.44(dd, 1H), 3.20(q, 1H), 2.89(t, 2H)

EXAMPLE 63: Preparation of 2-Methylbenzyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate

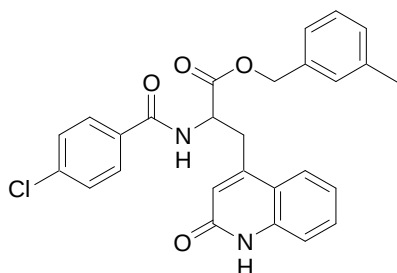


According to Experiment Prototocol C, 1.0 g(2.69 mmol) of rebamipide and 0.56 g(1.5 eq, 4.03 mmol) of 2-methylbenzyl chloride were reacted to afford the title compound as a white solid (0.9 g).

^1H NMR (700MHz, DMSO-d_6): δ 11.69(s, 1H), 9.09(d, 1H), 7.81(d, 2H), 7.80(s, 1H), 7.57-7.55(m, 2H), 7.51(t, 1H), 7.31(d, 1H), 7.27(d, 1H), 7.25-7.19(m, 3H), 7.16(t, 1H), 6.45(s, 1H), 5.21-5.12(q, 2H), 4.84-4.82(m, 1H), 3.48(dd, 1H),

3.32(q, 1H), 2.24(s, 3H)

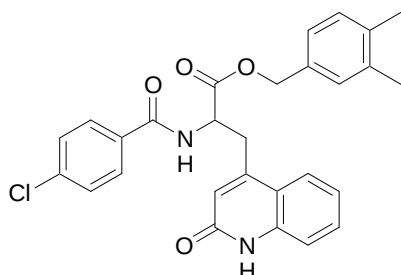
EXAMPLE 64: Preparation of 3-Methylbenzyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate



According to Experiment Prototocol C, 1.0 g(2.69 mmol) of rebamipide and 0.56 g(1.5 eq, 4.03 mmol) of 3-methylbenzyl chloride were reacted to afford the title compound as a white solid (0.9 g).

^1H NMR (700MHz, DMSO-d_6): δ 11.69(s, 1H), 9.10(d, 1H), 7.84-7.81(m, 3H), 7.58-7.56(m, 2H), 7.51(t, 1H), 7.32(d, 1H), 7.24-7.20(q, 2H), 7.13-7.09(m, 3H), 6.45(s, 1H), 5.15-5.07(q, 2H), 4.85-4.81(m, 1H), 3.48(dd, 1H), 3.32(q, 1H), 2.25(s, 3H)

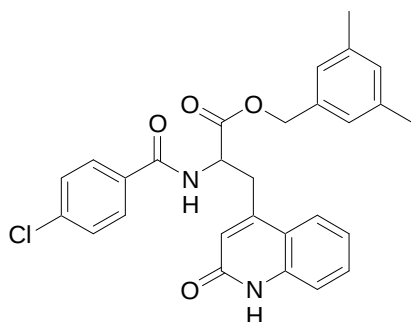
EXAMPLE 65: Preparation of 3,4-Dimethylbenzyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate



According to Experiment Prototocol C, 1.0 g(2.69 mmol) of rebamipide and 0.62 g(1.5 eq, 4.03 mmol) of 3,4-dimethylbenzyl chloride were reacted to afford the title compound as a white solid (0.9 g).

^1H NMR (700MHz, DMSO-d_6): δ 11.70(s, 1H), 9.09(d, 1H), 7.84-7.79(m, 3H), 7.58-7.56(m, 2H), 7.52-7.51(m, 1H), 7.32(d, 1H), 7.23-7.20(m, 1H), 7.14(t, 1H), 7.09(d, 1H), 7.06-7.03(m, 2H), 6.44(d, 1H), 5.11-5.03(q, 2H), 4.82(br-s, 1H), 3.48(dd, 1H), 3.32(q, 1H), 2.19(s, 3H), 2.16(s, 3H)

EXAMPLE 66: Preparation of 3,5-Dimethylbenzyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate

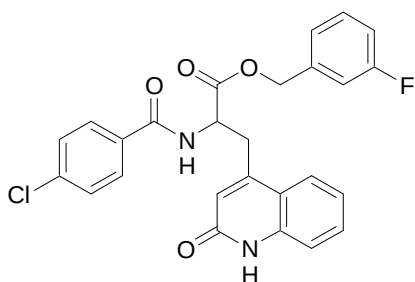


According to Experiment Prototocol C, 1.0 g(2.69 mmol) of rebamipide and 0.62 g(1.5 eq, 4.03 mmol) of 3,5-dimethylbenzyl

chloride were reacted to afford the title compound as a white solid (0.9 g).

¹H NMR (700MHz, DMSO-d₆): δ 11.70 (s, 1H), 9.11 (d, 1H), 7.84 (d, 2H), 7.81 (d, 1H), 7.57 (d, 2H), 7.52 (t, 1H), 7.32 (d, 1H), 7.22 (t, 1H), 6.93 (s, 1H), 6.89 (d, 1H), 6.46 (s, 1H), 5.11-5.01 (q, 2H), 4.83-4.82 (m, 1H), 3.48 (dd, 1H), 3.33 (q, 1H), 2.21 (s, 6H)

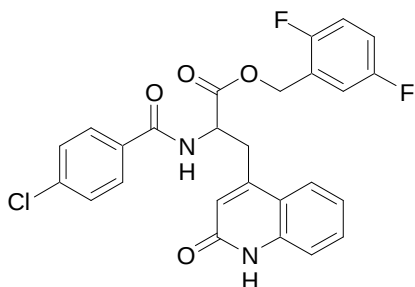
EXAMPLE 67: Preparation of 3-Fluorobenzyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate



According to Experiment Prototocol C, 1.0 g(2.69 mmol) of rebamipide and 0.58 g(1.5 eq, 4.03 mmol) of 3-fluorobenzyl chloride were reacted to afford the title compound as a white solid (0.9 g).

¹H NMR (700MHz, DMSO-d₆): δ 11.69 (s, 1H), 9.11 (d, 1H), 7.83-7.81 (m, 3H), 7.57-7.55 (m, 2H), 7.51 (t, 1H), 7.39 (q, 1H), 7.31 (d, 1H), 7.21 (t, 1H), 7.18-7.14 (m, 3H), 6.45 (s, 1H), 5.23-5.15 (q, 2H), 4.88-4.84 (m, 1H), 3.51 (dd, 1H), 3.33 (q, 1H)

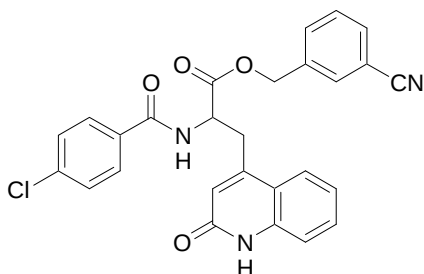
EXAMPLE 68: Preparation of 2,5-Difluorobenzyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate



According to Experiment Prototocol C, 1.0 g(2.69 mmol) of rebamipide and 0.83 g(1.5 eq, 4.03 mmol) of 2,5-difluorobenzyl bromide were reacted to afford the title compound as a white solid (0.8 g).

^1H NMR (400MHz, DMSO-d_6): δ 11.65(s, 1H), 9.08(d, 1H), 7.79(d, 3H), 7.57(s, 1H), 7.55(s, 1H), 7.50(t, 1H), 7.32-7.18(m, 5H), 6.44(s, 1H), 5.20(q, 2H), 4.86-4.83(m, 1H), 3.48(dd, 1H), 3.29(q, 1H)

EXAMPLE 69: Preparation of 3-Cyanobenzyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate

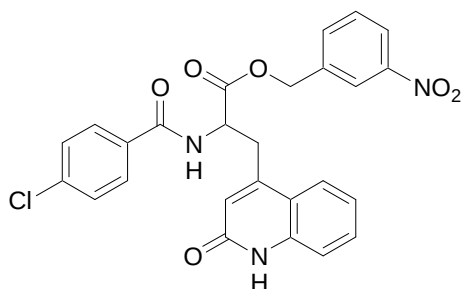


According to Experiment Prototocol C, 1.0 g(2.69 mmol) of

rebamipide and 0.79 g(1.5 eq, 4.03 mmol) of 2-methylbenzyl chloride3-(bromomethyl)benzonitrile were reacted to afford the title compound as a white solid (0.7 g).

¹H NMR (400MHz, DMSO-d₆):δ 11.68(s, 1H), 9.11(d, 1H), 7.84-7.80(m, 5H), 7.67(d, 1H), 7.60-7.55(m, 3H), 7.53-7.49(m, 1H), 7.31(dd, 1H), 7.24-7.20(m, 1H), 6.45(s, 1H), 5.18(q, 2H), 4.87(m, 1H), 3.52(dd, 1H), 3.33(q, 1H)

EXAMPLE 70: Preparation of 3-Nitrobenzyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate

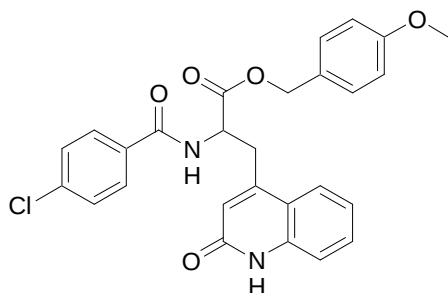


According to Experiment Prototocol C, 1.0 g(2.69 mmol) of rebamipide and 3-nitrobenzyl 클로라bromide 0.87 g(1.5 eq, 4.03 mmol)were reacted to afford the title compound as a white solid (0.9 g).

¹H NMR (700MHz, DMSO-d₆):δ 11.67(s, 1H), 9.13(d, 1H), 8.23(d, 1H), 8.18((dd, 1H), 7.83-7.80(m, 3H), 7.79(d, 1H), 7.66(t, 1H), 7.57-7.55(m, 2H), 7.51-7.49(m, 1H), 7.30(dd, 1H), 7.21(t, 1H), 6.43(s, 1H), 5.35-5.28(q, 2H), 4.88-4.85(m, 1H),

3.51(dd, 1H), 3.33(q, 1H)

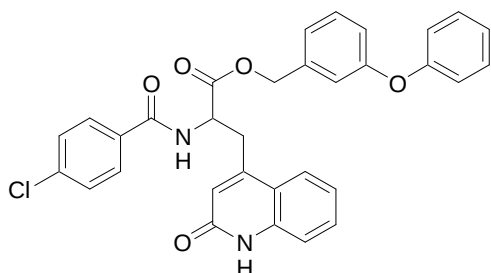
EXAMPLE 71: Preparation of 4-Methoxybenzyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate



According to Experiment Prototocol C, rebamipide 1.0 g(2.69 mmol) and 4-methoxybenzyl chloride 0.63 g(1.5 eq, 4.03 mmol)were reacted to afford the title compound as a white solid (0.9 g).

^1H NMR (700MHz, DMSO-d_6): δ 11.68(s, 1H), 9.06(d, 1H), 7.82-7.79(m, 3H), 7.57-7.55(m, 2H), 7.50(t, 1H), 7.31(d, 1H), 7.26(d, 2H), 7.21(t, 1H), 6.91-6.89(m, 2H), 6.44(s, 1H), 5.12-5.06(q, 2H), 4.81-4.79(m, 1H), 3.75(s, 3H), 3.46(dd, 1H), 3.28(q, 1H)

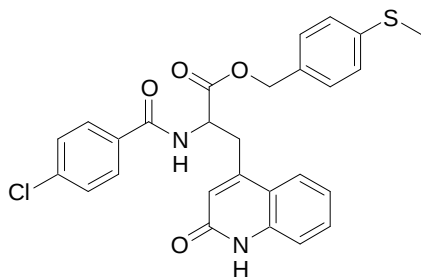
EXAMPLE 72: Preparation of 3-phenoxybenzyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate



According to Experiment Prototocol C, 1.0 g(2.69 mmol) of rebamipide and 0.88 g(1.5 eq, 4.03 mmol) of 3-phenoxybenzyl chloride were reacted to afford the title compound as a white solid (1.1 g).

^1H NMR (400MHz, DMSO-d_6): δ 11.67(s, 1H), 9.07(d, 1H), 7.81-7.78(m, 3H), 7.52(d, 2H), 7.50(t, 1H), 7.38-7.30(m, 4H), 7.19(t, 1H), 7.121(t, 2H), 7.03(s, 1H), 6.95(d, 2H), 6.93(dd, 1H), 6.44(s, 1H), 5.22-5.13(q, 2H), 4.83(m, 1H), 3.46(dd, 1H), 3.29(q, 1H)

EXAMPLE 73: Preparation of 4-Methylsulfanylbenzyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate

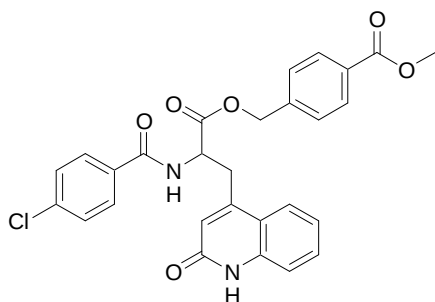


According to Experiment Prototocol C, 1.0 g(2.69 mmol) of rebamipide and 4-(methylthio)benzyl chloride 0.69 g(1.5 eq, 4.03 mmol)were reacted to afford the title compound as a white

solid (0.7 g).

^1H NMR (400MHz, DMSO-d_6): δ 11.68 (s, 1H), 9.06 (d, 1H), 7.82-7.80 (m, 3H), 7.55 (d, 2H), 7.51 (t, 1H), 7.31 (d, 1H), 7.28-7.19 (m, 5H), 6.45 (s, 1H), 5.11 (q, 2H), 4.86-4.80 (m, 1H), 3.47 (dd, 1H), 3.30 (q, 1H), 2.47 (s, 3H)

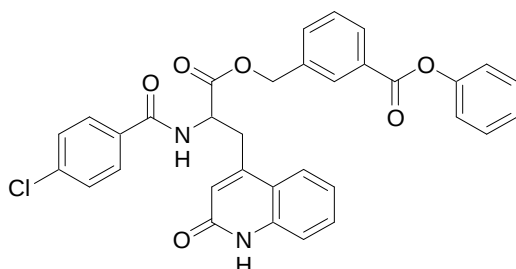
EXAMPLE 74: Preparation of (4-methyloxycarbonyl)benzyl 4-[2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate



According to Experiment Prototocol C, rebamipide 1.0 g(2.69 mmol) and methyl(4-bromomethyl)benzoate 0.92 g(1.5 eq, 4.03 mmol)were reacted to afford the title compound as a white solid (0.9 g).

^1H NMR (400MHz, DMSO-d_6): δ 11.66 (s, 1H), 9.09 (d, 1H), 7.96 (d, 1H), 7.93-7.90 (m, 1H), 7.83-7.79 (m, 3H), 7.60 (d, 1H), 7.57-7.48 (m, 4H), 7.32 (dd, 1H), 7.23-7.19 (m, 1H), 6.44 (s, 1H), 5.30-5.21 (q, 2H), 4.88-4.82 (m, 1H), 3.84 (s, 3H), 3.50 (dd, 1H), 3.31 (q, 1H)

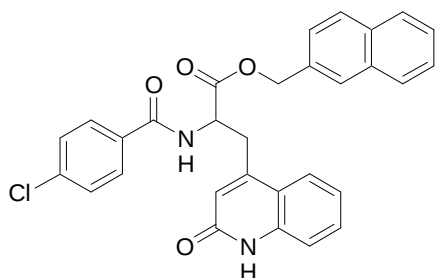
EXAMPLE 75: Preparation of (3-phenyloxycarbonyl)benzyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate



According to Experiment Prototocol D, 1.0 g(2.69 mmol) of rebamipide and 1.11 g(1.5 eq, 4.03 mmol) of (3-phenyloxycarbonyl)benzyl mesylate were reacted to afford the title compound as a white solid (0.9 g).

^1H NMR (400MHz, DMSO-d_6): δ 11.66(s, 1H), 9.10(d, 1H), 8.15(s, 1H), 8.08(d, 1H), 7.83-7.79(m, 3H), 7.69(d, 1H), 7.58(t, 1H), 7.58-7.46(m, 5H), 7.35-7.26(m, 4H), 7.21-7.17(m, 1H), 6.45(s, 1H), 5.30(q, 2H), 4.90-4.84(m, 1H), 3.51(dd, 1H), 3.30(q, 1H)

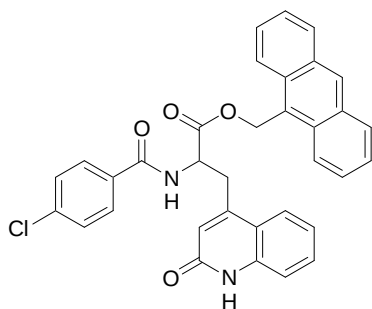
EXAMPLE 76: Preparation of Naphthalen-2-ylmethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate



According to Experiment Prototocol C, 1.0 g(2.69 mmol) of rebamipide and 0.71 g(1.5 eq, 4.03 mmol) of (1-chloromethyl)naphthalene were reacted to afford the title compound as a white solid (0.8 g).

^1H NMR (400MHz, DMSO-d_6): δ 11.71(s, 1H), 9.12(d, 1H), 7.93-7.82(m, 7H), 7.58-7.45(m, 6H), 7.31(d, 1H), 7.21(t, 1H), 6.48(s, 1H), 5.29(q, 2H), 4.88(m, 1H), 3.53(dd, 1H), 3.32(q, 1H)

EXAMPLE 77: Preparation of Anthracen-9-ylmethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate

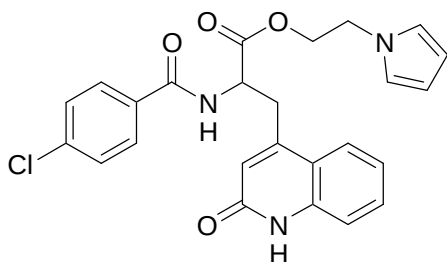


According to Experiment Prototocol C, 1.0 g(2.69 mmol) of rebamipide and 0.91 g(1.5 eq, 4.03 mmol) of (9-chloromethyl)anthracene were reacted to afford the title

compound as a white solid (0.8 g).

^1H NMR (400MHz, DMSO-d_6): δ 11.67(s, 1H), 9.01(d, 1H), 8.71(s, 1H), 8.32(d, 2H), 8.12(d, 2H), 7.70(t, 3H), 7.68-7.45(m, 7H), 7.28(d, 1H), 7.08(t, 1H), 6.40(s, 1H), 6.15(dd, 2H), 4.69(m, 1H), 3.40(dd, 1H), 3.22(q, 1H)

EXAMPLE 78: Preparation of 2-Pyrrol-1-ylethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate

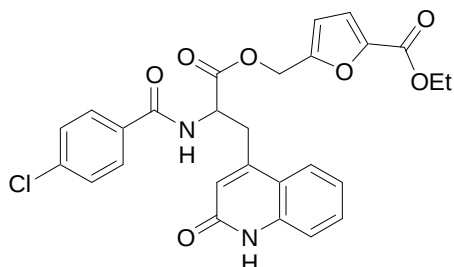


According to Experiment Prototocol C, 1.0 g(2.69 mmol) of rebamipide and 0.70 g(1.5 eq, 4.03 mmol) of 1-(2-bromoethyl)pyrrole were reacted to afford the title compound as a white solid (0.5 g).

^1H NMR (400MHz, DMSO-d_6): δ 11.69(s, 1H), 9.03(d, 1H), 7.83(t, 1H), 7.57(t, 1H), 7.73(d, 1H), 7.52(m, 1H), 7.31(dd, 1H), 7.24(m, 1H), 6.76(t, 2H), 6.44(s, 1H), 5.93(t, 2H), 4.74-4.73(m, 1H), 4.40-4.35(m, 1H), 4.33-4.27(m, 1H), 4.17-4.13(m, 2H), 3.37(dd, 1H), 3.20(q, 1H)

EXAMPLE 79: Preparation of (2-Ethoxycarbonyl)furan-4-

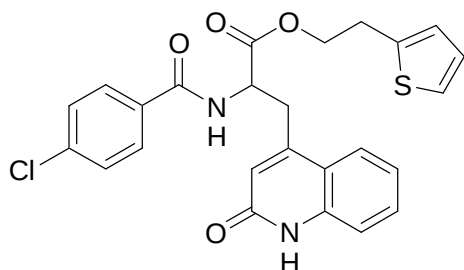
ylmethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate



According to Experiment Prototocol C, 1.0 g(2.69 mmol) of rebamipide and 0.76 g(1.5 eq, 4.03 mmol) of ethyl 5-(chloromethyl)-2-furancarboxylate were reacted to afford the title compound as a white solid (0.8 g).

^1H NMR (700MHz, DMSO-d_6): δ 11.67(s, 1H), 9.10(d, 1H), 7.79(d, 3H), 7.56(t, 2H), 7.50(t, 1H), 7.31-7.26(m, 2H), 7.21(t, 1H), 6.71(d, 1H), 6.43(s, 1H), 5.26-5.21(m, 2H), 4.82(br-s, 1H), 4.27(q, 2H), 3.45(dd, 1H), 3.30(q, 1H), 1.27(t, 3H)

EXAMPLE 80: Preparation of 2-Thiophen-2-ylethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate

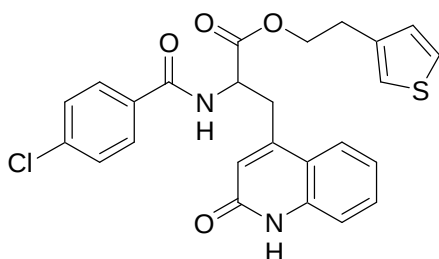


According to Experiment Prototocol D, 1.0 g(2.69 mmol) of

rebamipide and 0.83 g(1.5 eq, 4.03 mmol) of 2-thiophenethyl methanesulfonate were reacted to afford the title compound as a white solid (0.6 g).

^1H NMR (400MHz, DMSO-d_6): δ 11.70(s, 1H), 9.04(d, 1H), 7.83(t, 1H), 7.83(s, 1H), 7.81(s, 1H), 7.76(d, 1H), 7.58(s, 1H), 7.56(s, 1H), 7.52(t, 1H), 7.34-7.32(m, 2H), 7.25(t, 1H), 6.92-6.90(m, 2H), 6.45(s, 1H), 4.77(m, 1H), 4.37-4.26(m, 2H), 3.41(dd, 1H), 3.21(q, 1H), 3.14(t, 2H)

EXAMPLE 81: Preparation of 2-Thiophen-3-ylethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate

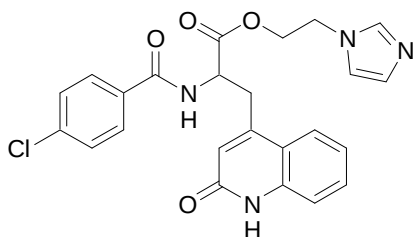


According to Experiment Prototocol D, 1.0 g(2.69 mmol) of rebamipide and 0.83 g(1.5 eq, 4.03 mmol) of 3-thiophenethyl methanesulfonate were reacted to afford the title compound as a white solid (0.6 g).

^1H NMR (400MHz, DMSO-d_6): δ 11.70(s, 1H), 9.04(d, 1H), 7.83(t, 1H), 7.84(s, 1H), 7.82(s, 1H), 7.73(d, 1H), 7.58(s, 1H), 7.56(s, 1H), 7.52(t, 1H), 7.42(q, 1H), 7.32(d, 1H), 7.24-7.21(m, 2H), 7.03(dd, 2H), 6.45(s, 1H), 4.75(m, 1H), 4.38-

4.26(m, 2H), 3.37(dd, 1H), 3.23(q, 1H), 2.90(t, 2H)

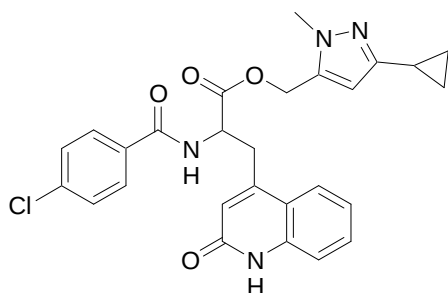
EXAMPLE 82: Preparation of 2-Imidazol-1-ylethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate



According to Experiment Prototocol A, 1.0 g(2.69 mmol) of rebamipide and 0.45 g(1.2 eq, 3.23 mmol)of 1-(2-hydroxyethyl)imidazole were reacted to afford the title compound as a white solid (0.3 g).

^1H NMR (400MHz, DMSO- d_6): δ 11.69(s, 1H), 9.04(d, 1H), 7.80(d, 2H), 7.73(d, 1H), 7.66(s, 1H), 7.56(d, 2H), 7.52(t, 1H), 7.31(d, 1H), 7.25(t, 1H), 7.18(s, 1H), 6.85(s, 1H), 6.43(s, 1H), 4.76(m, 1H), 4.40(m, 2H), 4.28(m, 2H), 3.42(dd, 1H), 3.21(q, 1H)

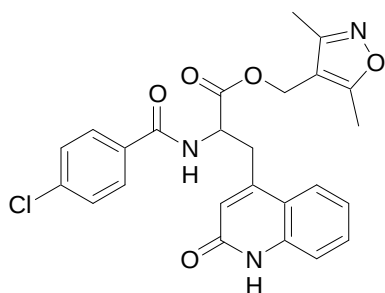
EXAMPLE 83: Preparation of 5-Cyclopropyl-2-methyl-2H-pyrazol-3-ylmethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate



According to Experiment Prototocol C, 1.0 g(2.69 mmol) of rebamipide and 0.68 g(1.5 eq, 4.03 mmol) of 5-chloromethyl-3-cyclopropyl-1-methyl-1*H*-pyrazole were reacted to afford the title compound as a white solid (0.5 g).

¹H NMR (400MHz, DMSO-*d*₆): δ 11.69(s, 1H), 9.08(d, 1H), 7.79(d, 3H), 7.55(d, 2H), 7.49(t, 1H), 7.31(d, 1H), 7.21(t, 1H), 6.44(s, 1H), 5.99(s, 1H), 5.12(q, 2H), 4.80(m, 1H), 3.63(s, 3H), 3.46(dd, 1H), 3.30(q, 1H), 1.80(m, 1H), 0.81(m, 2H), 0.57(m, 2H)

EXAMPLE 84: Preparation of 3,5-Dimethylisoxazol-4-ylmethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate

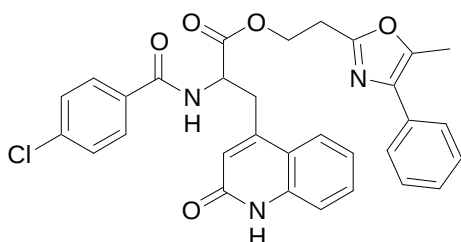


According to Experiment Prototocol C, 1.0 g(2.69 mmol) of

rebamipide and 0.58 g(1.5 eq, 4.03 mmol) of 4-chloromethyl-3,5-dimethylisoxazole were reacted to afford the title compound as a white solid (0.8 g).

¹H NMR (400MHz, DMSO-d₆):δ 11.67(s, 1H), 9.05(d, 1H), 7.78(m, 3H), 7.57(t, 1H), 7.52(t, 1H), 7.50(m, 1H), 7.30(d, 1H), 7.21(t, 1H), 6.42(s, 1H), 4.99(q, 2H), 4.78(m, 1H), 3.43(dd, 1H), 3.27(q, 1H), 2.36(s, 3H), 2.13(s, 3H)

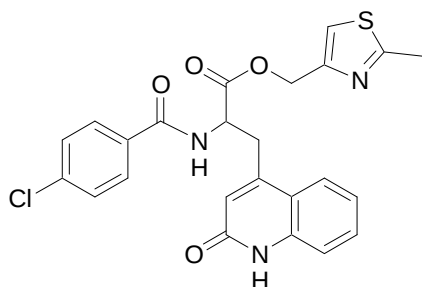
EXAMPLE 85: Preparation of 2-(5-Methyl-4-phenyloxazol-2-yl)ethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate



According to Experiment Prototocol C, 1.0 g(2.69 mmol) of rebamipide and 1.07 g(1.5 eq, 4.03 mmol) of 2-(2-bromoethyl)-5-methyl-4-phenyloxazole were reacted to afford the title compound as a white solid (0.6 g).

¹H NMR (400MHz, DMSO-d₆):δ 11.67(s, 1H), 8.98(d, 1H), 7.87(m, 2H), 7.79(s, 1H), 7.77(s, 1H), 7.73(d, 1H), 7.52-7.46(m, 6H), 7.30(d, 1H), 7.16(t, 1H), 6.43(s, 1H), 4.76(m, 1H), 4.38(m, 1H), 4.36(m, 1H), 3.43(dd, 1H), 3.22(dd, 1H), 2.80(t, 2H), 2.25(s, 3H)

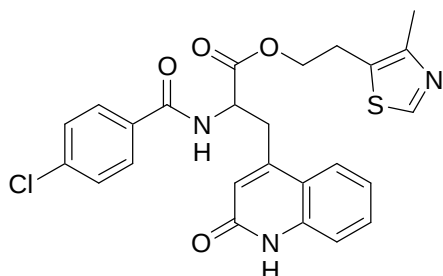
EXAMPLE 86: Preparation of 2-Methylthiazol-4-ylmethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate



According to Experiment Prototocol A, 1.0 g(2.69 mmol) of rebamipide and 0.42 g(1.2 eq, 3.23 mmol) of 2-methyl-4-thiazolemethanol were reacted to afford the title compound as a white solid (0.4 g).

^1H NMR (400MHz, DMSO-d_6): δ 11.68(s, 1H), 9.09(d, 1H), 7.81(d, 3H), 7.55(d, 2H), 7.51(t, 1H), 7.46(s, 1H), 7.36(d, 1H), 7.30(d, 1H), 7.22(t, 1H), 6.44(s, 1H), 5.19(s, 2H), 4.84(m, 1H), 3.48(dd, 1H), 3.30(q, 1H), 2.64(s, 3H)

EXAMPLE 87: Preparation of 2-(4-Methylthiazol-5-yl)ethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate

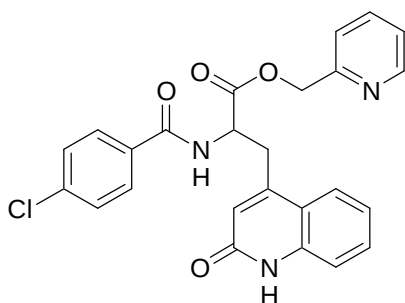


According to Experiment Prototocol A, 1.0 g(2.69 mmol) of

rebamipide and 0.46 g(1.2 eq, 3.23 mmol) of 4-methyl-5-thiazole ethanol were reacted to afford the title compound as a white solid (0.4 g).

¹H NMR (700MHz, DMSO-d₆):δ 11.70(s, 1H), 9.04(d, 1H), 8.82(s, 1H), 7.81(d, 3H), 7.76(d, 1H), 7.56(d, 2H), 7.52(t, 1H), 7.32(d, 1H), 7.23(t, 1H), 6.45(s, 1H), 4.80-4.77(m, 1H), 4.30-4.24(m, 2H), 3.42(dd, 1H), 3.24(q, 1H), 3.13-3.08(m, 2H), 2.30(s, 3H)

EXAMPLE 88: Preparation of Pyrimidin-2-ylmethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate

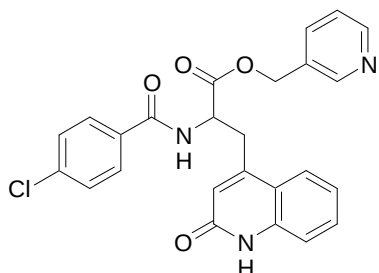


According to Experiment Prototocol C, 1.0 g(2.69 mmol) of rebamipide and 0.66 g(1.5 eq, 4.03 mmol) of 2-(Chloromethyl)pyridine HCl were reacted to afford the title compound as a white solid (0.9 g).

¹H NMR (400MHz, DMSO-d₆):δ 11.68(s, 1H), 9.13(d, 1H), 8.55(d, 1H), 7.86-7.78(m, 4H), 7.58(s, 1H), 7.56(s, 1H), 7.51(t, 1H), 7.36(d, 1H), 7.34(m, 1H), 7.22(t, 1H), 6.48(s,

1H), 5.26(s, 2H), 4.92(m, 1H), 3.56(dd, 1H), 3.32-3.41(m, 1H)

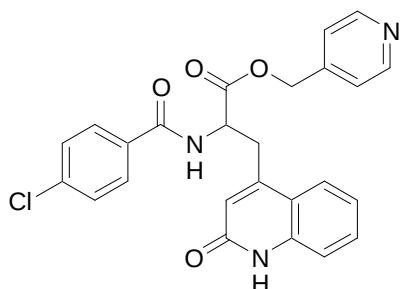
EXAMPLE 89: Preparation of Pyrimidin-3-ylmethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate



According to Experiment Prototocol C, 1.0 g(2.69 mmol) of rebamipide and 0.66 g(1.5 eq, 4.03 mmol) of 23-(chloromethyl)pyridine HCl were reacted to afford the title compound as a white solid (0.9 g).

¹H NMR (400MHz, DMSO-d₆): δ 11.68(s, 1H), 9.09(d, 1H), 8.58(d, 1H), 8.54(dd, 1H), 7.83(t, 3H), 7.74(m, 1H), 7.57(m, 2H), 7.48(m, 1H), 7.39(m, 1H), 7.31(dd, 1H), 7.21(m, 1H), 6.45(s, 1H), 5.21(q, 2H), 4.86(m, 1H), 3.50(dd, 1H), 3.33(m, 1H)

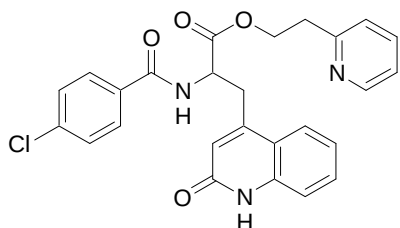
EXAMPLE 90: Preparation of Pyrimidin-4-ylmethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate



According to Experiment Prototocol C, 1.0 g(2.69 mmol) of rebamipide and 0.66 g(1.5 eq, 4.03 mmol) of 4-(chloromethyl)pyridine HCl were reacted to afford the title compound as a white solid (0.7 g).

^1H NMR (400MHz, DMSO- d_6): δ 11.70(s, 1H), 9.14(d, 1H), 8.55(d, 2H), 8.54(d, 1H), 7.85(t, 3H), 7.58(s, 1H), 7.56(s, 1H), 7.32(m, 3H), 7.21(t, 1H), 6.48(s, 1H), 5.23(q, 2H), 4.93(m, 1H), 3.54(dd, 1H), 3.38(m, 1H)

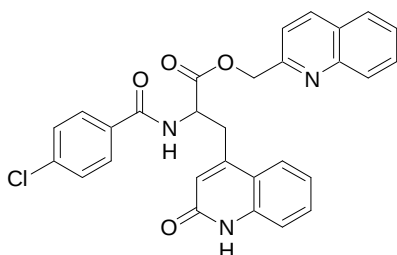
EXAMPLE 91: Preparation of 2-(Pyrimidin-2-yl)ethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate



According to Experiment Prototocol D, 1.0 g(2.69 mmol) of rebamipide and 0.81 g(1.5 eq, 4.03 mmol) of 2-pyridineethyl methanesulfonate were reacted to afford the title compound as a white solid (0.7 g).

¹H NMR (700MHz, DMSO-d₆): δ 11.68 (s, 1H), 8.99 (d, 1H), 8.55 (d, 2H), 8.48 (s, 1H), 7.78 (d, 2H), 7.66-7.51 (m, 5H), 7.32-7.20 (m, 4H), 6.42 (s, 1H), 4.69 (br-s, 1H), 4.54-4.45 (m, 2H), 3.34 (d, 1H), 3.18 (d, 1H), 3.06 (d, 2H)

EXAMPLE 92: Preparation of Quinolin-2-ylmethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate

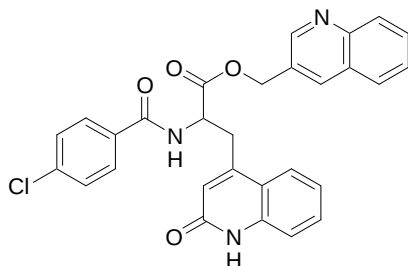


According to Experiment Prototocol C, 1.0 g(2.69 mmol) of rebamipide and 0.86 g(1.5 eq, 4.03 mmol) of 2-(chloromethyl)quinoline HCl were reacted to afford the title compound as a white solid (0.9 g).

¹H NMR (400MHz, DMSO-d₆): δ 11.70 (s, 1H), 9.16 (d, 1H), 8.38 (d, 2H), 7.99 (t, 2H), 7.88 (t, 1H), 7.86 (s, 1H), 7.84 (s, 1H), 7.78 (m, 1H), 7.62 (m, 1H), 7.58 (s, 1H), 7.56 (s, 1H), 7.52 (t, 2H), 7.32 (d, 1H), 7.21 (t, 1H), 6.52 (s, 1H), 5.47 (s, 2H), 4.97 (m, 1H), 3.67 (dd, 1H), 3.39 (m, 1H)

EXAMPLE 93: Preparation of Quinolin-3-ylmethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-

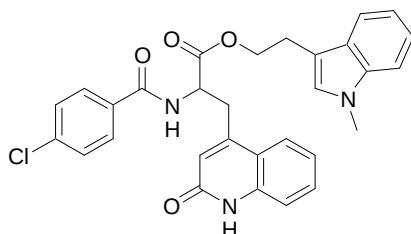
yl)propionate



According to Experiment Prototocol C, 1.0 g(2.69 mmol) of rebamipide and 0.66 g(1.5 eq, 4.03 mmol) of 3-(chloromethyl)pyridine HCl were reacted to afford the title compound as a white solid (0.8 g).

^1H NMR (400MHz, DMSO-d_6): δ 11.68(s, 1H), 9.31(s, 1H), 9.15(d, 1H), 8.13(d, 2H), 7.87-7.84(m, 4H), 7.81-7.78(m, 1H), 7.75(s, 1H), 7.72-7.68(m, 1H), 7.58-7.77(m, 2H), 7.52-7.48(m, 1H), 7.23(q, 1H), 7.21-7.20(m, 1H), 6.50(s, 1H), 5.39(q, 2H), 4.97-4.91(m, 1H), 3.57(dd, 1H), 3.37(m, 1H)

EXAMPLE 94: Preparation of 2-(1-Methyl-1H-indol-3-yl)ethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate

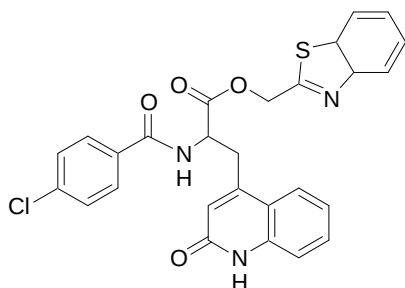


According to Experiment Prototocol B, 1.0 g(2.69 mmol) of rebamipide and 0.56 g(1.2 eq, 3.23 mmol) of 3-(2-

hydroxyethyl)-1-methylindole were reacted to afford the title compound as a white solid (0.3 g).

¹H NMR (400MHz, DMSO-d₆): δ 11.69(s, 1H), 9.03(d, 1H), 7.84(s, 1H), 7.82(s, 1H), 7.73(d, 1H), 7.57(s, 1H), 7.55(s, 1H), 7.34(q, 2H), 7.19(t, 1H), 7.13(t, 1H), 7.11(s, 1H), 6.99(t, 1H), 6.45(s, 1H), 4.78(m, 1H), 4.40-4.27(m, 2H), 3.65(s, 3H), 3.39(dd, 1H), 3.24(m, 1H), 2.98(t, 2H)

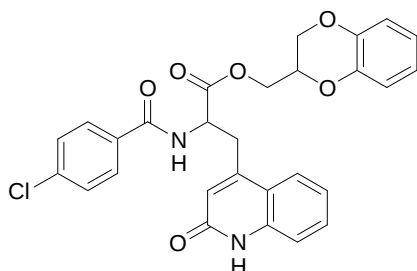
EXAMPLE 95: Preparation of Benzothiazol-2-ylmethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate



According to Experiment Prototocol C, 1.0 g(2.69 mmol) of rebamipide and 0.74 g(1.5 eq, 4.03 mmol) of 2-(chloromethyl)benzothiazole were reacted to afford the title compound as a white solid (0.8 g).

¹H NMR (400MHz, DMSO-d₆): δ 11.70(s, 1H), 9.17(d, 1H), 8.12(d, 2H), 8.01(d, 1H), 7.88-7.82(m, 3H), 7.56(d, 2H), 7.53-7.46(m, 3H), 7.31(d, 1H), 7.20(t, 1H), 6.50(s, 1H), 5.59(s, 2H), 4.93(m, 1H), 3.59(dd, 1H), 3.35(q, 1H)

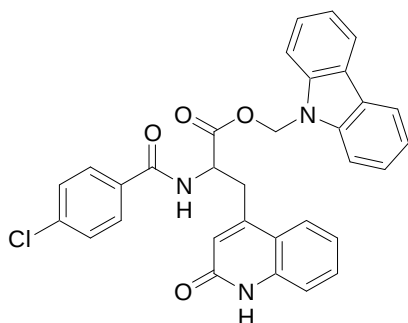
EXAMPLE 96: Preparation of 2,3-Dihydrobenzo[1,4]dioxin-2-ylmethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate



According to Experiment Prototocol C, 1.0 g(2.69 mmol) of rebamipide and 0.92 g(1.5 eq, 4.03 mmol) of 2-(bromomethyl)-1,4-benzodioxane were reacted to afford the title compound as a white solid (1.0 g).

^1H NMR (400MHz, DMSO-d_6): δ 11.70(d, 1H), 9.09(dd, 1H), 7.81(t, 3H), 7.55-7.50(m, 3H), 7.86(s, 1H), 7.84(s, 1H), 7.78(m, 1H), 7.62(m, 1H), 7.58(s, 1H), 7.56(s, 1H), 7.52(t, 2H), 7.32(q, 1H), 7.18(q, 1H), 6.88-6.81(m, 4H), 6.46(d, 1H), 4.81(m, 1H), 4.46-4.29(m, 4H), 4.06-3.98(m, 1H), 3.51-3.47(m, 1H), 3.36-3.30(m, 1H)

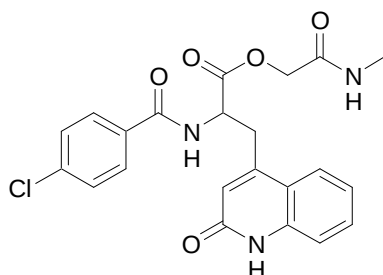
EXAMPLE 97: Preparation of Carbazol-9-ylmethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate



According to Experiment Prototocol B, 1.0 g(2.69 mmol) of rebamipide and 0.64 g(1.2 eq, 3.23 mmol) of 9H-carbazole 9-methanol were reacted to afford the title compound as a white solid (0.6 g).

^1H NMR (400MHz, DMSO-d_6): δ 11.64(s, 1H), 8.85(d, 1H), 8.13(d, 2H), 7.71(d, 2H), 7.65(d, 1H), 7.53-7.46(m, 4H), 7.36(t, 2H), 7.29(d, 1H), 7.18-7.12(m, 3H), 6.33(s, 1H), 4.64(m, 2H), 3.09(dd, 1H), 2.95(dd, 1H)

EXAMPLE 98: Preparation of Methylcarbamoylmethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate

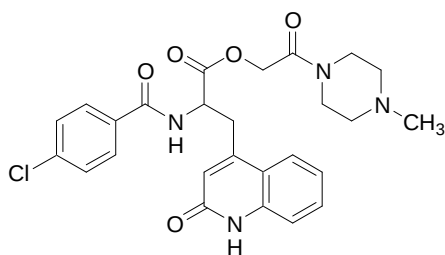


According to Experiment Prototocol C, 1.0 g(2.69 mmol) of rebamipide and 0.43 g(1.5 eq, 4.03 mmol) of 2-chloro-N-methylacetamide were reacted to afford the title compound as a

white solid (0.4 g).

^1H NMR (400MHz, DMSO-d_6): δ 11.68 (s, 1H), 9.09 (d, 1H), 7.95 (m, 1H), 7.84-7.81 (m, 3H), 7.55 (d, 2H), 7.51 (t, 1H), 7.31 (d, 1H), 7.23 (t, 1H), 6.47 (s, 1H), 4.96-4.90 (m, 1H), 4.59 (s, 2H), 3.58 (dd, 1H), 3.29 (q, 1H), 2.64 (d, 3H)

EXAMPLE 99: Preparation of 2-(4-Methylpiperazin-1-yl)-2-oxoethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate

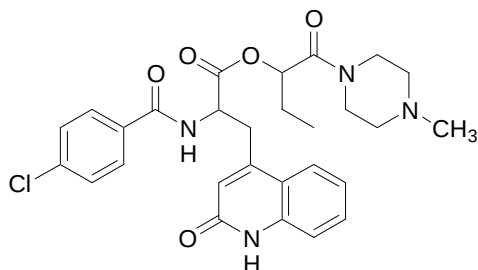


According to Experiment Prototocol C, 2.0 g(5.38 mmol) of rebamipide and 1.40 g(1.2 eq, 6.48 mmol) of 1-(2-bromoacetyl)-4-methylpiperazin-1-ium bromide were reacted to afford the title compound as a white solid (0.1 g).

^1H NMR (400MHz, DMSO-d_6): δ 9.10 (d, 1H), 7.81 (t, 3H), 7.53 (m, 4H), 7.31 (d, 1H), 7.23 (t, 1H), 6.48 (s, 1H), 4.93-4.90 (m, 2H), 4.23 (t, 1H), 3.45-3.42 (m, 4H), 2.71-2.50 (m, 2H), 2.29-2.25 (m, 4H), 2.12 (s, 3H)

EXAMPLE 100: Preparation of 1-(4-Methylpiperazine-1-carbonyl)propyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-

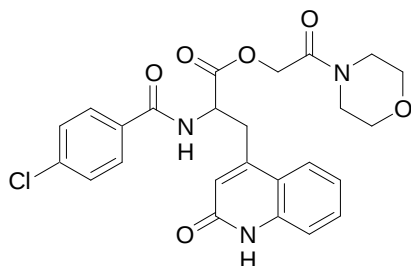
2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate



According to Experiment Prototocol C, 2.0 g(5.38 mmol) of rebamipide and 1.60 g(1.2 eq, 6.48 mmol) of 1-(2-bromobutanoyl)-4-methylpiperazin-1-ium bromide were reacted to afford the title compound as a white solid (0.1 g).

^1H NMR (400MHz, DMSO-d_6): δ 9.09(d, 1H), 7.81(t, 3H), 7.53(m, 4H), 7.31(d, 1H), 7.23(t, 1H), 7.25-7.23(m, 1H), 6.48(d, 1H), 5.06-4.78(m, 1H), 4.52-4.50(m, 1H), 3.33-3.30(m, 4H), 2.60-2.51(m, 6H), 2.16-2.10(m, 5H), 1.10(t, 3H)

EXAMPLE 101: Preparation of 2-Morpholin-4-yl-2-oxoethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate

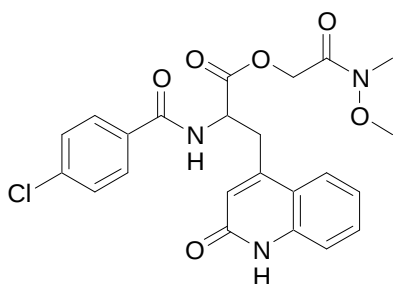


According to Experiment Prototocol C, 1.0 g(2.69 mmol) of rebamipide and 0.66 g(1.5 eq, 4.03 mmol) of 1-(2-chloroacetyl)morpholine were reacted to afford the title

compound as a white solid (0.5 g).

¹H NMR (400MHz, DMSO-d₆): δ 11.68 (s, 1H), 9.08 (d, 1H), 7.83 (t, 3H), 7.58 (s, 1H), 7.56 (s, 1H), 7.53 (t, 1H), 7.32 (d, 1H), 7.26 (t, 1H), 6.52 (s, 1H), 4.93 (dd, 2H), 4.87 (m, 1H), 3.65 (dd, 1H), 3.58 (br-s, 4H), 3.44 (m, 4H), 3.29 (m, 1H)

EXAMPLE 102: Preparation of (Methoxymethylcarbamoyl)methyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate

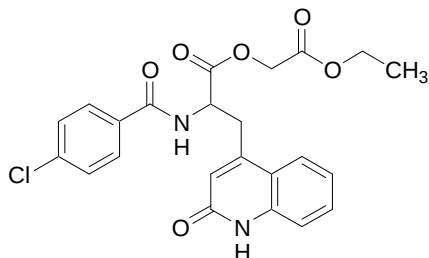


According to Experiment Prototocol C, 1.0 g(2.69 mmol) of rebamipide and 0.55 g(1.5 eq, 4.03 mmol) of 2-chloro-N-methoxy-N-methylacetamide were reacted to afford the title compound as a white solid (0.7 g).

¹H NMR (400MHz, DMSO-d₆): δ 11.70 (s, 1H), 9.10 (d, 1H), 7.86-7.81 (m, 3H), 7.59-7.51 (m, 3H), 7.33 (dd, 1H), 7.26 (m, 1H), 6.52 (s, 1H), 5.09-4.89 (m, 3H), 3.74 (s, 3H), 3.63 (dd, 1H), 3.29 (q, 1H), 3.14 (s, 3H)

EXAMPLE 103: Preparation of 2-Ethoxycarbonylmethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-

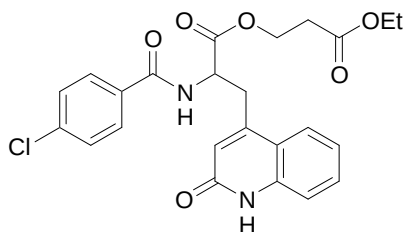
yl)propionate



According to Experiment Prototocol C, 1.0 g(2.69 mmol) of rebamipide and 0.49 g(1.5 eq, 4.03 mmol) of ethyl chloroacetate were reacted to afford the title compound as a white solid (0.8 g).

^1H NMR (400MHz, DMSO-d_6): δ 11.69(s, 1H), 9.10(d, 1H), 7.85(t, 1H), 7.83-7.80(m, 2H), 7.77(d, 1H), 7.57(t, 1H), 7.55(t, 1H), 7.54-7.50(m, 1H), 7.32(dd, 1H), 7.27-7.23(m, 1H), 6.51(s, 1H), 4.95-4.89(m, 1H), 4.81(q, 2H), 4.16(q, 2H), 3.55(dd, 1H), 3.30(q, 1H), 1.21(t, 3H)

EXAMPLE 104: Preparation of 2-Ethoxycarbonylethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate

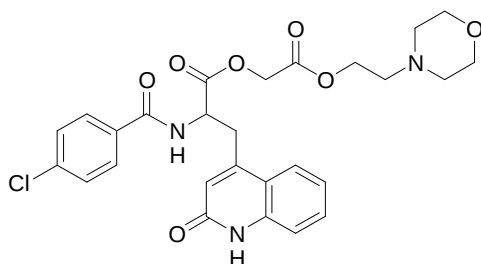


According to Experiment Prototocol C, 1.0 g(2.69 mmol) of rebamipide and 0.55 g(1.5 eq, 4.03 mmol) of ethyl 3-

chloropropionate were reacted to afford the title compound as a white solid (0.8 g).

^1H NMR (700MHz, DMSO-d_6): δ 11.69(s, 1H), 9.03(d, 1H), 7.82(t, 1H), 7.81(t, 1H), 7.77(d, 1H), 7.57(t, 1H), 7.56(t, 1H), 7.52-7.50(m, 1H), 7.32(dd, 1H), 7.23-7.21(m, 1H), 6.45(s, 1H), 4.77-4.73(m, 1H), 4.34-4.30(m, 2H), 4.01(q, 2H), 3.43(dd, 1H), 3.26(q, 1H), 2.69-2.66(m, 2H), 1.13(t, 3H)

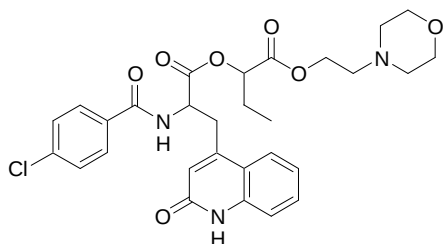
EXAMPLE 105: Preparation of 2-Morpholin-4-yl-ethoxycarbonylmethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate



According to Experiment Prototocol C, 1.0 g(2.69 mmol) of rebamipide and 1.07 g(1.2 eq, 3.23 mmol) of 4-[2-(2-bromoacetoxy)ethyl]morpholin-4-ium bromide were reacted to afford the title compound as a white solid (0.1 g).

^1H NMR (DMSO-d_6): δ 9.09(d, 1H), 7.81(t, 3H), 7.53(m, 3H), 7.31(d, 1H), 7.23(t, 1H), 6.48(s, 1H), 4.87-4.80(m, 2H), 4.23(t, 1H), 3.57-3.52(m, 4H), 3.31-3.25(m, 2H), 3.14(t, 4H), 2.62(t, 4H)

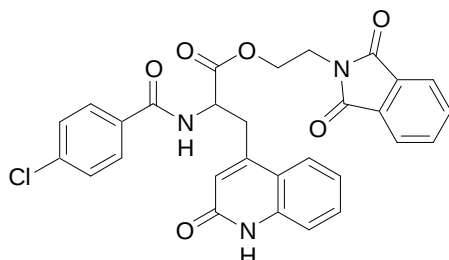
EXAMPLE 106: Preparation of 2-Morpholin-4-ylethyl 2-[2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionyloxy]butyrate



According to Experiment Prototocol C, 2.0 g(5.38 mmol) of rebamipide and 1.8 g(1.2 eq, 6.47 mmol) of ethyl chloroacetate were reacted to afford the title compound as a white solid (1.0 g).

^1H NMR (DMSO- d_6): δ 9.09(d, 1H), 7.81(t, 3H), 7.53(m, 3H), 7.31(d, 1H), 7.25-7.23(m, 1H), 6.48(d, 1H), 5.06-4.78(m, 1H), 4.30-4.11(m, 1H), 3.61-3.24(m, 8H), 3.35-3.25(m, 4H), 2.54-2.35(m, 2H), 1.90-1.75(m, 2H), 0.95(t, 3H)

EXAMPLE 107: Preparation of 2-(1,3-Dioxo-1,3-dihydroisoindol-2-yl)ethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate

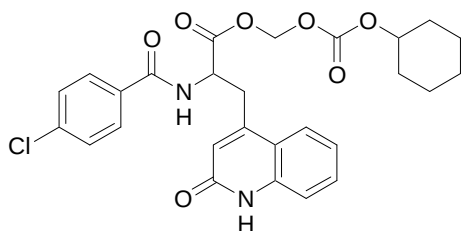


According to Experiment Prototocol C, 1.0 g(2.69 mmol) of

rebamipide and 0.79 g(1.5 eq, 4.03 mmol) of N-(chloromethyl)phthalimide were reacted to afford the title compound as a white solid (0.6 g).

^1H NMR (400MHz, DMSO-d_6): δ 11.65(s, 1H), 8.94(d, 1H), 7.82(s, 4H), 7.76-7.70(m, 3H), 7.52-7.48(m, 3H), 7.29(dd, 1H), 7.21(m, 1H), 6.41(s, 1H), 4.71(m, 1H), 4.48-4.42(m, 1H), 4.36-4.31(m, 1H), 3.92(t, 2H), 3.43(dd, 1H), 3.15(dd, 1H)

EXAMPLE 108: Preparation of Cyclohexyloxycarbonyloxymethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate

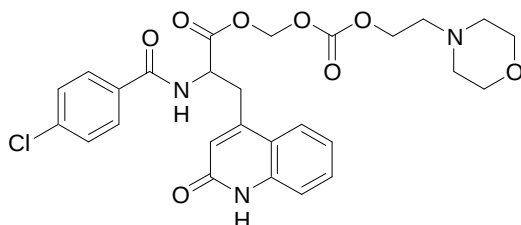


According to Experiment Prototocol C, 1.0 g(2.69 mmol) of rebamipide and 0.77 g(1.5 eq, 4.03 mmol) of ethyl chloromethyl cyclohexyl carbonate were reacted to afford the title compound as a white solid (0.4 g).

^1H NMR (400MHz, DMSO-d_6): δ 11.66(s, 1H), 9.09(d, 1H), 7.81(m, 3H), 7.52(m, 3H), 7.33(d, 1H), 7.21(m, 1H), 6.45(s, 1H), 5.77(s, 2H), 4.81(m, 1H), 4.53(m, 1H), 3.28-3.49(m, 2H), 1.80(m, 2H), 1.63(m, 2H), 1.14-1.51(m, 6H)

EXAMPLE 109: Preparation of 2-Morpholin-4-yl-

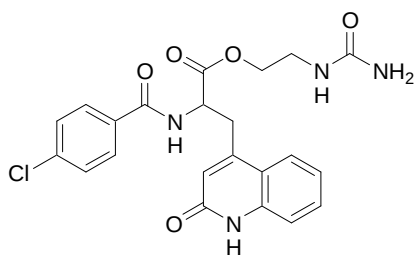
ethoxycarbonyloxymethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate



According to Experiment Prototocol C, 2.0 g(5.38 mmol) of rebamipide and 1.68 g(1.2 eq, 6.47 mmol) of chloromethyl(2-morpholin-4-yl)ethyl carbonate HCl were reacted to afford the title compound as a white solid (0.1 g).

^1H NMR (DMSO- d_6): δ 9.09(d, 1H), 7.81(t, 3H), 7.53(m, 4H), 7.31(d, 1H), 7.23(t, 1H), 7.26-6.95(m, 3H), 6.48(s, 1H), 4.23(t, 1H), 3.57-3.52(m, 4H), 3.31-3.25(m, 2H), 3.14(t, 4H), 2.62(t, 4H)

EXAMPLE 110: Preparation of 2-ureidoethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate

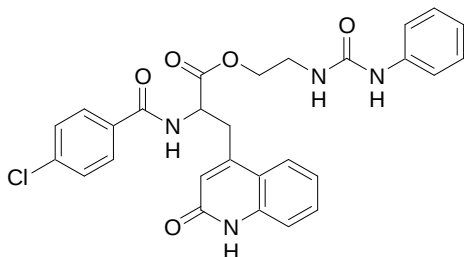


According to Experiment Prototocol C, 1.0 g(2.69 mmol) of rebamipide and 0.67 g(1.5 eq, 4.03 mmol) of (2-bromoethyl)urea

were reacted to afford the title compound as a white solid (0.2 g).

^1H NMR (400MHz, DMSO-d_6): δ 11.68 (s, 1H), 9.01 (d, 1H), 8.64 (t, 1H), 7.87-7.82 (m, 3H), 7.57 (t, 1H), 7.55 (t, 1H), 7.52 (m, 1H), 7.31 (d, 1H), 7.26 (m, 1H), 6.46 (s, 1H), 6.12 (t, 1H), 5.57 (s, 2H), 4.81 (m, 1H), 4.13 (m, 1H), 4.06 (m, 1H), 3.53 (dd, 1H), 3.28-3.22 (m, 3H)

EXAMPLE 111: Preparation of 2-(3-Phenyl-ureido)ethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate



According to Experiment Prototocol C, 1.0 g(2.69 mmol) of rebamipide and 0.98 g(1.5 eq, 4.03 mmol) of 1-(2-bromoethyl)-3-phenyl urea were reacted to afford the title compound as a white solid (0.3 g).

^1H NMR (400MHz, DMSO-d_6): δ 11.68 (s, 1H), 9.02 (d, 1H), 8.60 (s, 1H), 7.83 (t, 3H), 7.54 (s, 1H), 7.52 (s, 1H), 7.49 (t, 1H), 7.40 (s, 1H), 7.38 (s, 1H), 7.30 (d, 1H), 7.21-7.15 (m, 3H), 6.88 (t, 1H), 6.45 (s, 1H), 6.30 (t, 1H), 4.83 (m, 1H), 4.25 (m, 1H), 4.13 (m, 1H), 3.56 (dd, 1H), 3.41 (t, 2H), 3.27 (m, 1H)

O=C(NC(=O)OCCNC(=O)Nc1ccccc1)Cc2cnc(=O)c3ccccc23C(=O)c4ccc(Cl)cc4

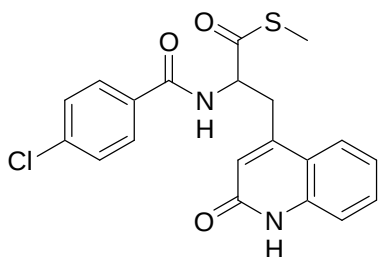
¹H NMR (400MHz, DMSO-d₆): δ 11.69(s, 1H), 9.03(d, 1H), 7.87-7.82(m, 3H), 7.55(d, 2H), 7.51(t, 1H), 7.33-7.17(m, 6H), 6.52(t, 1H), 6.46(s, 1H), 6.15(t, 1H), 4.82(m, 1H), 4.23-4.17(m, 3H), 4.07(m, 1H), 3.52(dd, 1H), 3.33(m, 2H), 3.24(dd, 1H)

O=C(NC(CS)Cc1c[nH]c2ccccc12)C(=O)c1ccc(Cl)cc1

According to Experiment Prototocol A or B, the title compound was prepared as a pale yellow solid (200 g).

^1H NMR (700MHz, DMSO-d_6): δ 11.52(s, 1H), 8.40(d, 1H), 8.22(d, 1H), 7.81(dd, 2H), 7.54(d, 1H), 7.52(d, 1H), 7.48(m, 1H), 7.28(d, 1H), 7.22(m, 1H), 6.37(s, 1H), 4.65-4.60(m, 1H), 4.11(q, 1H), 3.72(dd, 1H), 2.93(q, 1H)

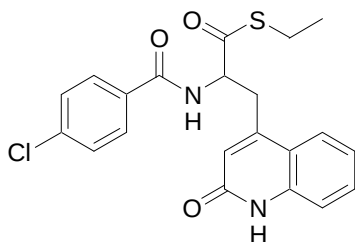
EXAMPLE 114: Preparation of S-Methyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate



According to Experiment Prototocol C, 2.0 g(5.17 mmol) of 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionic acid and 1.10 g(1.5 eq, 7.76 mmol) of iodomethane were reacted to afford the title compound as a white solid (1.2 g).

^1H NMR (400MHz, DMSO-d_6): δ 11.65(s, 1H), 9.24(d, 1H), 7.86(s, 1H), 7.84(s, 1H), 7.79(d, 1H), 7.60(s, 1H), 7.58(s, 2H), 7.51(t, 1H), 7.30(d, 1H), 7.23(t, 1H), 6.43(s, 1H), 4.97-4.92(m, 1H), 3.54(dd, 1H), 3.21(q, 1H), 2.28(s, 3H)

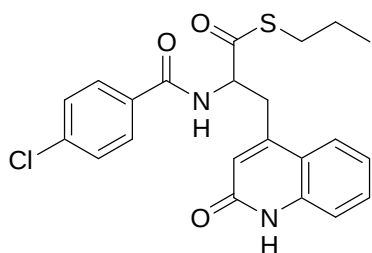
EXAMPLE 115: Preparation of S-Ethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate



According to Experiment Prototocol C, 2.0 g(5.17 mmol) of 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionic acid and 1.21 g(1.5 eq, 7.76 mmol) of iodoethane were reacted to afford the title compound as a white solid (1.2 g).

^1H NMR (700MHz, DMSO- d_6): δ 11.68(s, 1H), 9.28(d, 1H), 7.88(t, 1H), 7.85(t, 1H), 7.82(t, 1H), 7.60(t, 1H), 7.58(t, 1H), 7.53-7.49(m, 1H), 7.34-7.31(m, 1H), 7.26-7.22(m, 1H), 6.44(s, 1H), 4.95-4.90(m, 1H), 3.53(dd, 1H), 3.21(q, 1H), 2.86(q, 2H), 1.19(t, 3H)

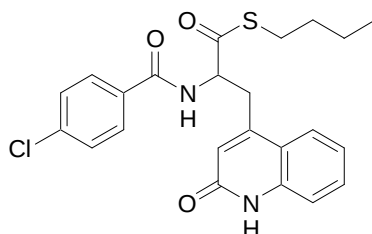
EXAMPLE 116: Preparation of S-Propyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate



According to Experiment Prototocol C, 2.0 g(5.17 mmol) of 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionic acid and 0.95 g(1.5 eq, 7.76 mmol) of 1-bromopropane were reacted to afford the title compound as a white solid (1.0 g).

^1H NMR (700MHz, DMSO-d_6): δ 11.65(s, 1H), 9.22(d, 1H), 7.86-7.79(m, 3H), 7.64(s, 1H), 7.62(s, 1H), 7.49(d, 1H), 7.26-7.22(m, 1H), 7.26-7.22(m, 1H), 6.43(s, 1H), 4.93-4.90(m, 1H), 3.52(dd, 1H), 3.20(q, 1H), 2.85(t, 2H), 1.51(q, 2H), 0.91(t, 3H)

EXAMPLE 117: Preparation of S-Butyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate

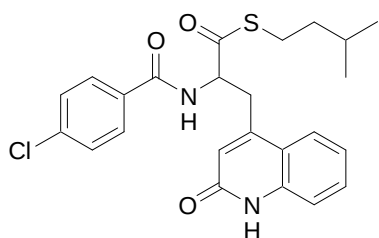


According to Experiment Prototocol C, 2.0 g(5.17 mmol) of 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-

yl)thiopropionic acid and 1.06 g(1.5 eq, 7.76 mmol) of 1-bromobutane were reacted to afford the title compound as a white solid (0.8 g).

¹H NMR (400MHz, DMSO-d₆):δ 11.64(s, 1H), 9.21(d, 1H), 7.87-7.79(m, 3H), 7.58(t, 1H), 7.55(t, 1H), 7.52-7.49(m, 1H), 7.30(dd, 1H), 7.25-7.20(m, 1H), 6.43(s, 1H), 4.96-4.90(m, 1H), 3.52(dd, 1H), 3.20(q, 1H), 2.87(t, 2H), 1.53-1.46(m, 2H), 1.35-1.24(m, 2H), 0.87(t, 3H)

EXAMPLE 118: Preparation of S-(3-Methylbutyl)2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate

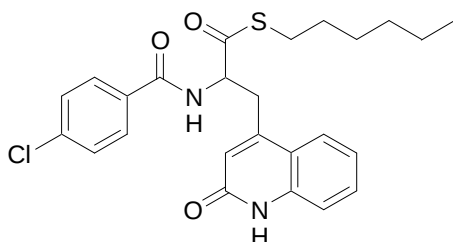


According to Experiment Prototocol C, 2.0 g(5.17 mmol) of 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionic acid and 1.17 g(1.5 eq, 7.76 mmol) of 1-bromo-3-methylbutane were reacted to afford the title compound as a white solid (0.7 g).

¹H NMR (400MHz, DMSO-d₆):δ 11.65(s, 1H), 9.22(d, 1H), 7.86-7.79(m, 3H), 7.60(t, 1H), 7.58(t, 1H), 7.53-7.49(m, 1H), 7.30(dd, 1H), 7.26-7.22(m, 1H), 6.43(s, 1H), 4.92(m, 1H), 3.52(dd, 1H), 3.20(q, 1H), 2.89-2.85(m, 2H), 1.60-1.55(m, 1H),

1.42-1.37(m, 2H), 0.87(dd, 6H)

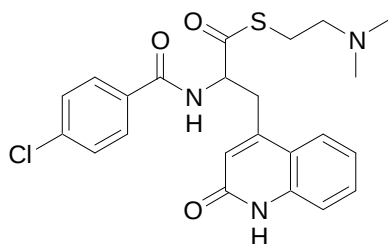
EXAMPLE 119: Preparation of S-Hexyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate



According to Experiment Prototocol C, 2.0 g(5.17 mmol) of 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionic acid and 1.28 g(1.5 eq, 7.76 mmol) of 1-bromohexane were reacted to afford the title compound as a white solid (0.6 g).

¹H NMR (400MHz, DMSO-d₆): δ 11.64(s, 1H), 9.21(d, 1H), 7.86-7.79(m, 3H), 7.58(t, 1H), 7.55(t, 1H), 7.53-7.49(m, 1H), 7.30(dd, 1H), 7.25-7.16(m, 1H), 6.43(s, 1H), 4.95-4.90(m, 1H), 3.52(dd, 1H), 3.20(q, 1H), 2.86(t, 2H), 1.54-1.47(m, 2H), 1.34-1.8(m, 6H), 0.85(t, 3H)

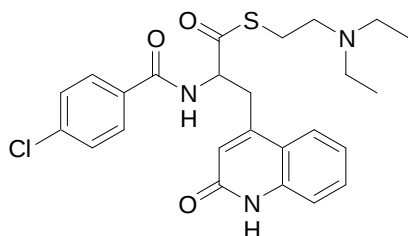
EXAMPLE 120: Preparation of S-(2-Dimethylamino)ethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate



According to Experiment Prototocol C, 2.0 g(5.17 mmol) of 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionic acid and 1.12 g(1.5 eq, 7.76 mmol) of 2-(dimethylamino)ethyl chloride HCl were reacted to afford the title compound as a white solid (0.7 g).

^1H NMR (400MHz, DMSO-d_6): δ 11.64(s, 1H), 9.23(d, 1H), 7.87-7.84(m, 2H), 7.79(d, 1H), 7.58(d, 2H), 7.51(t, 1H), 7.30(d, 1H), 7.24(t, 1H), 6.43(s, 1H), 4.95-4.92(m, 1H), 3.53(dd, 1H), 3.20(q, 1H), 2.99(t, 2H), 2.40(t, 2H), 2.16(s, 6H)

EXAMPLE 121: Preparation of S-(2-Diethylamino)ethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate

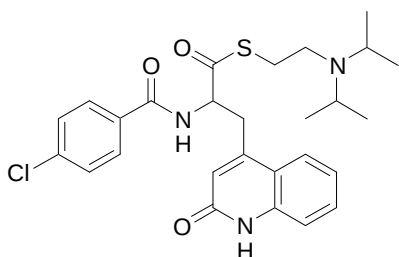


According to Experiment Prototocol C, 2.0 g(5.17 mmol) of 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-

yl)thiopropionic acid and 1.33 g(1.5 eq, 7.76 mmol) of 2-(diethylamino)ethyl chloride HCl were reacted to afford the title compound as a white solid (0.7 g).

^1H NMR (400MHz, DMSO- d_6): δ 11.65(s, 1H), 9.25(d, 1H), 7.87(t, 1H), 7.84(t, 1H), 7.79(d, 1H), 7.60(t, 1H), 7.58(t, 1H), 7.53-7.49(m, 1H), 7.31(d, 1H), 7.25-7.21(m, 1H), 6.43(s, 1H), 4.93-4.90(m, 1H), 3.52(dd, 1H), 3.22(q, 1H), 2.97(t, 2H), 2.62-2.58(m, 6H), 0.98(t, 6H)

EXAMPLE 122: Preparation of S-(2-Diisopropylamino)ethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate

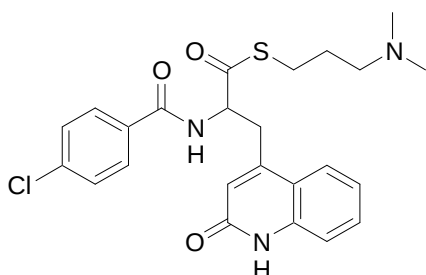


According to Experiment Prototocol C, 2.0 g(5.17 mmol) of 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionic acid and 1.55 g(1.5 eq, 7.76 mmol) of 2-(diisopropylamino)ethyl chloride HCl were reacted to afford the title compound as a white solid (0.8 g).

^1H NMR (400MHz, DMSO- d_6): δ 11.65(s, 1H), 9.23(d, 1H), 7.86(s, 1H), 7.84(s, 1H), 7.80(d, 1H), 7.64(s, 1H), 7.62(s, 1H), 7.51(t, 1H), 7.31(d, 1H), 7.23(t, 1H), 6.44(s, 1H), 4.96-

4.91(m, 1H), 3.52(dd, 1H), 3.21(q, 1H), 3.00(br-s, 2H), 2.87(br-s, 2H), 2.51(br-s, 2H), 0.99(d, 12H)

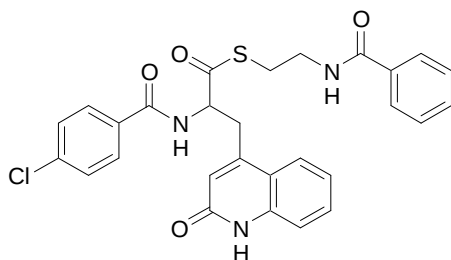
EXAMPLE 123: Preparation of S-(2-Dimethylamino)propyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate



According to Experiment Prototocol C, 2.0 g(5.17 mmol) of 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionic acid and 1.22 g(1.5 eq, 7.76 mmol) of 3-dimethylamino-1-propyl chloride HCl were reacted to afford the title compound as a white solid (0.9 g).

¹H NMR (400MHz, DMSO-d₆): δ 11.65(s, 1H), 9.22(d, 1H), 7.86(t, 1H), 7.84(t, 1H), 7.79(d, 1H), 7.60(t, 1H), 7.58(t, 1H), 7.53-7.49(m, 1H), 7.30(dd, 1H), 7.23-7.20(m, 1H), 6.43(s, 1H), 4.95-4.90(m, 1H), 3.52(dd, 1H), 3.20(q, 1H), 2.88(t, 2H), 2.25(t, 2H), 2.09(s, 6H), 1.68(m, 2H)

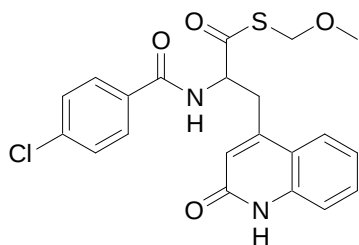
EXAMPLE 124: Preparation of S-(2-Benzoylamino)ethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate oxalate



According to Experiment Prototocol C, 2.0 g(5.17 mmol) of 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionic acid and 1.42 g(1.5 eq, 7.76 mmol) of N-(2-chloroethyl)benzamide were reacted to afford the title compound as a white solid (0.5 g).

^1H NMR (400MHz, DMSO-d_6): δ 11.64(s, 1H), 9.24(d, 1H), 8.66(t, 1H), 7.85-7.83(m, 4H), 7.77(d, 1H), 7.58(s, 1H), 7.56(s, 1H), 7.51-7.44(m, 3H), 7.30(d, 1H), 7.22(t, 1H), 6.43(s, 1H), 4.97-4.91(m, 1H), 3.55-3.42(m, 3H), 3.20(q, 1H), 3.11(t, 2H)

EXAMPLE 125: Preparation of S-Methoxymethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate

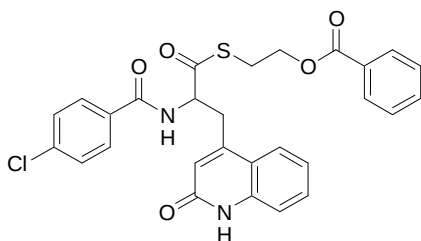


According to Experiment Prototocol C, 2.0 g(5.17 mmol) of 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-

yl)thiopropionic acid and 0.62 g(1.5 eq, 7.76 mmol) of chloromethyl methyl ether were reacted to afford the title compound as a white solid (1.2 g).

¹H NMR (400MHz, DMSO-d₆):δ 11.67(s, 1H), 9.29(d, 1H), 7.86-7.80(m, 3H), 7.60-7.58(dd, 2H), 7.53-7.49(m, 1H), 7.30(d, 1H), 7.25-7.21(m, 1H), 6.43(s, 1H), 5.08(s, 2H), 4.99-4.93(m, 1H), 3.54(dd, 1H), 3.24(q, 2H), 3.22(s, 3H)

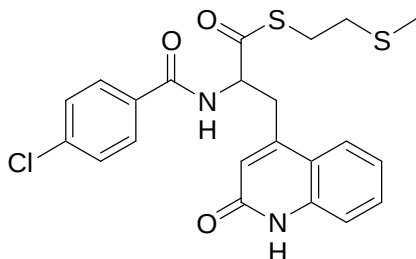
EXAMPLE 126: Preparation of S-(2-Benzoyloxy)ethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate



According to Experiment Prototocol C, 2.0 g(5.17 mmol) of 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionic acid and 1.43 g(1.5 eq, 7.76 mmol) of 2-chloroethyl benzoate were reacted to afford the title compound as a white solid (0.9 g).

¹H NMR (400MHz, DMSO-d₆):δ 11.66(s, 1H), 9.27(d, 1H), 7.96(s, 1H), 7.94(d, 1H), 7.84(s, 1H), 7.82(s, 1H), 7.72(d, 1H), 7.66(t, 1H), 7.58(s, 1H), 7.56(s, 1H), 7.50(q, 3H), 7.30(d, 1H), 7.21(t, 1H), 6.42(s, 1H), 4.95(m, 1H), 4.41(t, 2H), 3.49(dd, 1H), 3.34-3.30(m, 2H), 3.19(q, 1H)

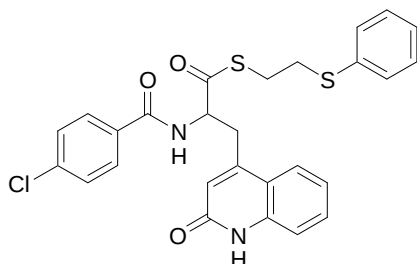
EXAMPLE 127: Preparation of S-(2-Methylsufanyl)ethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate



According to Experiment Prototocol C, 2.0 g(5.17 mmol) of 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionic acid and 0.86 g(1.5 eq, 7.76 mmol) of 2-chloroethyl methyl sulfide were reacted to afford the title compound as a white solid (0.8 g).

^1H NMR (400MHz, DMSO- d_6): δ 11.65(s, 1H), 9.25(d, 1H), 7.86(t, 1H), 7.84(t, 1H), 7.79(d, 1H), 7.60(t, 1H), 7.58(t, 1H), 7.53-7.49(m, 1H), 7.31(dd, 1H), 7.25-7.21(m, 1H), 6.43(s, 1H), 4.97-4.92(m, 1H), 3.53(dd, 1H), 3.21(q, 1H), 3.12-3.08(m, 2H), 2.65-2.49(m, 2H), 2.11(s, 3H)

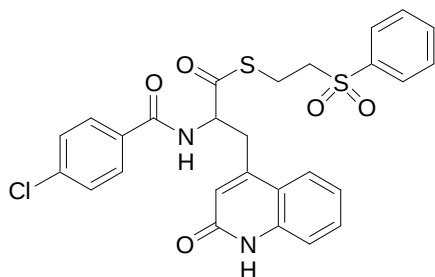
EXAMPLE 128: Preparation of S-(2-Phenylsufanyl)ethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate



According to Experiment Prototocol C, 2.0 g (5.17 mmol) of 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionic acid and 1.68 g (1.5 eq, 7.76 mmol) of 2-bromoethyl phenyl sulfide were reacted to afford the title compound as a white solid (0.6 g).

^1H NMR (400MHz, DMSO-d_6): δ 11.66(s, 1H), 9.26(d, 1H), 7.86(s, 1H), 7.84(s, 1H), 7.79(d, 1H), 7.60(s, 1H), 7.58(s, 1H), 7.51(t, 1H), 7.39(dd, 2H), 7.33(q, 3H), 7.25-7.21(m, 2H), 6.43(s, 1H), 4.98-4.93(m, 1H), 3.52(dd, 1H), 3.22(q, 1H), 3.15-3.07(m, 4H)

EXAMPLE 129: Preparation of S-(2-Benzenesulfonyl)ethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate

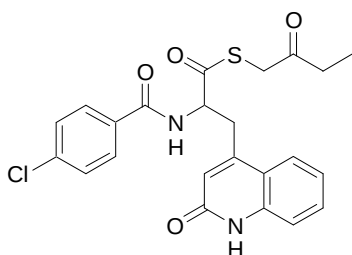


According to Experiment Prototocol C, 2.0 g (5.17 mmol) of 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-

yl)thiopropionic acid and 1.68 g (1.5 eq, 7.76 mmol) of 2-chloroethyl phenyl sulfone were reacted to afford the title compound as a white solid (0.6 g).

¹H NMR (400MHz, DMSO-d₆): δ 11.65(s, 1H), 9.22(d, 1H), 7.92(t, 2H), 7.83-7.79(m, 2H), 7.76(d, 2H), 7.70-7.64(m, 2H), 7.62-7.58(m, 2H), 7.53-7.47(m, 1H), 7.31(d, 1H), 7.21(t, 1H), 6.39(s, 1H), 4.92-4.86(m, 1H), 3.57-3.47(m, 3H), 3.17(q, 1H), 3.07-3.02(m, 2H)

EXAMPLE 130: Preparation of S-(2-Oxobutyl)-2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate

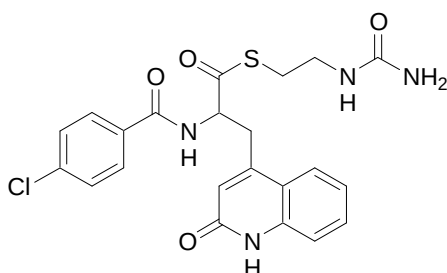


According to Experiment Prototocol C, 2.0 g(5.17 mmol) of 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionic acid and 0.82 g(1.5 eq, 7.76 mmol) of 1-chloro-2-butanone were reacted to afford the title compound as a white solid (1.1 g).

¹H NMR (400MHz, DMSO-d₆): δ 11.65(s, 1H), 9.32(d, 1H), 7.87(s, 1H), 7.85(s, 1H), 7.77(d, 1H), 7.61(s, 1H), 7.59(s, 1H), 7.51(t, 1H), 7.30(d, 1H), 7.23(t, 1H), 6.44(s, 1H), 4.96-

4.93(m, 1H), 3.91(d, 2H), 3.52(dd, 1H), 3.20(q, 1H), 2.58(q, 2H), 0.96(t, 3H)

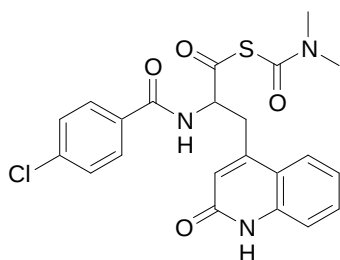
EXAMPLE 131: Preparation of S-(2-Ureido)ethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate



According to Experiment Prototocol C, 2.0 g(5.17 mmol) of 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionic acid and 0.95 g(1.5 eq, 7.76 mmol) of 2-chloroethylurea were reacted to afford the title compound as a white solid (1.1 g).

^1H NMR (400MHz, DMSO-d_6): δ 11.66(s, 1H), 9.24(d, 1H), 7.86(s, 1H), 7.84(s, 1H), 7.81(t, 1H), 7.60(s, 1H), 7.58(s, 1H), 7.57(d, 1H), 7.51(t, 1H), 7.30(d, 1H), 7.24(t, 1H), 6.43(s, 1H), 6.14(t, 1H), 5.51(s, 2H), 4.96-4.92(m, 1H), 3.54(dd, 1H), 3.21(q, 1H), 3.17-3.11(m, 2H), 2.93(t, 2H)

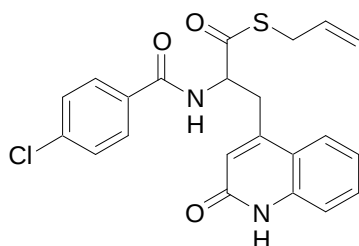
EXAMPLE 132: Preparation of N,N-Dimethyl S-[2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)]thiocarbamate



According to Experiment Prototocol C, 2.0 g(5.17 mmol) of 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionic acid and 0.83 g(1.5 eq, 7.76 mmol) of dimethyl carbamyl chloride were reacted to afford the title compound as a white solid (1.2 g).

^1H NMR (400MHz, DMSO-d_6): δ 11.61(s, 1H), 8.95(d, 1H), 7.89(d, 1H), 7.86(s, 1H), 7.84(s, 1H), 7.53-7.47(m, 3H), 7.29(d, 1H), 7.21(t, 1H), 6.44(s, 1H), 5.28-5.22(m, 1H), 3.28(dd, 1H), 3.19(q, 1H), 2.96(s, 3H), 2.84(s, 3H)

EXAMPLE 133: Preparation of S-Allyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate

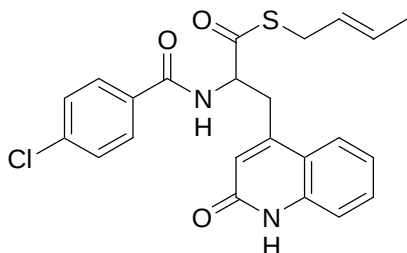


According to Experiment Prototocol C, 2.0 g(5.17 mmol) of 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionic acid and 0.94 g(1.5 eq, 7.76 mmol) of

allylbromide were reacted to afford the title compound as a white solid (1.2 g).

^1H NMR (700MHz, DMSO-d_6): δ 11.67(s, 1H), 9.26(d, 1H), 7.86-7.82(m, 2H), 7.79(d, 1H), 7.64-7.58(m, 2H), 7.53-7.49(m, 1H), 7.32-7.30(dd, 1H), 7.26-7.22(m, 1H), 6.43(s, 1H), 5.84-5.74(m, 1H), 5.29-5.24(m, 1H), 5.12-5.09(tt, 1H), 4.97-4.92(m, 1H), 3.57-3.52(m, 3H), 3.21(q, 2H)

EXAMPLE 134: Preparation of S-But-2-enyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate

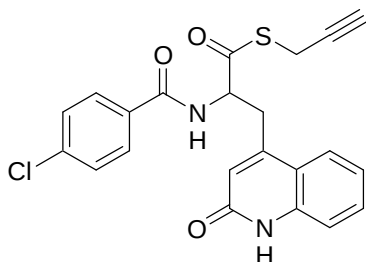


According to Experiment Prototocol C, 2.0 g(5.17 mmol) of 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionic acid and 1.05 g(1.5 eq, 7.76 mmol) of 1-bromo-2-butene were reacted to afford the title compound as a white solid (1.0 g).

^1H NMR (400MHz, DMSO-d_6): δ 11.66(s, 1H), 9.23(d, 1H), 7.86-7.79(m, 3H), 7.60(t, 1H), 7.58(t, 1H), 7.53-7.49(m, 1H), 7.31(dd, 1H), 7.26-7.22(m, 1H), 6.42(s, 1H), 5.71-5.66(m, 1H), 5.46-5.38(m, 1H), 4.97-4.91(m, 1H), 3.58-3.50(m, 3H), 3.20(q,

2H), 1.65(t, 3H)

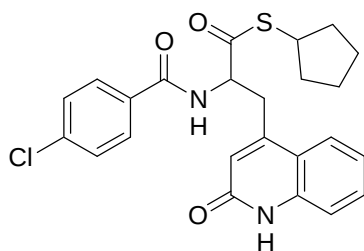
EXAMPLE 135: Preparation of S-Prop-2-ynyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate



According to Experiment Prototocol C, 2.0 g(5.17 mmol) of 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionic acid and 0.92 g(1.5 eq, 7.76 mmol) of progargyl bromide were reacted to afford the title compound as a white solid (1.0 g).

¹H NMR (400MHz, DMSO-d₆):δ 11.65(s, 1H), 9.29(d, 1H), 7.86(t, 1H), 7.83(t, 1H), 7.79(d, 1H), 7.60(t, 1H), 7.58(t, 1H), 7.53-7.49(m, 1H), 7.30(d, 1H), 7.25-7.21(m, 1H), 6.42(s, 1H), 4.99-4.96(m, 1H), 3.72(d, 1H), 3.53(dd, 3H), 3.32(s, 2H), 3.21(q, 2H)

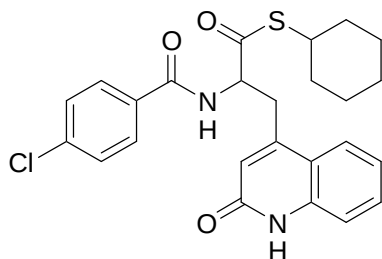
EXAMPLE 136: Preparation of S-cyclopentyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate



According to Experiment Prototocol C, 2.0 g(5.17 mmol) of 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionic acid and 0.81 g(1.5 eq, 7.76 mmol) of chlorocyclopentane were reacted to afford the title compound as a white solid (0.7 g).

^1H NMR (400MHz, DMSO-d_6): δ 11.64(s, 1H), 9.19(d, 1H), 7.85(d, 1H), 7.83(d, 1H), 7.79(d, 1H), 7.59(d, 1H), 7.58(d, 1H), 7.53-7.49(m, 1H), 7.30(d, 1H), 7.25-7.21(m, 1H), 6.42(s, 1H), 4.94-4.88(m, 1H), 3.65-3.62(m, 1H), 3.52(dd, 1H), 3.19(q, 2H), 2.09-2.02(m, 2H), 1.64-1.55(m, 4H), 1.49(m, 2H)

EXAMPLE 137: Preparation of S-Cyclohexyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate

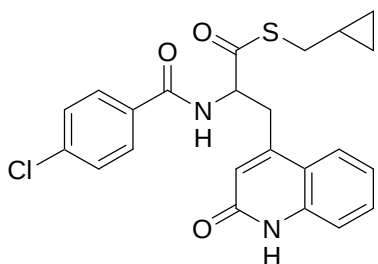


According to Experiment Prototocol C, 2.0 g(5.17 mmol) of 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-

yl)thiopropionic acid and 1.26 g(1.5 eq, 7.76 mmol) of bromocyclohexane were reacted to afford the title compound as a white solid (1.3 g).

¹H NMR (400MHz, DMSO-d₆):δ 11.65(s, 1H), 9.20(d, 1H), 7.86(s, 1H), 7.84(s, 1H), 7.60(s, 1H), 7.58(s, 1H), 7.51(t, 1H), 7.30(d, 1H), 7.24(t, 1H), 6.42(s, 1H), 4.93-4.88(m, 1H), 3.51(m, 1H), 3.42(m, 1H), 3.18(q, 2H), 1.86-1.82(m, 2H), 1.64-1.52(m, 3H), 1.45-1.32(m, 4H), 1.19(m, 1H)

EXAMPLE 138: Preparation of S-Cyclopropylmethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate

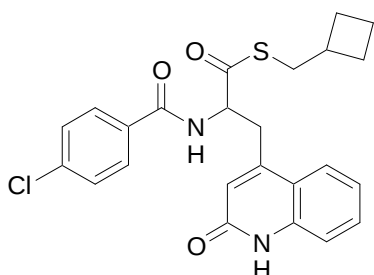


According to Experiment Prototocol C, 2.0 g(5.17 mmol) of 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionic acid and 0.70 g(1.5 eq, 7.76 mmol) of (chloromethyl)cyclopropane were reacted to afford the title compound as a white solid (1.1 g).

¹H NMR (400MHz, DMSO-d₆):δ 11.66(s, 1H), 9.24(d, 1H), 7.88-7.84(m, 2H), 7.80(d, 1H), 7.61-7.58(m, 2H), 7.53-7.49(m, 1H), 7.30(dd, 1H), 7.26-7.22(m, 1H), 6.43(s, 1H), 4.95(m, 1H),

3.54(dd, 1H), 3.20(q, 2H), 0.98-0.94(m, 1H), 0.53-0.48(m, 2H), 0.25-0.24(m, 2H)

EXAMPLE 139: Preparation of S-Cyclobutylmethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate

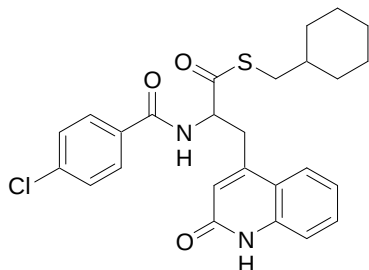


According to Experiment Prototocol C, 2.0 g(5.17 mmol) of 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionic acid and 1.12 g(1.5 eq, 7.76 mmol) of (bromomethyl)cyclobutane were reacted to afford the title compound as a white solid (1.4 g).

¹H NMR (400MHz, DMSO-d₆):δ 11.66(s, 1H), 9.23(d, 1H), 7.86-7.82(m, 2H), 7.79(d, 1H), 7.60-7.55(m, 2H), 7.53-7.49(m, 1H), 7.35-7.30(m, 1H), 7.26-7.20(m, 1H), 6.51(s, 1H), 4.95-4.90(m, 1H), 3.51(dd, 1H), 3.20(q, 1H), 2.89(d, 2H), 2.46-2.38(m, 1H), 2.03-1.96(m, 2H), 1.83-1.71(m, 2H), 1.68-1.66(m, 2H)

EXAMPLE 140: Preparation of S-Cyclohexylmethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-

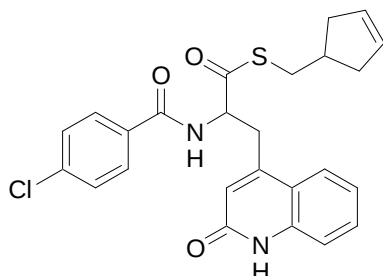
yl)thiopropionate



According to Experiment Prototocol C, 2.0 g(5.17 mmol) of 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionic acid and 1.37 g(1.5 eq, 7.76 mmol) of (bromomethyl)cyclohexane were reacted to afford the title compound as a white solid (1.3 g).

^1H NMR (400MHz, DMSO-d_6): δ 11.66(s, 1H), 9.22(d, 1H), 7.86-7.82(m, 2H), 7.79(d, 1H), 7.62-7.58(m, 2H), 7.51(t, 1H), 7.30(d, 1H), 7.24(t, 1H), 6.43(s, 1H), 4.97-4.91(m, 1H), 3.52(dd, 1H), 3.20(q, 1H), 2.78(d, 2H), 1.67(t, 4H), 1.41(d, 1H), 1.40-1.34(m, 3H), 1.22-1.16(m, 2H)

EXAMPLE 141: Preparation of S-(Cyclopent-3-enyl)methyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate

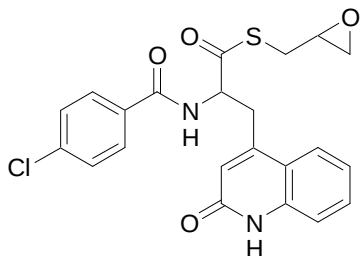


According to Experiment Prototocol D, 2.0 g(5.17 mmol) of

2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionic acid and 1.96 g(1.5 eq, 7.76 mmol) of (cyclopent-3-enyl)methyl toluenesulfonate were reacted to afford the title compound as a white solid (0.7 g).

¹H NMR (400MHz, DMSO-d₆):δ 11.38(s, 1H), 9.24(d, 1H), 7.86-7.84(m, 2H), 7.79(d, 1H), 7.64-7.62(m, 2H), 7.50(t, 1H), 7.32(d, 1H), 7.24(t, 1H), 6.50(s, 1H), 5.63(s, 2H), 4.95-4.93(m, 1H), 3.52(dd, 1H), 3.21(q, 1H), 2.93(d, 2H), 2.46-2.43(m, 3H), 2.00(dd, 2H)

EXAMPLE 142: Preparation of S-Oxiranylmethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate

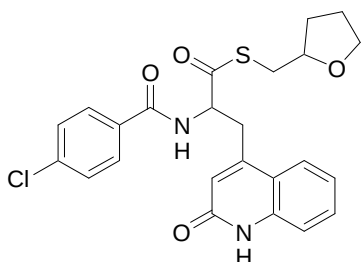


According to Experiment Prototocol C, 2.0 g(5.17 mmol) of 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionic acid and 0.72 g(1.5 eq, 7.76 mmol) of 2-(chloromethyl)oxirane were reacted to afford the title compound as a white solid (1.0 g).

¹H NMR (400MHz, DMSO-d₆):δ 11.67(s, 1H), 9.06(d, 1H), 7.83-7.72(m, 3H), 7.57-7.41(m, 3H), 7.31(dd, 1H), 7.24-7.20(m,

1H), 6.46(s, 1H), 5.24-5.20(m, 1H), 4.96(m, 1H), 4.81-4.76(m, 1H), 3.87-3.84(m, 2H), 3.45(dd, 1H), 2.86(q, 2H)

EXAMPLE 143: Preparation of S-(Tetrahydrofuran-2-yl)methyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate

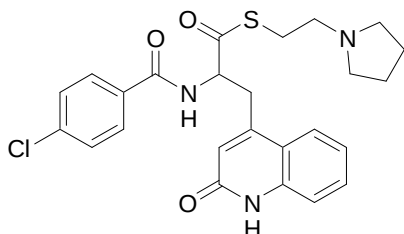


According to Experiment Prototocol C, 2.0 g(5.17 mmol) of 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionic acid and 0.94 g(1.5 eq, 7.76 mmol) of tetrahydrofurfuryl chloride were reacted to afford the title compound as a white solid (1.3 g).

¹H NMR (400MHz, DMSO-d₆): δ 11.65(s, 1H), 9.25(d, 1H), 7.86(s, 1H), 7.84(s, 1H), 7.79(d, 1H), 7.64(s, 1H), 7.61(s, 1H), 7.51(t, 1H), 7.30(d, 1H), 7.24(t, 1H), 6.43(s, 1H), 4.97-4.92(m, 1H), 3.89(s, 1H), 3.77(t, 1H), 3.61(t, 1H), 3.52(dd, 1H), 3.18(q, 2H), 3.09-2.98(m, 2H), 1.97-1.89(m, 1H), 1.87-1.78(m, 2H), 1.54-1.48(m, 1H)

EXAMPLE 144: Preparation of S-(2-Pyrrolidin-1-yl)ethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-

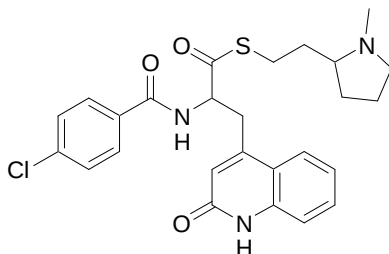
yl)thiopropionate



According to Experiment Prototocol D, 2.0 g(5.17 mmol) of 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionic acid and 1.50 g(1.5 eq, 7.76 mmol) of 2-pyrrolidine ethylmethanesulfonate were reacted to afford the title compound as a white solid (0.6 g).

¹H NMR (400MHz, DMSO-d₆): δ 11.65(s, 1H), 9.25(d, 1H), 7.87(s, 1H), 7.85(s, 1H), 7.81(t, 1H), 7.61(s, 1H), 7.60(s, 1H), 7.58-7.47(m, 1H), 7.30(d, 1H), 7.23(t, 1H), 6.43(s, 1H), 4.96-4.91(m, 1H), 3.53(dd, 1H), 3.21(q, 2H), 3.01(t, 2H), 2.62-2.50(m, 6H), 1.68(s, 4H)

EXAMPLE 145: Preparation of S-[2-(1-Methylpyrrolidin-2-yl)]ethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate

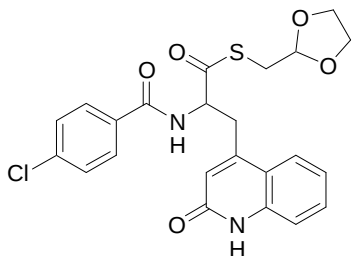


According to Experiment Prototocol D, 2.0 g(5.17 mmol) of

2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionic acid and 1.61 g(1.5 eq, 7.76 mmol) of 1-methyl-2-pyrrolidine ethylmethanesulfonate were reacted to afford the title compound as a white solid (0.4 g).

¹H NMR (400MHz, DMSO-d₆):δ 11.64(s, 1H), 9.22(d, 1H), 7.86(s, 1H), 7.84(d, 1H), 7.81(t, 1H), 7.59(d, 1H), 7.58(d, 1H), 7.52-7.48(m, 1H), 7.35-7.30(m, 1H), 7.25-7.18(t, 1H), 6.43(s, 1H), 4.93(m, 1H), 3.52(dd, 1H), 3.20(q, 2H), 2.94-2.80(m, 2H), 2.19(s, 3H), 2.09-2.05(m, 2H), 1.90-1.85(m, 1H), 1.77-1.75(m, 1H), 1.64-1.58(m, 2H), 1.50-1.45(m, 2H)

EXAMPLE 146: Preparation of S-([1,3]-Dioxolan-2-yl)methyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate

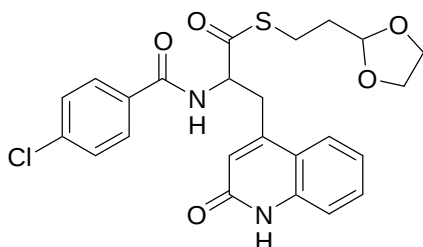


According to Experiment Prototocol C, 2.0 g(5.17 mmol) of 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionic acid and 1.30 g(1.5 eq, 7.76 mmol) of 2-bromomethyl-1,3-dioxolane were reacted to afford the title compound as a white solid (0.8 g).

¹H NMR (400MHz, DMSO-d₆):δ 11.65(s, 1H), 9.27(d, 1H),

7.86(s, 1H), 7.84(s, 1H), 7.68(d, 1H), 7.61(s, 1H), 7.59(s, 1H), 7.53-7.48(m, 1H), 7.32(d, 1H), 7.24(t, 1H), 6.43(s, 1H), 4.97-4.95(m, 1H), 4.33(s, 1H), 3.92-3.89(m, 2H), 3.82-3.78(m, 2H), 3.53(dd, 1H), 3.21(q, 2H), 3.13(d, 2H)

EXAMPLE 147: Preparation of S-(2-[1,3]-Dioxolan-2-yl)ethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate

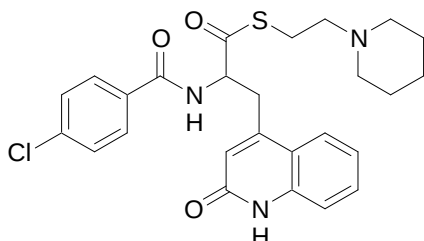


According to Experiment Prototocol C, 2.0 g(5.17 mmol) of 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionic acid and 1.40 g(1.5 eq, 7.76 mmol) of 2-(2-bromoethyl)-1,3-dioxolane were reacted to afford the title compound as a white solid (0.8 g).

¹H NMR (400MHz, DMSO-d₆): δ 11.65(s, 1H), 9.23(d, 1H), 7.86-7.80(m, 3H), 7.61-7.55(m, 2H), 7.53-7.49(m, 1H), 7.31(dd, 1H), 7.25-7.21(m, 1H), 6.43(s, 1H), 4.93-4.91(m, 1H), 4.84(t, 1H), 3.91-3.85(m, 2H), 3.79-3.74(m, 2H), 3.53(dd, 1H), 3.20(q, 2H), 2.91(t, 2H), 1.86-1.82(m, 2H)

EXAMPLE 148: Preparation of S-(2-Piperidin-1-yl)ethyl 2-

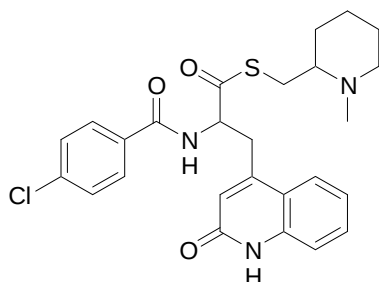
(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate



According to Experiment Prototocol D, 2.0 g(5.17 mmol) of 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionic acid and 1.43 g(1.5 eq, 7.76 mmol) of 1-(2-chloroethyl)piperidine HCl were reacted to afford the title compound as a white solid (0.9 g).

^1H NMR (400MHz, DMSO-d_6): δ 11.64(s, 1H), 9.27(d, 1H), 7.87-7.79(m, 3H), 7.58-7.48(m, 3H), 7.31(d, 1H), 7.21(t, 1H), 6.45(s, 1H), 4.93(m, 1H), 3.52(dd, 1H), 3.21(q, 2H), 3.05(t, 2H), 2.74-2.67(m, 2H), 2.54(br-s, 4H), 1.52-1.44(m, 4H), 1.39-1.34(m, 2H)

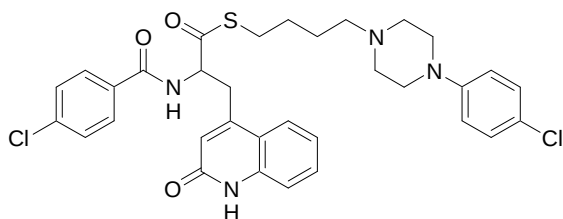
EXAMPLE 149: Preparation of S-(1-Methylpiperidin-2-yl)methyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate



According to Experiment Prototocol D, 2.0 g(5.17 mmol) of 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionic acid and 1.61 g(1.5 eq, 7.76 mmol) of 1-methyl-2-piperidinemethyl methanesulfonate were reacted to afford the title compound as a white solid (0.4 g).

^1H NMR (400MHz, DMSO-d_6): δ 11.64(s, 1H), 9.24(d, 1H), 7.87(s, 1H), 7.85(s, 1H), 7.81(t, 1H), 7.62(s, 1H), 7.61(s, 1H), 7.51(t, 1H), 7.30(d, 1H), 7.24(t, 1H), 6.43(s, 1H), 4.95-4.92(m, 1H), 3.52(dd, 1H), 3.32(br-s, 2H), 3.21(q, 2H), 3.13-3.06(m, 1H), 2.74-2.71(m, 1H), 2.15-2.02(m, 4H), 2.02-1.97(m, 1H), 1.65-1.47(m, 4H), 1.24-1.16(m, 2H)

EXAMPLE 150: Preparation of S-{4-[4-(4-Chlorophenyl)piperazin-1-yl]-butyl} 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate

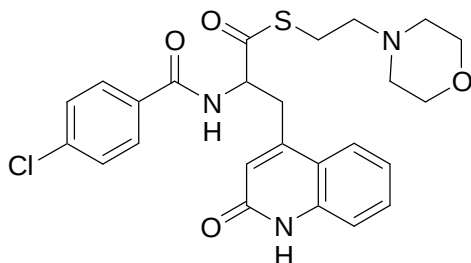


According to Experiment Prototocol C, 2.0 g (5.17 mmol)

of 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionic acid and 2.57 g(1.5 eq, 7.76 mmol) of [4-(4-chlorophenyl)piperazin-1-yl]butyl bromide were reacted to afford the title compound as a white solid (0.7 g).

^1H NMR (400MHz, DMSO- d_6): δ 11.67(s, 1H), 9.24(d, 1H), 7.86(s, 1H), 7.84(s, 1H), 7.80(d, 1H), 7.59(s, 1H), 7.57(s, 1H), 7.51(t, 1H), 7.30(d, 1H), 7.25-7.18(m, 2H), 6.92(s, 1H), 6.86(d, 1H), 6.77(d, 1H), 6.43(s, 1H), 4.96-4.90(m, 1H), 3.53(dd, 3H), 3.21(q, 1H), 3.14(br-s, 4H), 2.91(t, 2H), 2.33(br-s, 2H), 1.73(br-s, 2H)

EXAMPLE 151: Preparation of S-(2-Morpholin-4-yl)ethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate

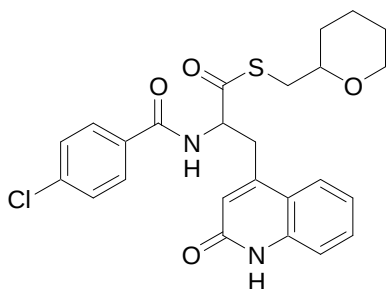


According to Experiment Prototocol C, 2.0 g(5.17 mmol) of 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionic acid and 1.44 g(1.5 eq, 7.76 mmol) of 4-(2-chloroethyl)morpholine HCl were reacted to afford the title compound as a white solid (0.9 g).

^1H NMR (400MHz, DMSO- d_6): δ 11.65(s, 1H), 9.24(d, 1H),

7.87(t, 1H), 7.84(t, 1H), 7.79(d, 1H), 7.60(t, 1H), 7.58(t, 1H), 7.53-7.49(m, 1H), 7.30(dd, 1H), 7.26-7.22(m, 1H), 6.43(s, 1H), 4.96-4.90(m, 1H), 3.56-3.51(m, 3H), 3.32(s, 2H), 3.21(q, 1H), 2.12(t, 2H), 2.53(t, 2H), 2.39(br-s, 4H)

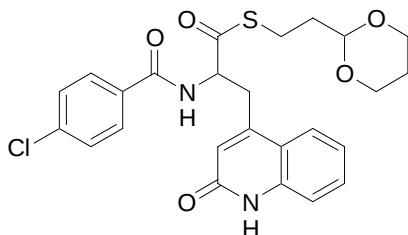
EXAMPLE 152: Preparation of S-(Tetrahydropyran 2-yl)methyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate



According to Experiment Prototocol C, 2.0 g(5.17 mmol) of 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionic acid and 1.04 g(1.5 eq, 7.76 mmol) of 2-(chloromethyl)tetrahydro-2H-pyran were reacted to afford the title compound as a white solid (0.9 g).

^1H NMR (400MHz, DMSO- d_6): δ 11.65(s, 1H), 9.25(dd, 1H), 7.87(s, 1H), 7.85(s, 1H), 7.79(d, 1H), 7.61(t, 1H), 7.59(t, 1H), 7.54-7.49(m, 1H), 7.29(d, 1H), 7.24(t, 1H), 6.43(s, 1H), 4.97-4.92(m, 1H), 3.84-2.81(m, 1H), 3.53(dd, 1H), 3.33-3.28(m, 2H), 3.21(q, 2H), 3.06-3.00(m, 1H), 2.94-2.86(m, 1H), 1.74(br-d, 1H), 1.60(d, 1H), 1.45-1.40(m, 3H), 1.23-1.16(m, 1H)

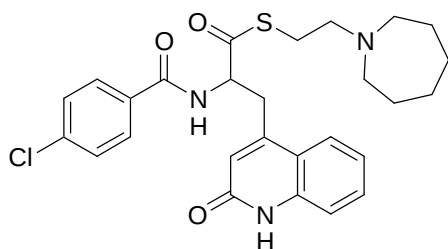
EXAMPLE 153: Preparation of S-(2-[1,3]Dioxan-2-yl)ethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate



According to Experiment Prototocol C, 2.0 g(5.17 mmol) of 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionic acid and 1.51 g(1.5 eq, 7.76 mmol) of 2-(2-bromoethyl)-1,3-dioxane were reacted to afford the title compound as a white solid (0.8 g).

^1H NMR (400MHz, DMSO-d_6): δ 11.65(s, 1H), 9.23(d, 1H), 7.85(d, 1H), 7.83(d, 1H), 7.79(d, 1H), 7.59(s, 1H), 7.58(s, 1H), 7.53-7.49(m, 1H), 7.30(d, 1H), 7.23(t, 1H), 6.42(s, 1H), 4.93-4.92(m, 1H), 4.56(t, 1H), 4.04-3.97(m, 2H), 3.72-3.66(m, 2H), 3.52(dd, 1H), 2.91-2.87(m, 2H), 1.87-1.72(m, 4H)

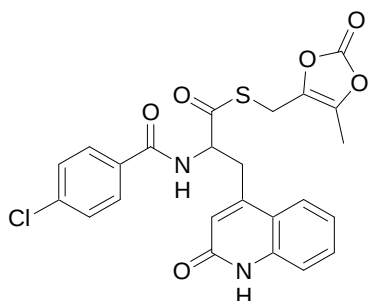
EXAMPLE 154: Preparation of S-(2-Azepan-1-yl)ethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate



According to Experiment Prototocol C, 2.0 g(5.17 mmol) of 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionic acid and 1.54 g(1.5 eq, 7.76 mmol) of 2-(hexamethyleneimino)ethyl chloride HCl were reacted to afford the title compound as a white solid (0.7 g).

^1H NMR (400MHz, DMSO-d_6): δ 11.65(s, 1H), 9.24(d, 1H), 7.87(s, 1H), 7.84(s, 1H), 7.79(d, 1H), 7.60(s, 1H), 7.58(s, 1H), 7.51(t, 1H), 7.31(d, 1H), 7.23(t, 1H), 6.43(s, 1H), 4.95-4.90(m, 1H), 3.52(dd, 1H), 3.21(q, 2H), 2.98(t, 2H), 2.67-2.62(m, 6H), 1.56-1.51(d, 8H)

EXAMPLE 155: Preparation of S-(5-Methyl-2-oxo-[1,3]dioxol-4-yl)methyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate

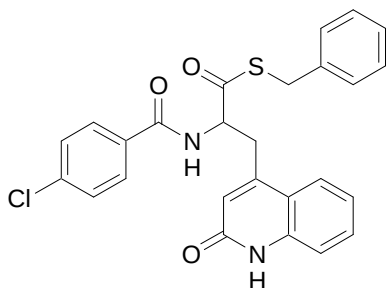


According to Experiment Prototocol C, 2.0 g(5.17 mmol) of

2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionic acid and 1.15 g(1.5 eq, 7.76 mmol) of 4-chloromethyl-5-methyl-1,3-dioxol-2-one were reacted to afford the title compound as a white solid (0.6 g).

¹H NMR (400MHz, DMSO-d₆):δ 11.65(s, 1H), 9.29(d, 1H), 7.85(s, 1H), 7.83(s, 1H), 7.78(d, 1H), 7.60(s, 1H), 7.58(s, 1H), 7.50(t, 1H), 7.30(d, 1H), 7.22(t, 1H), 6.41(s, 1H), 5.03-4.98(m, 1H), 4.06(s, 2H), 3.55(dd, 1H), 3.22(q, 1H), 2.15(s, 3H)

EXAMPLE 156: Preparation of S-Benzyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate

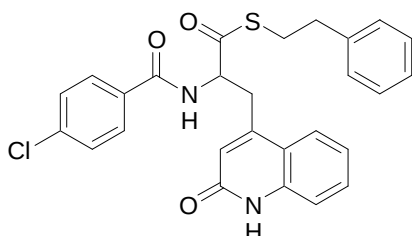


According to Experiment Prototocol C, 2.0 g(5.17 mmol) of 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionic acid and 1.33 g(1.5 eq, 7.76 mmol) of benzyl bromide were reacted to afford the title compound as a white solid (1.3 g).

¹H NMR (400MHz, DMSO-d₆):δ 11.67(s, 1H), 9.26(d, 1H),

7.84-7.80(m, 3H), 7.59-7.55(m, 2H), 7.51(t, 1H), 7.35-7.29(m, 5H), 7.28-7.22(m, 2H), 6.42(s, 1H), 5.02-4.96(m, 1H), 4.15(q, 2H), 3.56(dd, 1H), 3.20(q, 2H)

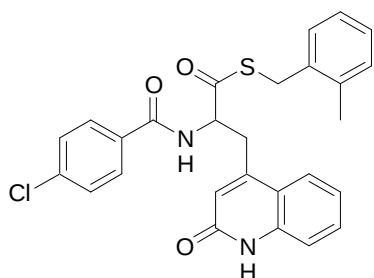
EXAMPLE 157: Preparation of S-Phenethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate



According to Experiment Prototocol C, 2.0 g (5.17 mmol) of 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionic acid and 1.43 g (1.5 eq, 7.76 mmol) of phenethyl bromide were reacted to afford the title compound as a white solid (1.2 g).

^1H NMR (400MHz, DMSO-d_6): δ 11.67(s, 1H), 9.24(d, 1H), 7.85-7.79(m, 3H), 7.62-7.49(m, 4H), 7.33-7.16(m, 6H), 6.43(s, 1H), 4.96-4.87(m, 1H), 4.34(s, 1H), 3.50(dd, 1H), 3.21(q, 2H), 3.13(t, 1H), 2.90-2.73(m, 2H)

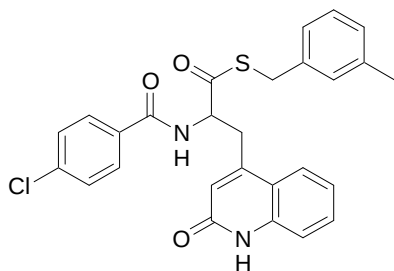
EXAMPLE 158: Preparation of S-(2-Methylbenzyl) 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate



According to Experiment Prototocol C, 2.0 g(5.17 mmol) of 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionic acid and 1.44 g(1.5 eq, 7.76 mmol) of 2-methylbenzyl bromide were reacted to afford the title compound as a white solid (1.2 g).

^1H NMR (400MHz, DMSO-d_6): δ 11.65(s, 1H), 9.23(d, 1H), 7.83-7.79(m, 3H), 7.58-7.54(m, 2H), 7.51(t, 1H), 7.30(t, 2H), 7.26-7.19(m, 1H), 7.17-7.12(m, 3H), 6.42(s, 1H), 5.02-4.96(m, 1H), 4.16(q, 2H), 3.56(dd, 1H), 3.21(q, 2H), 2.27(s, 3H)

EXAMPLE 159: Preparation of S-(3-Methylbenzyl) 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate

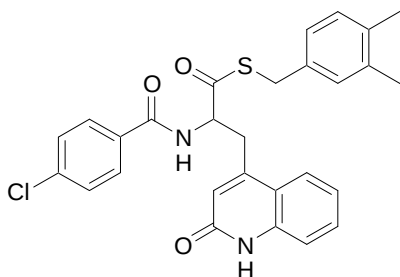


According to Experiment Prototocol C, 2.0 g(5.17 mmol) of 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionic acid and 1.44 g(1.5 eq, 7.76 mmol) of 3-

methylbenzyl bromide were reacted to afford the title compound as a white solid (1.2 g).

¹H NMR (400MHz, DMSO-d₆): δ 11.65(s, 1H), 9.24(d, 1H), 7.83-7.80(m, 3H), 7.58-7.55(m, 2H), 7.51(t, 1H), 7.30(d, 1H), 7.25-7.18(m, 2H), 7.12-7.05(m, 3H), 6.43(s, 1H), 5.02-4.96(m, 1H), 4.11(q, 2H), 3.56(dd, 1H), 3.20(q, 2H), 2.27(s, 3H)

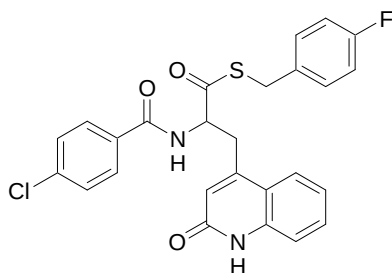
EXAMPLE 160: Preparation of S-(3,4-Dimethylbenzyl) 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate



According to Experiment Prototocol C, 2.0 g(5.17 mmol) of 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionic acid and 1.20 g(1.5 eq, 7.76 mmol) of 3,4-dimethylbenzyl chloride were reacted to afford the title compound as a white solid (0.9 g).

¹H NMR (400MHz, DMSO-d₆): δ 11.65(s, 1H), 9.23(d, 1H), 7.87-7.79(m, 3H), 7.58-7.55(m, 2H), 7.51(t, 1H), 7.30(d, 1H), 7.24(t, 1H), 7.13(d, 1H), 7.08-7.02(m, 2H), 6.42(s, 1H), 5.00-4.96(m, 1H), 4.17(d, 1H), 4.08(d, 1H), 3.56(d, 1H), 3.20(t, 1H), 2.22-2.09(m, 6H)

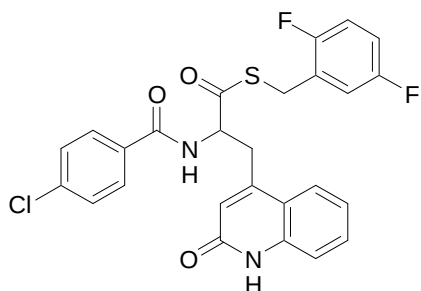
EXAMPLE 161: Preparation of S-(4-Fluorobenzyl) 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate



According to Experiment Prototocol C, 2.0 g(5.17 mmol) of 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionic acid and 1.47 g(1.5 eq, 7.76 mmol) of 4-fluorobenzyl bromide were reacted to afford the title compound as a white solid (1.1 g).

^1H NMR (400MHz, DMSO- d_6): δ 11.64(s, 1H), 9.25(d, 1H), 7.84-7.72(m, 3H), 7.74-7.72(m, 2H), 7.68-7.64(q, 1H), 7.59-7.48(m, 4H), 7.33-7.30(m, 1H), 7.24-7.19(m, 1H), 6.41(s, 1H), 5.03-4.97(m, 1H), 4.21(d, 2H), 3.55(dd, 1H), 3.21(q, 2H)

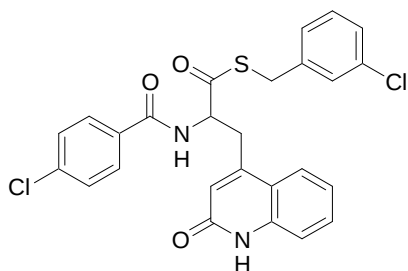
EXAMPLE 162: Preparation of S-(2,5-Difluorobenzyl) 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate



According to Experiment Prototocol C, 2.0 g(5.17 mmol) of 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionic acid and 1.61 g(1.5 eq, 7.76 mmol) of 2,5-difluorobenzyl bromide were reacted to afford the title compound as a white solid (0.9 g).

^1H NMR (400MHz, DMSO-d_6): δ 11.64(s, 1H), 9.26(d, 1H), 7.84-7.79(m, 3H), 7.59-7.55(m, 1H), 7.52-7.48(m, 1H), 7.35-7.15(m, 5H), 6.41(s, 1H), 5.03-4.97(m, 1H), 4.16(q, 2H), 3.56(dd, 1H), 3.20(q, 1H)

EXAMPLE 163: Preparation of S-(3-Chlorobenzyl) 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate

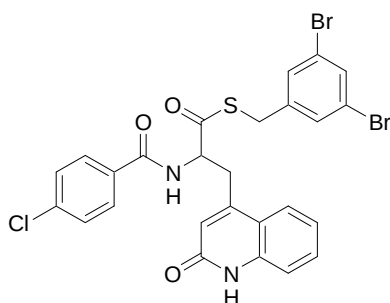


According to Experiment Prototocol C, 2.0 g (5.17 mmol) of 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-

yl)thiopropionic acid and 1.59 g (1.5 eq, 7.76 mmol) of 3-chlorobenzyl bromide were reacted to afford the title compound as a white solid (1.5 g).

¹H NMR (400MHz, DMSO-d₆): δ 11.65(s, 1H), 9.26(d, 1H), 7.84-7.79(m, 3H), 7.59(s, 1H), 7.56(s, 1H), 7.50(t, 1H), 7.40(s, 1H), 7.38-7.28(m, 4H), 7.23(t, 1H), 6.42(s, 1H), 5.00(m, 1H), 4.16(d, 2H), 3.56(dd, 1H), 3.20(q, 1H)

EXAMPLE 164: Preparation of S-(3,5-Dibromobenzyl) 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate

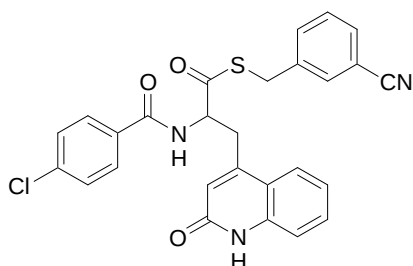


According to Experiment Prototocol C, 2.0 g (5.17 mmol) of 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionic acid and 2.55 g (1.5 eq, 7.76 mmol) of 3,5-dibromobenzyl bromide were reacted to afford the title compound as a white solid (1.5 g).

¹H NMR (400MHz, DMSO-d₆): δ 11.65(s, 1H), 9.26(d, 1H), 7.84-7.78(m, 4H), 7.59-7.55(m, 4H), 7.50(t, 1H), 7.31(t, 1H), 7.22(t, 1H), 6.42(s, 1H), 5.02-4.97(m, 1H), 4.14(q, 2H),

3.56(dd, 1H), 3.20(q, 1H)

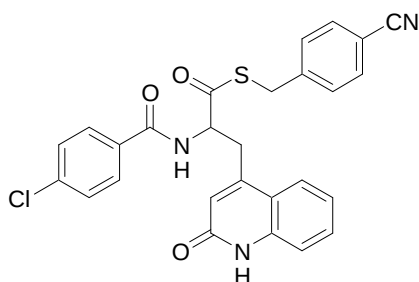
EXAMPLE 165: Preparation of S-(3-Cyanobenzyl) 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate



According to Experiment Prototocol C, 2.0 g(5.17 mmol) of 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionic acid and 1.28 g(1.5 eq, 7.76 mmol) of 3-cyanobenzyl chloride were reacted to afford the title compound as a white solid (0.9 g).

^1H NMR (400MHz, DMSO- d_6): δ 11.64(s, 1H), 9.24(d, 1H), 7.84-7.79(m, 3H), 7.59-7.55(m, 2H), 7.53-7.49(m, 1H), 7.38-7.30(m, 3H), 7.25(t, 1H), 7.21-7.12(m, 2H), 6.42(s, 1H), 5.00-4.96(m, 1H), 4.15(d, 2H), 3.55(dd, 1H), 3.20(q, 2H)

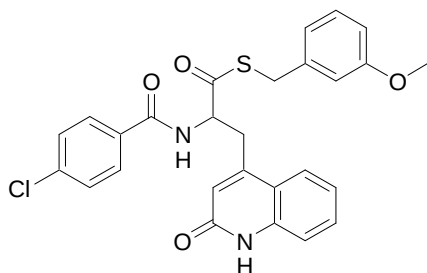
EXAMPLE 166: Preparation of S-(4-Cyanobenzyl)2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate



According to Experiment Prototocol C, 2.0 g (5.17 mmol) of 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionic acid and 1.28 g (1.5 eq, 7.76 mmol) of 4-cyanobenzyl chloride were reacted to afford the title compound as a white solid (1.0 g).

^1H NMR (400MHz, DMSO-d_6): δ 11.65(s, 1H), 9.27(d, 1H), 7.84-7.78(m, 5H), 7.59-7.55(m, 2H), 7.53-7.49(m, 3H), 7.30(d, 1H), 7.22(t, 1H), 6.40(s, 1H), 5.02-4.96(m, 1H), 4.23(s, 2H), 3.54(dd, 1H), 3.21(q, 2H)

EXAMPLE 167: Preparation of S-(3-Methoxybenzyl)2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate

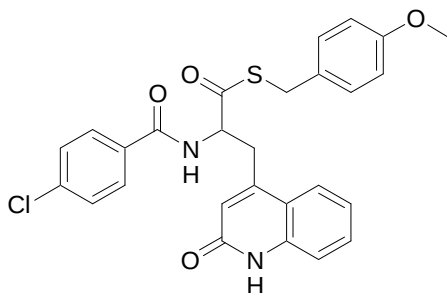


According to Experiment Prototocol C, 2.0 g (5.17 mmol) of 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionic acid and 1.21 g (1.5 eq, 7.76 mmol) of 3-

methoxybenzyl chloride were reacted to afford the title compound as a white solid (1.2 g).

^1H NMR (400MHz, DMSO-d_6): δ 11.66 (s, 1H), 9.25 (d, 1H), 7.83-7.80 (m, 3H), 7.59 (s, 1H), 7.58 (s, 1H), 7.51 (t, 1H), 7.30 (d, 1H), 7.26-7.21 (m, 2H), 6.88 (d, 2H), 6.81 (d, 1H), 6.43 (s, 1H), 5.01-4.97 (m, 1H), 4.13 (q, 2H), 3.71 (s, 3H), 3.50 (dd, 1H), 3.21 (q, 2H)

EXAMPLE 168: Preparation of S-(4-Methoxybenzyl)2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate

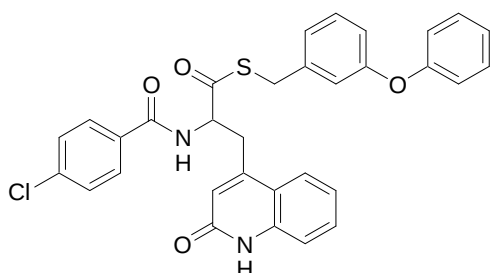


According to Experiment Prototocol C, 2.0 g(5.17 mmol) of 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionic acid and 1.21 g(1.5 eq, 7.76 mmol) of 4-methoxybenzyl chloride were reacted to afford the title compound as a white solid (1.2 g).

^1H NMR (400MHz, DMSO-d_6): δ 11.66 (s, 1H), 9.24 (d, 1H), 7.84-7.79 (m, 3H), 7.59-7.55 (m, 2H), 7.51 (t, 1H), 7.53-7.48 (m, 1H), 7.35-7.30 (m, 1H), 7.25-7.18 (m, 3H), 6.87-6.51 (dd, 2H),

6.42(s, 1H), 5.00-4.94(m, 1H), 4.10(d, 2H), 3.73(s, 3H), 3.56(dd, 1H), 3.19(q, 2H)

EXAMPLE 169: Preparation of S-(3-Phenoxybenzyl) 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate

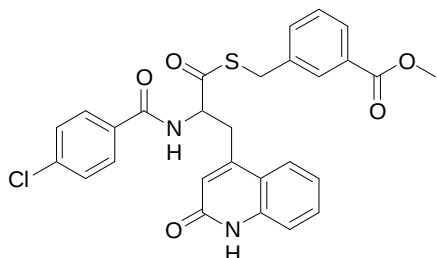


According to Experiment Prototocol C, 2.0 g(5.17 mmol) of 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionic acid and 1.70 g(1.5 eq, 7.76 mmol) of 3-phenoxybenzyl chloride were reacted to afford the title compound as a white solid (1.2 g).

¹H NMR (400MHz, DMSO-d₆): δ 11.66(s, 1H), 9.28(d, 1H), 7.84(t, 1H), 7.82(t, 1H), 7.78(d, 1H), 7.59(t, 1H), 7.56(t, 1H), 7.53-7.48(m, 1H), 7.40-7.36(m, 2H), 7.32(t, 2H), 7.25-7.21(m, 1H), 7.16-7.11(m, 1H), 7.10(t, 1H), 7.02(t, 1H), 6.99(t, 2H), 6.89-6.86(m, 1H), 6.43(s, 1H), 5.01-4.95(m, 1H), 4.14(q, 2H), 3.53(dd, 1H), 3.20(q, 1H)

EXAMPLE 170: Preparation of S-(3-Methoxycarbonyl)benzyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-

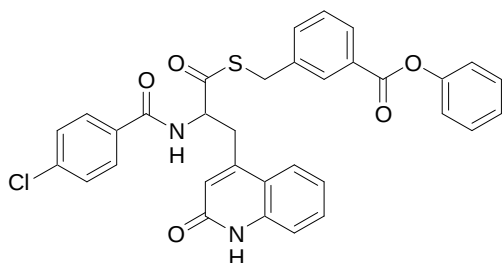
yl)thiopropionate



According to Experiment Prototocol C, 2.0 g(5.17 mmol) of 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionic acid and 1.78 g(1.5 eq, 7.76 mmol) of methyl(3-bromomethyl)benzoate were reacted to afford the title compound as a white solid (0.8 g).

^1H NMR (400MHz, DMSO-d_6): δ 11.64(s, 1H), 9.25(d, 1H), 7.94(t, 1H), 7.86-7.79(m, 4H), 7.64-7.56(m, 3H), 7.54-7.51(m, 2H), 7.32-7.29(m, 1H), 7.25-7.21(m, 1H), 6.41(s, 1H), 5.02-4.96(m, 1H), 4.23(d, 2H), 3.85(s, 3H), 3.55(dd, 1H), 3.32(s, 2H), 3.20(q, 2H)

EXAMPLE 171: Preparation of S-(3-Phenylloxycarbonyl)benzyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate

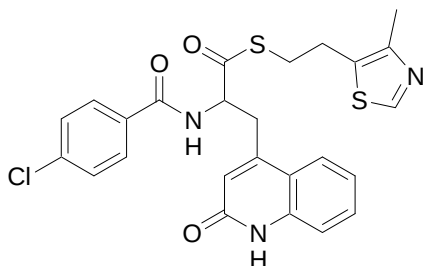


According to Experiment Prototocol A, 2.0 g(5.17 mmol) of

2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionic acid and 1.33 g(1.2 eq, 6.20 mmol) of phenyl 2-hydroxybenzoate were reacted to afford the title compound as a white solid (0.4 g).

¹H NMR (400MHz, DMSO-d₆): δ 11.65(s, 1H), 9.27(d, 1H), 8.11(s, 1H), 8.01(d, 1H), 7.94(t, 1H), 7.84-7.79(m, 3H), 7.69(d, 1H), 7.59-7.55(m, 3H), 7.52-7.46(m, 3H), 7.34-7.28(m, 4H), 7.22(t, 1H), 6.41(s, 1H), 5.02-4.99(m, 1H), 4.29(s, 2H), 3.56(dd, 1H), 3.21(s, 1H)

EXAMPLE 172: Preparation of S-[2-(4-Methylthiazol-5yl)ethyl] 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate

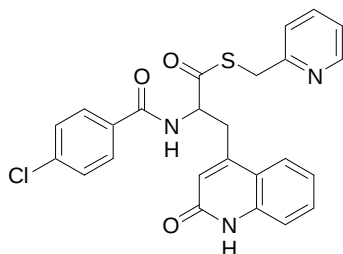


According to Experiment Prototocol B, 2.0 g(5.17 mmol) of 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionic acid and 0.89 g(1.2 eq, 6.20 mmol) of 4-methyl-5-thiazole ethanol were reacted to afford the title compound as a white solid (0.5 g).

¹H NMR (400MHz, DMSO-d₆): δ 11.67(s, 1H), 9.25(d, 1H), 8.84(s, 1H), 7.83(d, 2H), 7.79(d, 1H), 7.64-7.55(m, 2H),

7.51(t, 1H), 7.30(d, 1H), 7.24(t, 1H), 6.43(s, 1H), 4.95-4.90(m, 1H), 3.50(dd, 1H), 3.20(q, 2H), 3.11-2.99(m, 4H), 2.32(s, 3H)

EXAMPLE 173: Preparation of S-(Pyrimidin-2-yl)methyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate

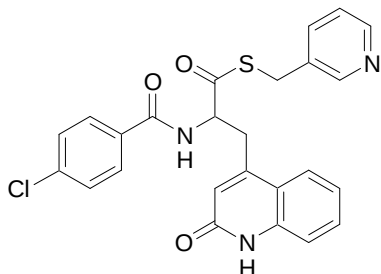


According to Experiment Prototocol C, 2.0 g (5.17 mmol) of 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionic acid and 1.27 g (1.5 eq, 7.76 mmol) of 2-(chloromethyl)pyridine HCl are reacted to afford the title compound as as a white solid (0.8 g).

^1H NMR (400MHz, DMSO- d_6): δ 11.65(s, 1H), 9.28(d, 1H), 8.48(d, 1H), 7.82-7.79(dd, 2H), 7.78-7.74(m, 1H), 7.59(s, 1H), 7.57(s, 1H), 7.51(t, 1H), 7.40(d, 1H), 7.32-7.21(m, 3H), 6.42(s, 1H), 5.02-4.97(m, 1H), 4.26(q, 2H), 3.56(dd, 1H), 3.20(q, 1H)

EXAMPLE 174: Preparation of S-(Pyrimidin-3-yl)methyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-

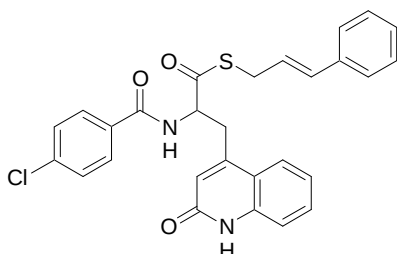
yl)thiopropionate



According to Experiment Prototocol C, 2.0 g(5.17 mmol) of 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionic acid and 1.27 g(1.5 eq, 7.76 mmol) of 3-(chloromethyl)pyridine HCl were reacted to afford the title compound as a white solid (0.9 g).

^1H NMR (400MHz, DMSO- d_6): δ 11.64(s, 1H), 9.25(d, 1H), 8.55(d, 1H), 8.45(dd, 1H), 7.83-7.79(m, 3H), 7.73-7.70(m, 1H), 7.59(s, 1H), 7.56(s, 1H), 7.50(t, 1H), 7.36-7.30(m, 3H), 7.25-7.21(m, 1H), 6.42(s, 1H), 5.02-4.97(m, 1H), 4.18(q, 2H), 3.55(dd, 1H), 3.20(q, 1H)

EXAMPLE 175: Preparation of S-(3-Phenylallyl) 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate

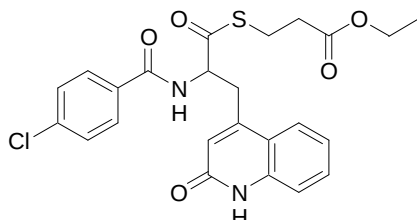


According to Experiment Prototocol C, 2.0 g (5.17 mmol)

of 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionic acid and 1.52 g (1.5 eq, 7.76 mmol) of cinnamyl bromide were reacted to afford the title compound as a white solid (1.3 g).

^1H NMR (400MHz, DMSO- d_6): δ 11.66(s, 1H), 9.26(d, 1H), 7.86-7.80(m, 3H), 7.59(d, 1H), 7.55(d, 1H), 7.51(m, 1H), 7.42-7.40(m, 2H), 7.34-7.31(m, 3H), 7.26-7.21(m, 2H), 6.62(d, 1H), 6.44(s, 1H), 6.28-6.23(m, 1H), 4.99-4.98(m, 1H), 3.74(d, 2H), 3.57(dd, 1H), 3.23(q, 1H)

EXAMPLE 176: Preparation of S-Ethoxy-3-oxopropyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate

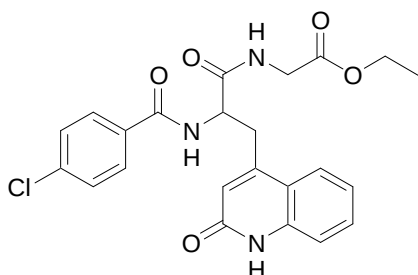


According to Experiment Prototocol C, 2.0 g(5.17 mmol) of 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionic acid and 1.06 g(1.5 eq, 7.76 mmol) of ethyl 3-chloropropionate were reacted to afford the title compound as a white solid (0.7 g).

^1H NMR (400MHz, DMSO- d_6): δ 11.66(s, 1H), 9.24(d, 1H), 7.85-7.82(m, 2H), 7.79(d, 1H), 7.60-7.58(dd, 2H), 7.51(t, 1H), 7.30(d, 1H), 7.23(t, 1H), 6.42(s, 1H), 4.93(m, 1H), 4.06(q,

2H), 3.52(dd, 1H), 3.19(q, 1H), 3.06(t, 2H), 2.61(t, 2H), 1.17(t, 3H)

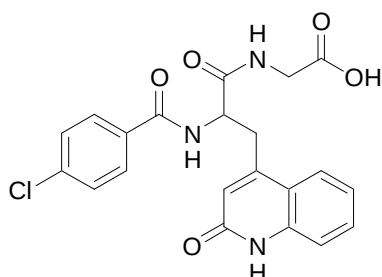
EXAMPLE 177: Preparation of Ethyl [2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionylamino]acetate



According to Experiment Prototocol B, 2.0 g(5.17 mmol) of 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionic acid and 0.87 g(1.2 eq, 6.20 mmol) of glycine ethyl ester HCl were reacted to afford the title compound as a white solid (1.4 g).

¹H NMR (400MHz, DMSO-d₆): δ 11.63(s, 1H), 8.88(d, 1H), 8.67(t, 1H), 7.91(d, 1H), 7.87(t, 1H), 7.85(t, 1H), 7.55(t, 1H), 7.53(t, 1H), 7.49(m, 1H), 7.31(dd, 1H), 7.24(m, 1H), 6.50(s, 1H), 4.89(m, 1H), 4.10(q, 2H), 3.89(t, 2H), 3.44(dd, 1H), 3.16(q, 1H), 1.19(t, 3H)

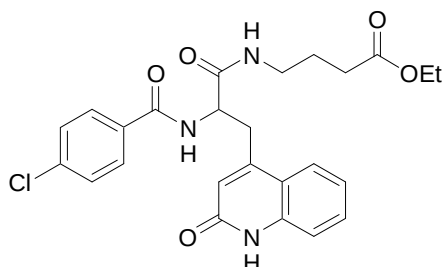
EXAMPLE 178: Preparation of [2-(4-Chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionylamino]acetic acid



To a solution of 1.0 g (2.19 mmol) of ethyl [2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionylamino]acetate in 10 mL of dimethylformamide was added 0.5 mL of trifluoroacetic acid, followed by stirring the solution at room temperature for 30 min. The resulting reaction mixture was added with 20 mL of water, and extracted three times with 20 mL of ethyl acetate. The organic layers thus formed were pooled, dried over anhydrous magnesium sulfate, and concentrated by filtration. The concentrate was crystallized in ethyl acetate to afford the title compound as a pale yellowish solid (0.4 g).

^1H NMR (400MHz, DMSO- d_6): δ 11.61 (s, 1H), 8.86 (d, 1H), 8.49 (t, 1H), 7.92 (d, 1H), 7.87 (s, 1H), 7.85 (s, 1H), 7.55 (s, 1H), 7.53 (s, 1H), 7.50 (t, 1H), 7.29 (d, 1H), 7.23 (t, 1H), 6.49 (s, 1H), 4.89 (m, 1H), 3.79 (d, 2H), 3.46 (dd, 1H), 3.14 (q, 1H)

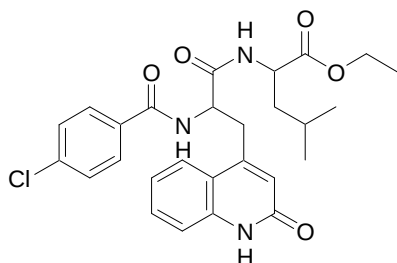
EXAMPLE 179: Preparation of Ethyl 4-[2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionylamino]butyrate



According to Experiment Prototocol B, 2.0 g(5.17 mmol) of 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionic acid and 1.04 g(1.2 eq, 6.20 mmol) of ethyl 4-aminobutyrate HCl were reacted to afford the title compound as a white solid (1.0 g).

^1H NMR (400MHz, DMSO-d_6): δ 11.61(s, 1H), 8.77(d, 1H), 8.23(t, 1H), 7.92(d, 1H), 7.86(t, 1H), 7.85(t, 1H), 7.55(t, 1H), 7.53(t, 1H), 7.48(m, 1H), 7.31(dd, 1H), 7.23(m, 1H), 6.47(s, 1H), 4.78(m, 1H), 4.04(q, 2H), 3.42(dd, 1H), 3.13(m, 3H), 2.29(t, 2H), 1.67(m, 2H), 1.17(t, 3H)

EXAMPLE 180: Preparation of Ethyl 2-[2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionylamino]-4-methyl pentanoate

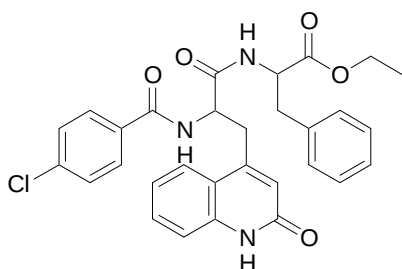


According to Experiment Prototocol B, 2.0 g (5.17 mmol) of 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-

yl)propionic acid and 1.18 g (1.2 eq, 6.20 mmol) of L-leucine ethyl ester HCl were reacted to afford the title compound as a white solid (1.5 g).

^1H NMR (400MHz, DMSO- d_6): δ 11.62 (d, 1H), 8.77 (t, 1H), 8.59 (dd, 1H), 7.94 (t, 1H), 7.85 (t, 2H), 7.54-7.48 (m, 3H), 7.29 (dd, 1H), 7.22 (q, 1H), 6.50 (d, 1H), 4.95-4.92 (m, 1H), 4.34-4.28 (m, 1H), 4.12-4.05 (m, 2H), 3.29 (dd, 1H), 3.18 (t, 1H), 1.68-1.48 (m, 3H), 1.16 (q, 3H), 0.92-0.87 (m, 6H)

EXAMPLE 181: Preparation of ethyl 2-[2-(4-Chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionylamino]-3-phenyl propionate

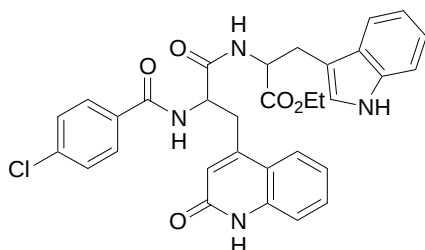


According to Experiment Prototocol B, 2.0 g (5.17 mmol) of 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionic acid and 1.38 g (1.2 eq, 6.20 mmol) of phenylalanine ethyl ester HCl were reacted to afford the title compound as a white solid (1.4 g).

^1H NMR (400MHz, DMSO- d_6): δ 11.61 (d, 1H), 8.75 (dd, 1H), 7.84 (d, 2H), 7.55-7.49 (m, 3H), 7.31-7.14 (m, 8H), 6.46 (s, 1H), 4.91-4.87 (m, 1H), 4.60-4.57 (m, 1H), 4.06 (q, 2H), 3.34 (m, 1H),

3.09(q, 1H), 2.936-2.90(m, 2H), 1.13(t, 3H)

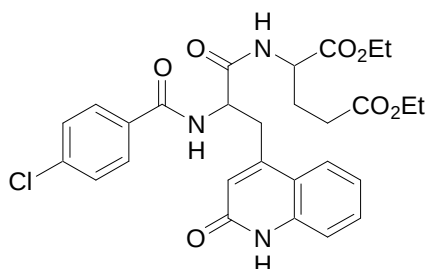
EXAMPLE 182: Preparation of Ethyl 2-[2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionylamino]-3-(1H-indol-3-yl)propionate



According to Experiment Prototocol B, 2.0 g (5.17 mmol) of 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionic acid and 1.67 g (1.2 eq, 6.20 mmol) of L-tryptophan ethyl ester HCl were reacted to afford the title compound as a white solid (1.1 g).

¹H NMR (400MHz, DMSO-d₆): δ 11.60(d, 1H), 9.22(s, 1H), 8.77-8.67(m, 2H), 7.90-7.81(m, 3H), 7.53-7.48(m, 3H), 7.31-7.23(m, 2H), 7.02(t, 2H), 6.62(t, 2H), 6.45(s, 1H), 4.89-4.87(m, 1H), 4.51-4.48(m, 1H), 4.12-4.02(m, 2H), 3.16(dd, 1H), 2.99-2.89(m, 2H), 2.81(q, 1H), 1.16(t, 3H)

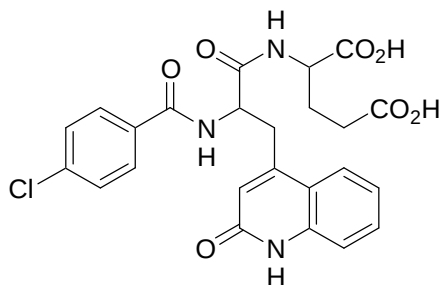
EXAMPLE 183: Preparation of Diethyl 2-[2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionylamino]pentane-1,5-dioate



According to Experiment Prototocol B, 2.0 g(5.17 mmol) of 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionic acid and 1.49 g(1.2 eq, 6.20 mmol) of L-glutamic acid diethylester HCl were reacted to afford the title compound as a white solid (1.2 g).

^1H NMR (400MHz, DMSO-d_6): δ 11.61(d, 1H), 8.79(t, 1H), 8.64(dd, 1H), 7.93(t, 1H), 7.84(m, 2H), 7.50(m, 3H), 7.31(dd, 1H), 7.23(m, 1H), 6.51(s, 1H), 4.92(m, 1H), 4.31(m, 1H), 4.08(m, 4H), 3.38(m, 1H), 3.18(m, 1H), 2.43(t, 1H), 2.35(t, 1H), 2.03(m, 1H), 1.88(m, 1H), 1.18(m, 6H)

EXAMPLE 184: Preparation of Diethyl 2-[2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionylamino]pentane-1,5-dioic acid

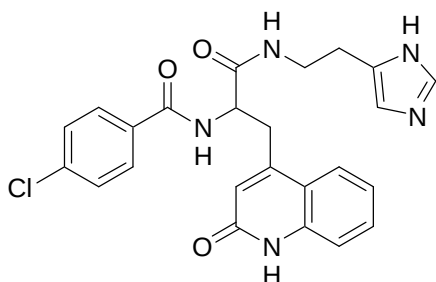


From 1.0 g (1.80 mmol) of diethyl 2-[2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-

yl)propionylamino]pentane-1,5-dioate, the title compound was synthesized as a pale yellow solid in the same manner as in Example 164 (0.4 g).

¹H NMR (400MHz, DMSO-d₆): δ 11.62 (s, 1H), 8.84 (t, 1H), 8.44 (dd, 1H), 7.92 (q, 1H), 7.84 (m, 2H), 7.52 (m, 3H), 7.32 (m, 1H), 7.25 (m, 1H), 6.51 (d, 1H), 4.92 (m, 1H), 4.27 (m, 1H), 4.08 (m, 4H), 3.40 (m, 1H), 3.18 (m, 1H), 2.29 (m, 2H), 2.00 (m, 1H), 1.86 (m, 1H)

EXAMPLE 185: Preparation of 4-Chloro-N-[1-[2-(3H-imidazol-4-yl)ethylcarbamoyl]-2-(2-oxo-1,2-dihydroquinolin-4-yl)ethyl]benzamide

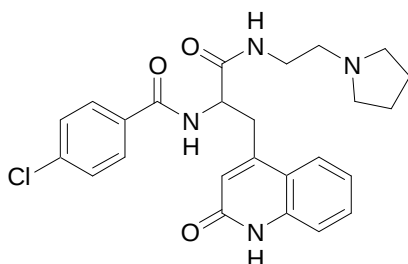


According to Experiment Prototocol B, 2.0 g (5.17 mmol) of 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionic acid and 0.69 g (1.2 eq, 6.20 mmol) of histamine were reacted to afford the title compound as a white solid (0.9 g).

¹H NMR (400MHz, DMSO-d₆): δ 11.64 (d, 1H), 8.83 (d, 1H), 8.729 (t, 1H), 7.93 (d, 1H), 7.86 (d, 2H), 7.71 (s, 2H), 7.55-7.48 (m, 3H), 7.30 (d, 1H), 7.23 (d, 1H), 7.20 (s, 1H), 6.94 (s,

1H), 6.62(t, 2H), 6.48(s, 1H), 4.81-4.75(m, 1H), 3.40(dd, 1H), 3.18(q, 1H), 3.11-3.00(m, 2H), 1.87-1.80(m, 2H)

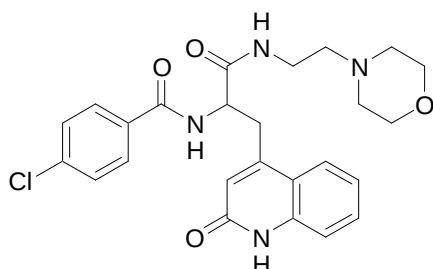
EXAMPLE 186: Preparation of 4-Chloro-N-[2-(2-oxo-1,2-dihydroquinolin-4-yl)-1-(2-pyrrolidin-1-ylethylcarbamoyl)ethyl]benzamide



According to Experiment Prototocol B, 2.0 g(5.17 mmol) of 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionic acid and 0.71 g(1.2 eq, 6.20 mmol)of 1-(2-aminoethyl)pyrrolidine were reacted to afford the title compound as a white solid (0.6 g).

¹H NMR (400MHz, DMSO-d₆):δ 11.63(s, 1H), 8.80(d, 1H), 8.15(t, 1H), 7.91(d, 1H), 7.87(t, 1H), 7.85(t, 1H), 7.55(t, 1H), 7.54(t, 1H), 7.48(t, 1H), 7.29(dd, 1H), 7.24(m, 1H), 6.46(s, 1H), 4.79(m, 1H), 3.41(m, 1H), 3.21(m, 3H), 2.42(m, 6H), 1.64(m, 4H)

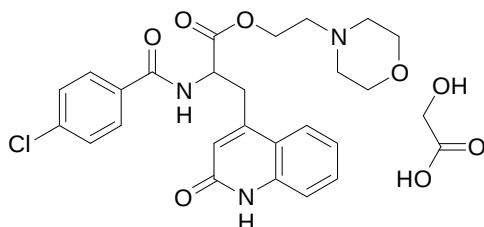
EXAMPLE 187: Preparation of 4-Chloro-N-[1-(2-morpholin-4-yl-ethylcarbamoyl)-2-(2-oxo-1,2-dihydroquinolin-4-yl)ethyl]benzamide



According to Experiment Prototocol B, 2.0 g(5.17 mmol) of 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionic acid and 0.81 g(1.2 eq, 6.20 mmol) of 4-(2-aminoethyl)morpholine were reacted to afford the title compound as a white solid (0.5 g).

^1H NMR (400MHz, DMSO-d_6): δ 11.63(s, 1H), 8.81(d, 1H), 8.09(t, 1H), 7.91(d, 1H), 7.87(t, 1H), 7.86(t, 1H), 7.56(t, 1H), 7.54(t, 1H), 7.48(t, 1H), 7.29(dd, 1H), 7.23(m, 1H), 6.47(s, 1H), 4.78(m, 1H), 3.52(t, 4H), 3.39(m, 1H), 3.19(m, 3H), 2.31(m, 6H)

EXAMPLE 188: Preparation of 2-(Morpholin-4-yl)ethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate glycolate

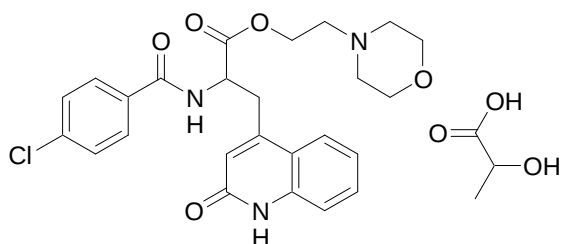


According to Experiment Prototocol E, 1 g(2.07 mmol) of 2-morpholin-4-ylethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-

dihydroquinolin-4-yl)propionate and 0.16 g(2.07 mmol) of glycolic acid were reacted to afford the title compound as a white solid (0.8 g).

¹H NMR (400MHz, DMSO-d₆):δ 11.71(s, 1H), 9.06(d, 1H), 7.83(t, 3H), 7.59(s, 1H), 7.57(s, 1H), 7.52(t, 1H), 7.32(d, 1H), 7.24(t, 1H), 6.47(s, 1H), 4.76(m, 1H), 4.26-4.15(m, 2H), 3.50-3.45(m, 5H), 3.35(s, 2H), 3.29(q, 1H), 2.57-2.47(m, 4H), 2.35(br-s, 4H)

EXAMPLE 189: Preparation of 2-(Morpholin-4-yl)ethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate lactate

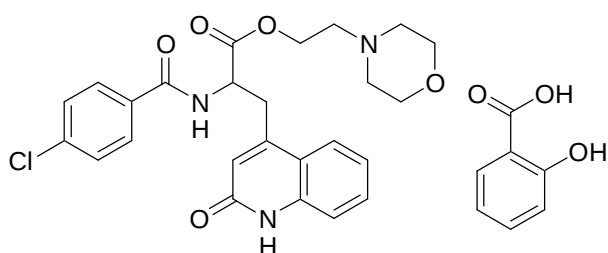


According to Experiment Prototocol E, 1 g(2.07 mmol) of 2-morpholin-4-ylethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate and 0.19 g(2.07 mmol) of lactic acid were reacted to afford the title compound as a white solid (0.9 g).

¹H NMR (400MHz, DMSO-d₆):δ 11.71(s, 1H), 9.06(d, 1H), 7.83(t, 3H), 7.59(s, 1H), 7.57(s, 1H), 7.52(t, 1H), 7.32(d, 1H), 7.24(t, 1H), 6.46(s, 1H), 4.75(m, 1H), 4.27-4.14(m, 2H),

3.50-3.45(m, 2H), 3.35-3.26(m, 5H), 2.58-2.46(m, 5H), 2.35(br-s, 4H)

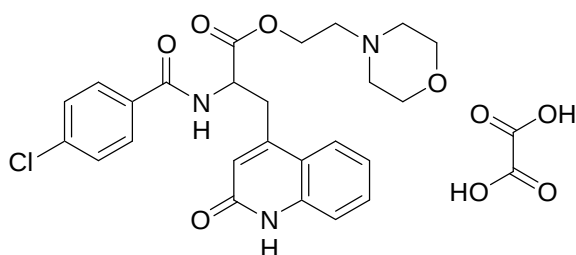
EXAMPLE 190: Preparation of 2-(Morpholin-4-yl)ethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate salicylate



According to Experiment Prototocol E, 1 g(2.07 mmol) of 2-morpholin-4-ylethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate and 0.29 g(2.07 mmol) of salicylic acid were reacted to afford the title compound as a white solid (0.8 g).

¹H NMR (400MHz, DMSO-d₆): δ 11.71(s, 1H), 9.08(d, 1H), 7.83(t, 3H), 7.76(dd, 1H), 7.59(s, 1H), 7.56(s, 1H), 7.52(t, 1H), 7.42(m, 1H), 7.32(d, 1H), 7.23(t, 1H), 6.85(q, 1H), 6.46(s, 1H), 4.78(m, 1H), 4.32-4.21(m, 2H), 3.54-3.47(m, 5H), 3.29(q, 2H), 2.78-2.67(m, 2H), 2.54(br-s, 4H)

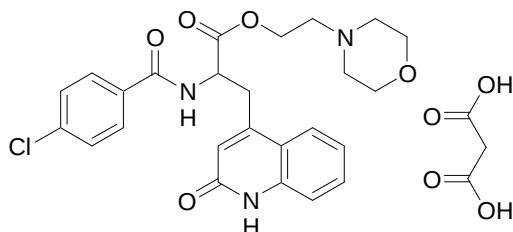
EXAMPLE 191: Preparation of 2-(Morpholin-4-yl)ethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate oxalate



According to Experiment Prototocol E, 1 g(2.07 mmol) of 2-morpholin-4-ylethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate and 0.19 g(2.07 mmol) of oxalic acid were reacted to afford the title compound as a white solid (1.0 g).

^1H NMR (400MHz, DMSO-d_6): δ 11.71(s, 1H), 9.09(d, 1H), 7.83(t, 3H), 7.58(s, 1H), 7.56(s, 1H), 7.52(t, 1H), 7.32(d, 1H), 7.23(t, 1H), 6.46(s, 1H), 4.79(m, 1H), 4.34-4.25(m, 2H), 3.56(t, 4H), 3.49(dd, 1H), 3.29(q, 1H), 2.87-2.78(m, 2H), 2.65(br-s, 4H)

EXAMPLE 192: Preparation of 2-(Morpholin-4-yl)ethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate malonate

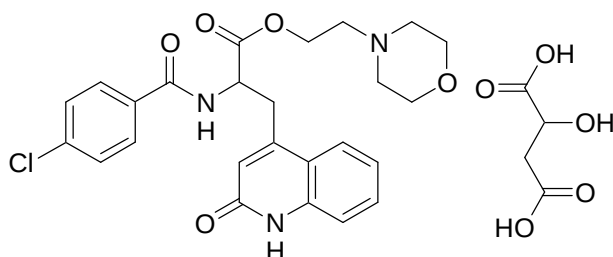


According to Experiment Prototocol E, 1 g(2.07 mmol) of 2-morpholin-4-ylethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-

dihydroquinolin-4-yl)propionate and 0.22 g(2.07 mmol) of malonic acid were reacted to afford the title compound as a white solid (1.1 g).

^1H NMR (400MHz, DMSO-d_6): δ 11.71(s, 1H), 9.06(d, 1H), 7.83(t, 3H), 7.59(s, 1H), 7.56(s, 1H), 7.52(t, 1H), 7.32(d, 1H), 7.24(t, 1H), 6.46(s, 1H), 4.77(m, 1H), 4.24(m, 2H), 3.51-3.46(m, 5H), 3.29(q, 1H), 3.19(s, 2H), 2.70-2.61(m, 2H), 2.51(t, 2H), 2.47(br-s, 4H)

EXAMPLE 193: Preparation of 2-(Morpholin-4-yl)ethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate malate

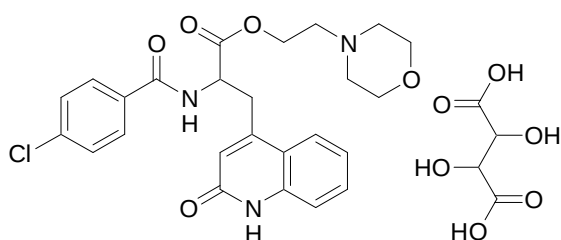


According to Experiment Prototocol E, 1 g(2.07 mmol) of 2-morpholin-4-ylethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate and 0.28 g(2.07 mmol) of malic acid were reacted to afford the title compound as a white solid (0.6 g).

^1H NMR (700MHz, DMSO-d_6): δ 11.70(s, 1H), 9.06(d, 1H), 7.85-7.82(m, 3H), 7.59-7.57(m, 2H), 7.52(t, 1H), 7.32(q, 1H), 7.23(t, 1H), 6.47(s, 1H), 4.78-4.75(m, 1H), 4.26-4.16(m, 3H),

3.49-3.47(m, 5H), 3.29(q, 2H), 2.63-2.51(m, 2H), 2.45-2.38(m, 5H)

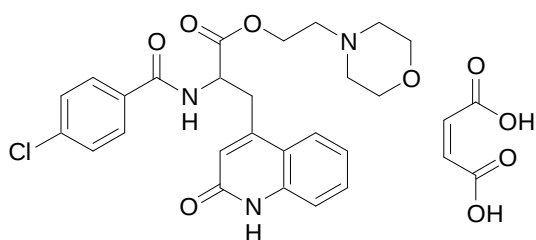
EXAMPLE 194: Preparation of 2-(Morpholin-4-yl)ethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate tartarate



According to Experiment Prototocol E, 1 g(2.07 mmol) of 2-morpholin-4-ylethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate and 0.31 g(2.07 mmol) of tartaric acid were reacted to afford the title compound as a white solid (0.4 g).

^1H NMR (400MHz, DMSO-d_6): δ 11.71(s, 1H), 9.06(d, 1H), 7.83(t, 3H), 7.58(s, 1H), 7.56(s, 1H), 7.52(t, 1H), 7.32(d, 1H), 7.23(t, 1H), 6.47(s, 1H), 4.75(m, 1H), 4.29-4.15(m, 4H), 3.51-3.46(m, 5H), 3.29(q, 1H), 2.60-2.48(m, 2H), 2.37(br-s, 4H)

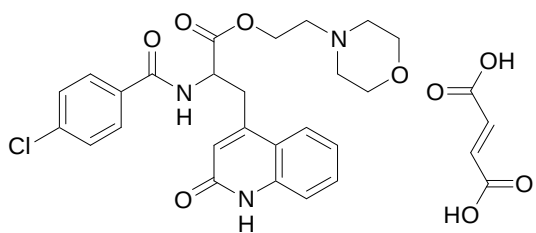
EXAMPLE 195: Preparation of 2-(Morpholin-4-yl)ethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate maleate



According to Experiment Prototocol E, 1 g(2.07 mmol) of 2-morpholin-4-ylethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate and 0.24 g(2.07 mmol) of maleic acid were reacted to afford the title compound as a white solid (0.8 g).

^1H NMR (400MHz, DMSO-d_6): δ 11.71(s, 1H), 9.09(d, 1H), 7.83(m, 3H), 7.59(s, 1H), 7.57(s, 1H), 7.52(t, 1H), 7.32(d, 1H), 7.23(t, 1H), 6.45(s, 1H), 6.11(s, 2H), 4.82(m, 1H), 4.37(m, 2H), 3.65(br-s, 4H), 3.49(dd, 1H), 3.31(q, 1H), 3.14(br-s, 2H), 2.95(br-s, 4H), 2.51(t, 2H)

EXAMPLE 196: Preparation of 2-(Morpholin-4-yl)ethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate fumarate

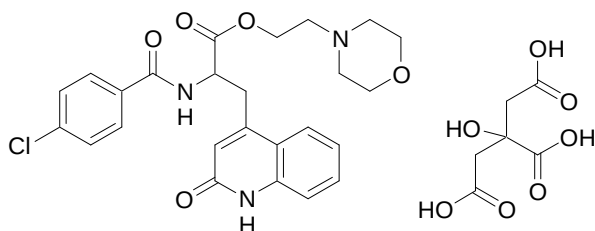


According to Experiment Prototocol E, 1 g(2.07 mmol) of 2-morpholin-4-ylethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate and 0.16 g(2.07 mmol) of

fumaric acid were reacted to afford the title compound as a white solid (0.9 g).

^1H NMR (400MHz, DMSO-d_6): δ 11.71(s, 1H), 9.08(d, 1H), 7.83(m, 3H), 7.59(s, 1H), 7.56(s, 1H), 7.52(t, 1H), 7.32(d, 1H), 7.24(t, 1H), 6.46(s, 1H), 6.12(s, 2H), 4.82(m, 1H), 4.37(m, 2H), 3.65(br-s, 4H), 3.48(dd, 1H), 3.32(q, 1H), 3.15(br-s, 2H), 2.96(br-s, 4H), 2.52(t, 2H)

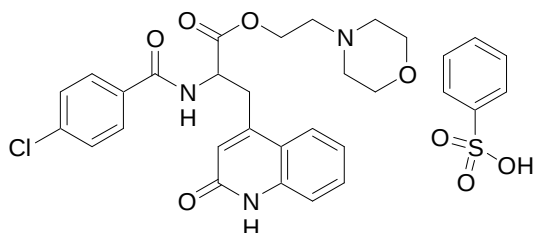
EXAMPLE 197: Preparation of 2-(Morpholin-4-yl)ethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate citrate



According to Experiment Prototocol E, 1 g(2.07 mmol) of 2-morpholin-4-ylethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate and 0.40 g(2.07 mmol) of citric acid were reacted to afford the title compound as a white solid (0.7 g).

^1H NMR (400MHz, DMSO-d_6): δ 11.71(s, 1H), 9.06(d, 1H), 7.83(t, 3H), 7.59(s, 1H), 7.56(s, 1H), 7.52(t, 1H), 7.32(d, 1H), 7.24(t, 1H), 6.47(s, 1H), 4.77(m, 1H), 4.28-4.18(m, 2H), 3.50-3.46(m, 5H), 3.29(q, 1H), 2.65(dd, 2H), 2.64-2.57(m, 2H), 2.51(t, 2H), 2.43(br-s, 4H)

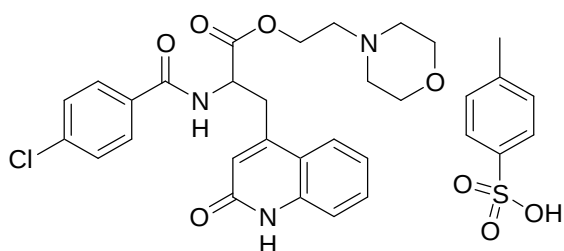
EXAMPLE 198: Preparation of 2-(Morpholin-4-yl)ethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate benzene sulfonate



According to Experiment Prototocol E, 1 g(2.07 mmol) of 2-morpholin-4-ylethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate and 0.33 g(2.07 mmol) of benzenesulfonic acid were reacted to afford the title compound as a white solid (1.0 g).

^1H NMR (700MHz, DMSO- d_6): δ 11.71(s, 1H), 9.80(br-s, 1H), 9.11(d, 1H), 7.84-7.81(m, 3H), 7.62-7.61(m, 2H), 7.60-7.57(m, 2H), 7.52(t, 1H), 7.35-7.30(m, 4H), 7.23(t, 1H), 6.45(s, 1H), 6.11(s, 2H), 4.89-4.85(m, 1H), 4.52-4.42(m, 2H), 3.89(t, 2H), 3.62(t, 2H), 3.54-3.52(m, 3H), 3.44(t, 2H), 3.33(q, 1H), 3.15(br-s, 2H)

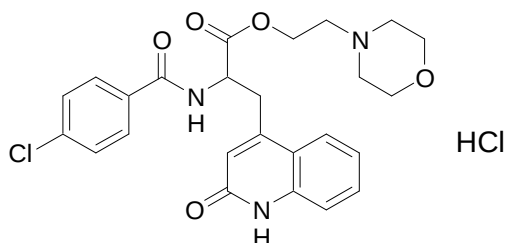
EXAMPLE 199: Preparation of 2-(Morpholin-4-yl)ethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate tosylate



According to Experiment Prototocol E, 1 g(2.07 mmol) of 2-morpholin-4-ylethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate and 0.39 g(2.07 mmol) of toluene sulfonic acid monohydrate were reacted to afford the title compound as a white solid (0.9 g).

^1H NMR (400MHz, DMSO-d_6): δ 11.71(s, 1H), 9.78(br-s, 1H), 9.10(d, 1H), 7.84-7.81(m, 3H), 7.59-7.47(m, 5H), 7.32(d, 1H), 7.23(t, 1H), 7.11(d, 2H), 6.45(s, 1H), 6.11(s, 2H), 4.86(m, 1H), 4.52-4.40(m, 2H), 4.02(m, 2H), 3.62(t, 2H), 3.55-3.29(m, 6H), 3.14(m, 2H), 2.29(s, 3H)

EXAMPLE 200: Preparation of 2-(Morpholin-4-yl)ethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate hydrochlorate

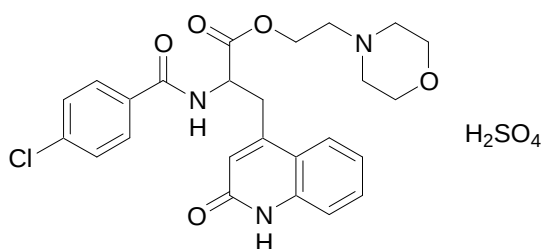


According to Experiment Prototocol E, 1 g(2.07 mmol) of 2-morpholin-4-ylethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-

dihydroquinolin-4-yl)propionate and 0.19 mL(2.07 mmol) of HCl were reacted to afford the title compound as a white solid (0.4 g).

^1H NMR (400MHz, DMSO- d_6): δ 11.69(s, 1H), 11.52(br-s, 1H), 9.24(d, 1H), 7.89-7.86(m, 3H), 7.57(t, 1H), 7.55(t, 1H), 7.51(m, 1H), 7.32(dd, 1H), 7.22(m, 1H), 6.46(s, 1H), 4.93(m, 1H), 4.60-4.47(m, 2H), 3.87-3.82(m, 4H), 3.57(dd, 1H), 3.60-3.33(m, 5H), 3.12(m, 2H)

EXAMPLE 201: Preparation of 2-(Morpholin-4-yl)ethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate sulfate

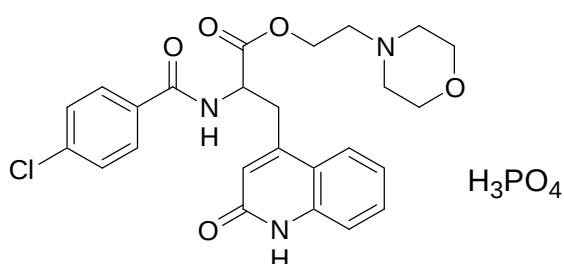


According to Experiment Prototocol E, 1 g(2.07 mmol) of 2-morpholin-4-ylethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate and 0.20 g(2.07 mmol) of sulfuric acid were reacted to afford the title compound as a white solid (0.4 g).

^1H NMR (400MHz, DMSO- d_6): δ 11.71(s, 1H), 9.09(d, 1H), 7.83(t, 3H), 7.59(s, 1H), 7.56(s, 1H), 7.52(t, 1H), 7.32(d, 1H), 7.23(t, 1H), 6.46(s, 1H), 4.82(m, 1H), 4.35(t, 2H),

3.63(s, 4H), 3.50(dd, 1H), 3.1(q, 1H), 3.05(br-s, 2H), 2.86(br-s, 4H), 2.55(s, 1H), 2.51(s, 1H)

EXAMPLE 202: Preparation of 2-(Morpholin-4-yl)ethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate phosphate



According to Experiment Prototocol E, 1 g(2.07 mmol) of 2-morpholin-4-ylethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate and 0.17 g(2.07 mmol) of phosphoric acid were reacted to afford the title compound as a white solid (0.6 g).

^1H NMR (700MHz, DMSO-d_6): δ 11.72(br-s, 1H), 9.08(d, 1H), 7.86-7.82(m, 3H), 7.58-7.57(m, 2H), 7.52(t, 1H), 7.33(dd, 1H), 7.24(m, 1H), 6.47(s, 1H), 4.77-4.75(m, 1H), 4.27-4.17(m, 2H), 3.50-3.47(m, 5H), 3.30(dd, 1H), 2.60-2.57(m, 2H), 2.56-2.50(m, 1H), 2.39(br-s, 4H)

The substitutents X and Y established in Examples 1 to 202, based on the backbone of Chemical Formula I, are summarized in Table 1, below.

[Chemical Formula I]

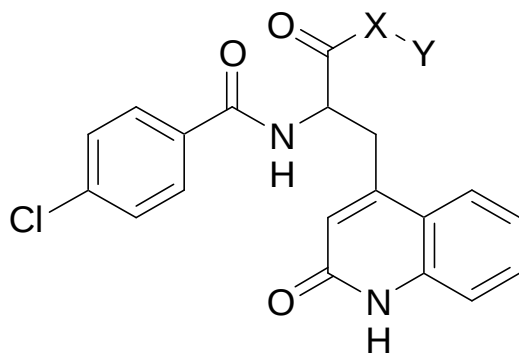
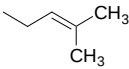
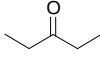
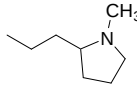
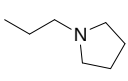
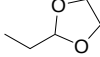
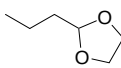
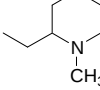
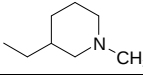
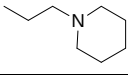
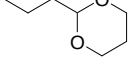
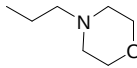
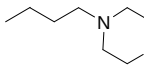
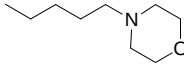
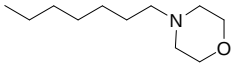
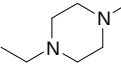
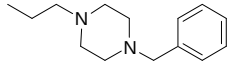
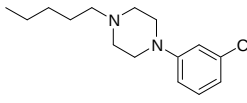
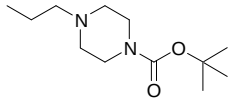
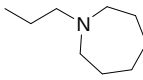
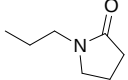
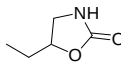
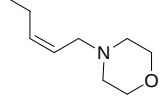
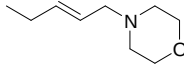
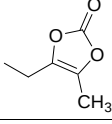
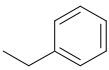
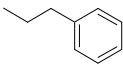
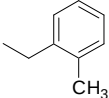
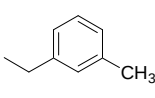
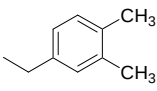
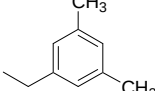
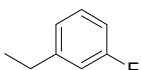
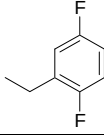
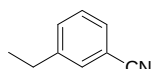
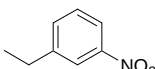
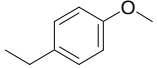
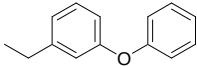
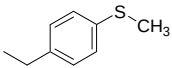
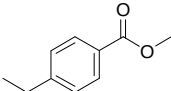
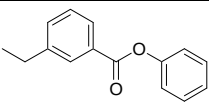
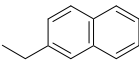
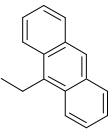
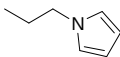
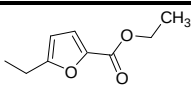
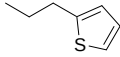
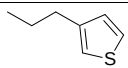
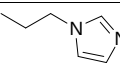
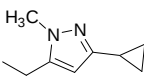
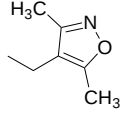
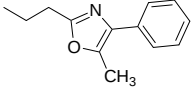
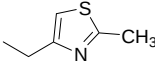
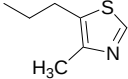
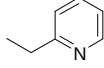
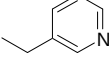
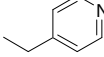


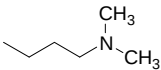
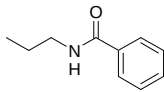
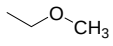
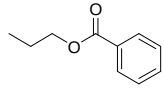
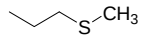
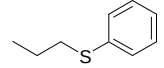
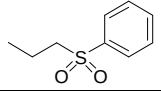
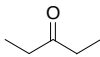
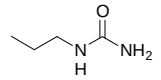
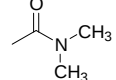
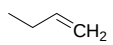
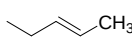
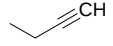
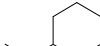
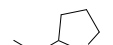
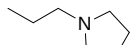
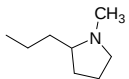
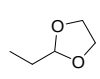
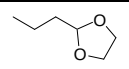
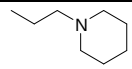
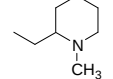
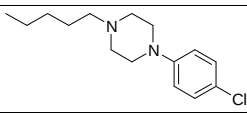
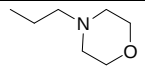
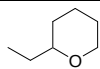
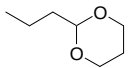
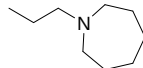
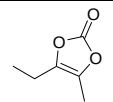
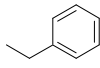
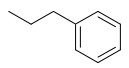
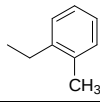
TABLE 1

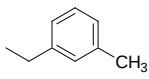
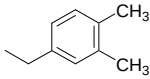
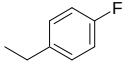
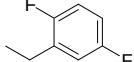
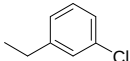
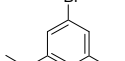
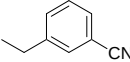
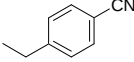
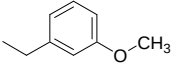
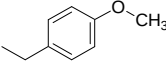
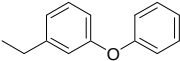
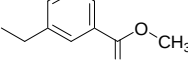
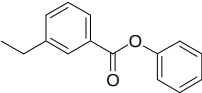
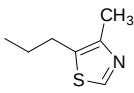
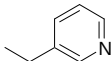
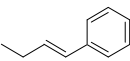
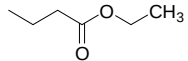
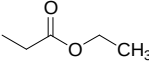
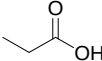
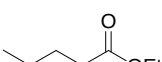
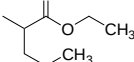
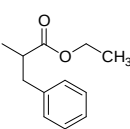
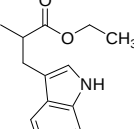
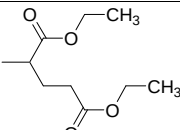
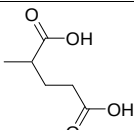
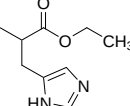
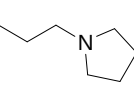
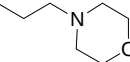
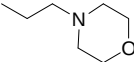
Ex.	X	Y	Ex.	X	Y
1	0	—CH_3	2	0	$\text{—CH}_2\text{CH}_3$
3	0	$\text{—CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$	4	0	$\text{—CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$
5	0	$\text{—CH}_2\text{CH}_2\text{Br}$	6	0	$\text{—CH}_2\text{CH}_2\text{OH}$
7	0	$\text{—CH}_2\text{CH}_2\text{OCH}_3$	8	0	$\text{—CH}_2\text{CH}_2\text{OC(=O)CH}_3$
9	0	$\text{—CH}_2\text{CH}_2\text{OCH=CH}_2$	10	0	$\text{—CH}_2\text{CH}_2\text{OC(=O)CH}_3$
11	0	$\text{—CH}_2\text{CH}_2\text{SCH}_3$	12	0	$\text{—CH}_2\text{CH}_2\text{S—C}_6\text{H}_5$
13	0	$\text{—CH}_2\text{CH}_2\text{N(CH}_3\text{)H}$	14	0	$\text{—CH}_2\text{CH}_2\text{N(CH}_3\text{)}_2$
15	0	$\text{—CH}_2\text{CH}_2\text{N(CH}_3\text{)}_2$	16	0	$\text{—CH}_2\text{CH}_2\text{N(CH}_3\text{)CH}_2\text{CH}_3$
17	0	$\text{—CH}_2\text{CH}_2\text{N(CH}_3\text{)}_2$	18	0	$\text{—CH}_2\text{CH}_2\text{N(CH}_3\text{)}_2$
19	0	$\text{—CH}_2\text{CH}_2\text{N(CH}_3\text{)C}_6\text{H}_5$	20	0	$\text{—CH}_2\text{CH}_2\text{N(CH}_3\text{)C}_6\text{H}_5$
21	0	$\text{—CH}_2\text{CH}_2\text{N(CH}_3\text{)C}_6\text{H}_5$	22	0	$\text{—CH}_2\text{CH}_2\text{N(CH}_3\text{)C}_6\text{H}_5$
23	0	—CH=CH_2	24	0	—CH=CHCH_3

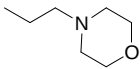
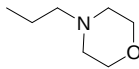
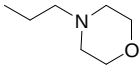
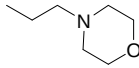
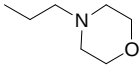
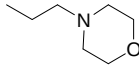
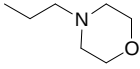
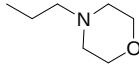
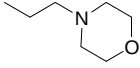
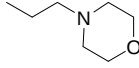
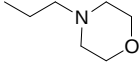
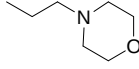
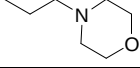
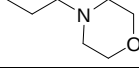
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EXPERIMENTAL EXAMPLE 1: Assay for Body Absorption Rates of Rebamipide Prodrugs

1. Preparation of standard solutions for calibration curve

1) Preparation of MeOH rebamipide solutions

Rebamipide weighing about 5mg was dissolved in 250 mL of methanol (MeOH) to give a stock solution (20000 ng/mL) from which 1000 ng/mL, 500 ng/mL, 200 ng/mL, and 100 ng/mL MeOH-rebamipide solutions were prepared.

2) Preparation of standard solutions

In a 1.5 mL tube, 100 μ L of each of the MeOH-rebamipide solutions was shaken, together with 100 μ L of blank plasma,

and 300 μ L of methanol (MeOH), for 5 min, and centrifuged for 5 min at 10,000 rpm. To establish standard solutions, 200 μ L was taken from each of the supernatants.

(For a blank, MeOH was used, instead of the MeOH rebamipide solution, and a vial with 250 μ L insert was employed.)

2. Preparation of specimen solutions

In a 1.5 mL tube, 100 μ L of each blood specimen, and 400 μ L of MeOH were shaken together for 5 min, and centrifuged at 10,000 rpm for 5 min. The supernatant was taken in a volume of 200 μ L for use as a specimen solution.

3. Information on specimen

SD (Sprague Dawley) rats were employed as experimental animals. The dose of the control drug rebamipide administered to the subject was 100 mg/kg while the prodrugs prepared in the above Examples were administered in amounts corresponding to 100 mg/kg of rebamipide.

Blood samples were taken from the subject 2 hr after administration, and sera were separated therefrom and stored at -24°C.

The separated sera were monitored for rebamipide concentration with time.

4. Test result

TABLE 2

Example No.	Concentration of Stock
Rebamipide	128.69ng/mL
1, 2, 4, 6, 8, 24, 26, 30, 33, 34, 39, 61, 62, 67, 71, 74, 89, 117, 134, 137, 177, 178	100~500ng/mL
11, 13, 21, 31, 36, 40, 50, 78, 83, 86, 90, 94, 95, 110, 115, 130, 153, 157, 161, 168, 175	500~1,000 ng/mL
15, 19, 38, 48, 51, 55, 58, 82, 95, 103, 108, 120, 125, 154	1,000~2,000 ng/mL
14, 16, 44, 47, 99, 100, 102, 105, 106, 109, 121, 144, 151, 155	> 2,000 ng/mL

Sera taken from the animals to which rebamipide or rebamipid prodrugs prepared in the above Examples were administered were measured for a change in rebamipid level with time. The results are summarized in Table 2. As apparent from the data of Table 2, the serum level of rebamipide was significantly lower at 2 hrs after rebamipide was administered as a free acid than in the form of the prodrugs of the Examples, indicating that the prodrugs according to the present invention are absorbed at higher rates in animal bodies than is remipide, and are completely converted into the acting drug remipide.

EXPERIMENTAL EXAMPLE 2: Hydrolysis of Prodrug into Acting Drug in Whole Blood of Rat

1. Experiment procedure

Frozen rat blood was thawed for about 1 hr in a 37°C water bath and homogenized.

A stock solution was prepared by dissolving 10 mg of the compound of each Example in 1 mL of CAN. Optionally, a buffer (prepared by mixing 750 mL of a solution of Na₂HPO₄ 0.58 g and KH₂PO₄ 2 g in 1 L of H₂O with 250 mL of CAN) was added. In a 4 mL tube, 40 µL of the stock solution was uniformly mixed with 2 mL of blood by shaking, followed by storage at 30 rpm in a water bath.

At 0, 2, 4, 6, 8, 10, 15, 30, 45, 60, 90, and 120 min after storage, a sample was taken in a volume of 200 µL, diluted in 400 µL of CAN, vortexed for 1 min, and centrifuged for 1 min. The supernatant was analyzed by HPLC (but, for the compound of Example 47, sampling was performed at 0, 1, 3, 5, 7, and 10 min after storage). In addition, measurement was made of the time that it took for the prodrugs to be converted into the acting drug (rebamipide).

2. Result

The results of the experiment are given in Table 3 and FIG. 1. The conversion times (half lives) taken for the

prodrugs to be converted to rebamipide are listed in Table 3. In FIG. 1, conversion rates of the rebamipide prodrug of Example 47 to rebamipide are plotted as area ratios versus time.

As is understood from the data of FIG. 1, the rebamipide prodrug was converted into rebamipide by half after 2.57 min of storage, and completely after about 10 min of storage, with the conversion rate rapidly increasing from 3 min after storage onwards.

TABLE 3
Conversion Time (Half Life) from Rebamipide Prodrugs to
Rebamipide

Cpd.	Conversion Time in Whole Rat Blood ($t_{1/2}$)
Example 14	< 2 min
Example 16	< 2 min
Example 44	< 2 min
Example 47	2.57 min
Example 99	< 2 min
Example 100	< 2 min
Example 102	< 2 min
Example 105	< 2 min
Example 106	< 2 min
Example 109	< 2 min
Example 121	< 2 min

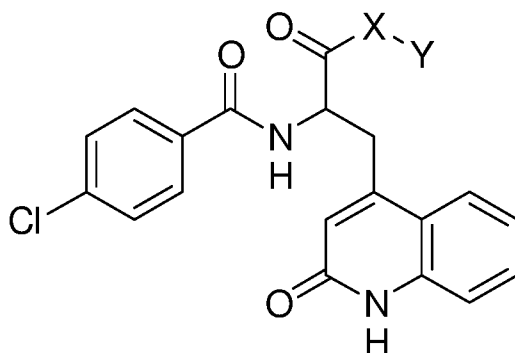
Example 144	< 2 min
Example 151	< 2 min
Example 155	< 2 min

As can be seen in Table 3, it took 2.57 min for the rebamipide prodrug of Example 47 to be converted into rebamipide by half while the rebamipide prodrugs of the other Examples were converted by half into rebamipide within less than 2 min. Accordingly, the rebamipide prodrugs according to the present invention are highly prone to conversion into rabamipide in vivo, thus guaranteeing a high pharmaceutical efficacy.

CLAIMS:

1. A compound, selected from among a compound represented by the following Chemical Formula 1, a pharmaceutically acceptable salt thereof, an optical isomer thereof, a hydrate thereof, or a solvate thereof:

[Chemical Formula I]



wherein,

X is an oxygen atom, a nitrogen atom, or a sulfur atom; and

- 10 Y is a radical selected from the group consisting of C₁-C₆ alkyl, C₁-C₆ haloalkyl, (C₁-C₃ alkyloxy)C₁-C₆ alkyl, (C₂-C₆ alkenyloxy)C₁-C₆ alkyl, (C₁-C₆ alkylcarbonyloxy)C₁-C₆ alkyl, (C₁-C₆ alkylsufanyl)C₁-C₆ alkyl, (arylsufanyl)C₁-C₆ alkyl, (arylsulfonyl)C₁-C₆ alkyl, (C₁-C₆ alkylamino)C₁-C₆ alkyl, [(C₁-C₆ alkyl)(C₁-C₆ alkyl)amino]C₁-C₆ alkyl, [(C₁-C₃ alkyl)(aryl)amino]C₁-C₆ alkyl, {[(C₁-C₃ alkyl)(aryl)C₁-C₃ alkyl]amino}C₁-C₆ alkyl, [(C₁-C₃ alkyl)(heteroaryl)amino]C₁-C₆ alkyl, (arylcarbonylamino)C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₂-C₆ oxoalkyl, C₃-C₈ cycloalkyl, (C₃-C₈ cycloalkyl)C₁-C₆ alkyl, (C₃-C₈ cycloalkenyl)C₁-C₆ alkyl, (C₃-C₈ heterocycloalkyl)C₁-C₆ alkyl, [(C₁-C₃ alkyl)C₃-C₈ heterocycloalkyl]C₁-C₆ alkyl, [{(aryl)C₁-C₃ alkyl}C₃-C₈ heterocycloalkyl]C₁-C₆ alkyl, [(C₁-C₆ alkyloxycarbonyl)C₃-C₈ heterocycloalkyl]C₁-C₆ alkyl, [(C₁-C₃ alkyloxycarbonyl)C₃-C₈ heterocycloalkyl]C₁-C₆ alkyl, (C₃-C₈ heterocycloalkyl)C₁-C₆ alkenyl, [(C₁-C₃ alkyl)C₃-C₈ heterocycloalkenyl]C₁-C₆ alkyl, (aryl)C₁-C₆ alkyl, [(C₁-C₃ alkyl)aryl]C₁-C₆ alkyl, [(C₁-C₃ alkyloxy)aryl]C₁-C₆ alkyl, [(aryloxy)aryl]C₁-C₆ alkyl, [(C₁-C₃ alkylsufanyl)aryl]C₁-C₆ alkyl, [(C₁-C₃ alkyloxycarbonyl)aryl]C₁-C₆ alkyl, [(aryloxycarbonyl)aryl]C₁-C₆ alkyl, (aryl)C₃-C₆ alkenyl, (heteroaryl)C₁-C₆ alkyl, [(alkyloxycarbonyl)heteroaryl]C₁-C₆ alkyl, [(C₁-C₃
- 15
- 20

- alkyl)C₃-C₈ heteroaryl]C₁-C₆ alkyl, [(C₃-C₈ cycloalkyl)heteroaryl]C₁-C₆ alkyl, [(aryl)heteroaryl]C₁-C₆ alkyl, [(C₁-C₃ alkyl)heteroaryl]C₁-C₆ alkyl, {(aryl)C₁-C₃ alkyl]heteroaryl}C₁-C₆ alkyl, (C₁-C₆ alkyloxycarbonyl)C₁-C₆ alkyl, [(C₃-C₈ heterocycloalkyl)C₁-C₆ alkyloxycarbonyl]C₁-C₆ alkyl, (C₃-C₈ heterocycloalkylcarbonyl)C₁-C₆ alkyl, [(C₁-C₃ alkyl)C₃-C₈ heterocycloalkylcarbonyl]C₁-C₆ alkyl, [(C₁-C₃ alkyl)C₃-C₈ heterocycloalkylcarbonyl]C₁-C₆ alkyl, [(C₃-C₈ cycloalkyl)oxycarbonyloxy]C₁-C₆ alkyl, [(C₃-C₈ heterocycloalkyl)oxycarbonyloxy]C₁-C₆ alkyl, (ureido)C₁-C₆ alkyl, (ary lureido)C₁-C₆ alkyl, [(aryl)(C₁-C₃ alkylureido)C₁-C₆ alkyl, (C₁-C₆ alkylaminocarbonyl)C₁-C₆ alkyl, [(C₃-C₈ heterocycloalkyl)aminocarbonyl]C₁-C₆ alkyl, {[(C₁-C₃ alkyl)C₃-C₈ heterocycloalkyl]aminocarbonyl}C₁-C₆ alkyl, [(C₁-C₃ alkyl)(C₁-C₃ alkyloxy)aminocarbonyl]C₁-C₆ alkyl and (oxoC₃-C₈ heterocycloalkyl)C₁-C₆ alkyl,
- with a proviso that the C₁-C₆ alkyl radical, the C₂-C₆ alkenyl radical, the C₂-C₆ alkynyl radical, the C₂-C₆ oxoalkyl radical, the C₃-C₈ cycloalkyl radical, the C₃-C₈ cycloalkenyl radical, the C₃-C₈ heterocycloalkenyl radical, the aryl radical or the heteroaryl radical may be substituted with at least one substituent selected from the group consisting of C₁-C₃ alkyl, fluoro, chloro, bromo, hydroxy, oxo, nitro, and cyano, wherein the compound is selected from the group consisting of:
- 11) 2-methylsulfanylethyl2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4yl)propionate;
 - 13) 2-methylaminoethyl2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;
 - 14) 2-dimethylaminoethyl2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4yl)propionate;
 - 15) 2-dimethylamino-1-methyl-ethyl2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4yl)propionate;
 - 16) 2-diethylaminoethyl2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4yl)propionate;
 - 19) 2-(methylphenylamino)ethyl2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4yl)propionate;

- 21) 2-(benzoxazol-2-ylmethylamino)ethyl2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;
- 31) cyclomethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;
- 5 36) 3-methyloxetan-3-ylmethyl2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;
- 38) 2-pyrrolidin-1-yl-ethyl2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;
- 40) [1,3]dioxolan-2-ylmethyl2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;
- 10 44) 2-piperidin-1-ylethyl2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;
- 47) 2-morpholin-4-ylethyl2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;
- 15 48) 3-morpholin-4-ylpropyl2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;
- 50) 6-morpholin-4-ylhexyl2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;
- 51) (4-methylpiperazin-1-yl)methyl2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;
- 20 55) 2-azepan-1-ylethyl2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;
- 58) 4-morpholin-4-yl-*cis*-but-2-enyl2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;
- 25 78) 2-pyrrol-1-ylethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;
- 82) 2-imidazol-1-ylethyl2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;

- 83) 5-cyclopropyl-2-methyl-2H-pyrazol-3-ylmethyl-2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;
- 86) 2-methylthiazol-4-ylmethyl-2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;
- 5 90) pyrimidin-4-ylmethyl-2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;
- 94) 2-(1-methyl-1H-indol-3-yl)ethyl-2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;
- 95) benzothiazol-2-ylmethyl-2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;
- 10 99) 2-(4-methylpiperazin-1-yl)-2-oxoethyl-2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;
- 100) 1-(4-methylpiperazine-1-carbonyl)propyl-2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;
- 15 102) (methoxymethylcarbonyl)methyl-2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;
- 103) 2-ethoxycarbonyl-ethyl-2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;
- 105) 2-morpholin-4-yl-ethoxycarbonylmethyl-2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;
- 20 106) 2-morpholin-4-ylethyl-2-[2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionyloxy]butyrate;
- 108) cyclohexyloxycarbonyloxymethyl-2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;
- 25 109) 2-morpholin-4-yl-ethoxycarbonyloxymethyl-2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;
- 110) 2-ureidoethyl-2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;

- 115) *S*-ethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate;
- 120) *S*-(2-dimethylamino)ethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate;
- 5 121) *S*-(2-diethylamino)ethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate;
- 125) *S*-methoxymethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate;
- 130) *S*-(2-oxobutyl) 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate;
- 10 144) *S*-(2-pyrrolidin-1-yl)ethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate;
- 151) *S*-(2-morpholin-4-yl)ethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)propionate;
- 15 153) *S*-(2-[1,3]-dioxan-2-yl)ethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate;
- 154) *S*-(2-azepan-1-yl)ethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate;
- 155) *S*-(5-methyl-2-oxo-[1,3]dioxol-4-yl)methyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate;
- 20 157) *S*-phenethyl 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate;
- 161) *S*-(4-fluorobenzyl) 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate;
- 25 168) *S*-(4-methoxybenzyl) 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate; and
- 175) *S*-(3-phenylallyl) 2-(4-chlorobenzoylamino)-3-(2-oxo-1,2-dihydroquinolin-4-yl)thiopropionate.

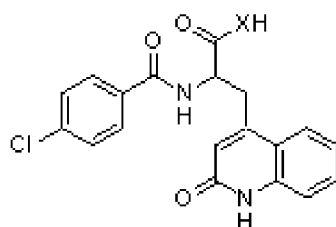
2. The compound of claim 1, wherein the salt is an acid addition salt formed with a pharmaceutically acceptable free acid.

3. The compound of claim 2, wherein the free acid is an organic acid or an inorganic acid.

4. The compound of claim 3, wherein the organic acid is selected from the group consisting of citric acid, acetic acid, lactic acid, tartaric acid, maleic acid, fumaric acid, formic acid, propionic acid, oxalic acid, trifluoroacetic acid, benzoic acid, gluconic acid, methanesulfonic acid, glycolic acid, succinic acid, 4-toluenesulfonic acid, camphorsulfonic acid, glutamic acid, aspartic acid, salicylic acid, malonic acid, malic acid, and benzosulfonic acid, and the inorganic acid is selected from the group consisting of hydrochloric acid, bromic acid, sulfuric acid, and phosphoric acid.

5. A method for preparing the compound represented by Chemical Formula I of claim 1, comprising reacting a compound represented by the following Chemical Formula II with a compound represented by the following Chemical Formula III:

[Chemical Formula II]



[Chemical Formula III]

Y-Z

wherein,

X and Y are as defined in claim 1, and Z is hydroxy, amino, amine, halogen or a leaving group.

6. The method of claim 5, wherein Z is hydroxy, -NH₂, Cl, Br, alkylsulfonyl, or arylsulfonyl.

7. A pharmaceutical composition for prophylaxis or therapy of a disease,
comprising the compound of claim 1 as an active ingredient, said disease being
selected from among gastric ulcer, acute gastritis, chronic gastritis, xerophthalmia,
cancer, osteoarthritis, rheumatoid arthritis, hyperlipidemia, hypertriglyceridemia,
5 diabetes, irritable bowel syndrome, and obesity.

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