

## Compounds for the Reducing Lipotoxic Damage

### **CROSS-REFERENCE TO RELATED APPLICATIONS**

This application claims priority to U.S. Provisional Application Serial No. 62/531,454, filed on July 12, 2017, the contents of which are incorporated by reference in their entirety.

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### **TECHNICAL FIELD**

The present disclosure relates to the use of lipase inhibitors for the treatment of severe pancreatitis and/or acne.

### **BACKGROUND**

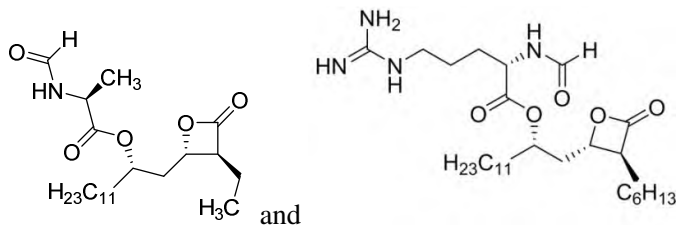
10           The pancreas produces enzymes that aid in digestion and absorption of food; one such enzyme is lipase, which digests fat. Certain individuals (e.g., obese individuals) have an increased risk of developing multisystem organ failure in acute inflammatory conditions such as severe burns, severe trauma, critical illness, and acute pancreatitis (AP). Pancreatitis is associated with the release of destructive  
15           digestive enzymes from pancreatic acinar cells into the pancreas itself. When AP is initiated, it can quickly become severe AP (SAP). This is a concern because SAP results in 40 to 50% mortality when complicated by acute renal failure, respiratory failure, hypocalcemia, and other manifestations of multisystem organ failure or by large areas of pancreatic necrosis. With no effective therapies, the current  
20           management standard is supportive care and managing complications when they occur.

### **SUMMARY**

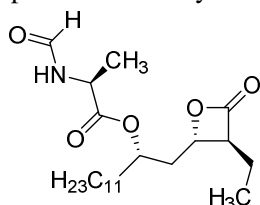
          Provided herein are novel lipase inhibitors and methods for using the same to treat pancreatitis and/or organ failure and/or acne comprising administering, to a  
25           subject in need of such treatment, an effective amount of a lipase inhibitor as provided herein. The methods provided herein are based, at least in part, on the discoveries that lipotoxicity contributes to inflammation, multisystem organ failure, necrotic pancreatic acinar cell death, acute pancreatitis, sepsis (e.g., culture negative sepsis), burns, acne, and infections, and that inhibition of lipase activity is able to reduce

indices associated with these conditions. Accordingly, in some examples, provided herein are methods and compositions for limiting lipotoxicity and thereby reducing the likelihood of poor outcomes associated with acute pancreatitis and other severe systemic conditions.

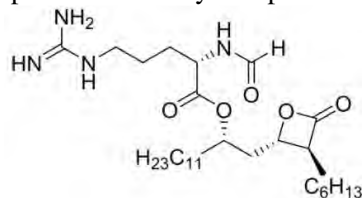
5 In one aspect, the present disclosure refers to a compound selected from the group consisting of:



or a pharmaceutically acceptable salt thereof. In some examples, the compound is:



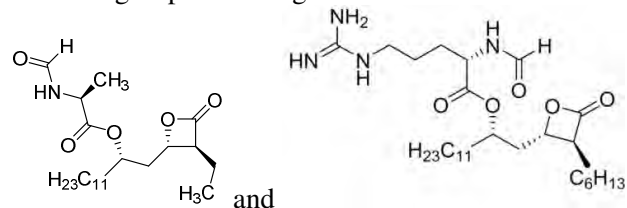
10 or a pharmaceutically acceptable salt thereof. In some examples, the compound is:



or a pharmaceutically acceptable salt thereof.

Further provided herein is a pharmaceutical composition comprising one or more of the compounds provided herein and a pharmaceutically acceptable excipient. In one aspect, the present disclosure refers to a pharmaceutical composition comprising any one of the compounds disclosed herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

In another aspect, the present disclosure refers to use of a compound selected from the group consisting of:

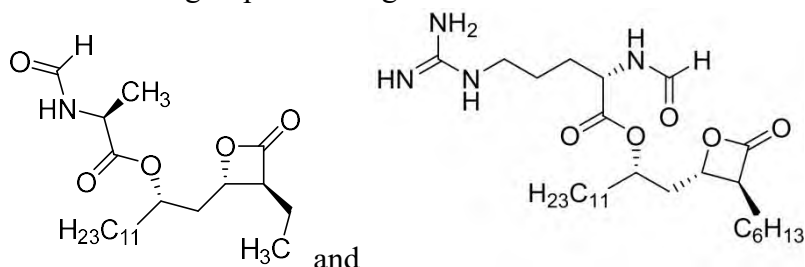


20 or a pharmaceutically acceptable

salt thereof, in the manufacture of a medicament for treating acute pancreatitis in a subject in need thereof. This disclosure also provides methods of treating acute pancreatitis in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound provided herein or a pharmaceutically acceptable salt thereof. In some examples, the acute pancreatitis is severe. In some examples, the acute pancreatitis is downgraded from severe to mild following administration. In some examples, the subject is obese. In some

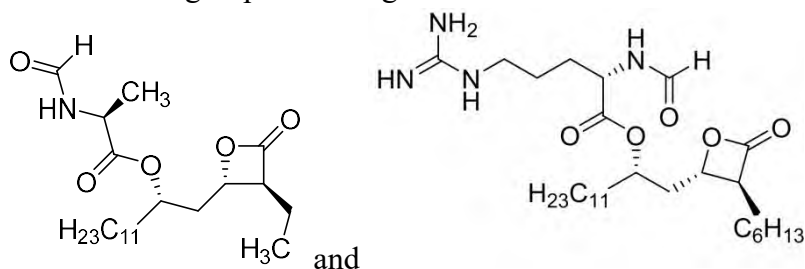
examples, the risk of developing shock, renal failure, and/or pulmonary failure is reduced.

In yet another example, the present disclosure refers to use of a compound selected from the group consisting of:



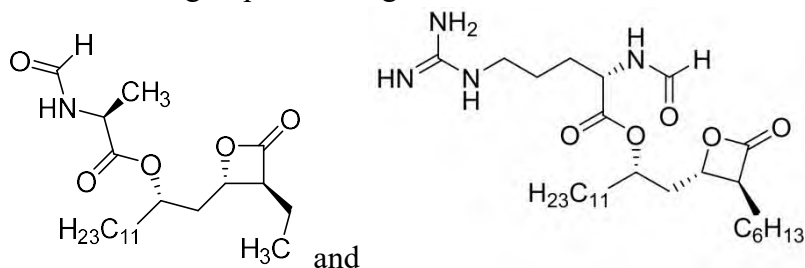
or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating acne in a subject in need thereof. Also provided herein is a method of treating acne in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound provided herein or a pharmaceutically acceptable salt thereof.

In yet a further example, the present disclosure refers to use of a compound selected from the group consisting of:



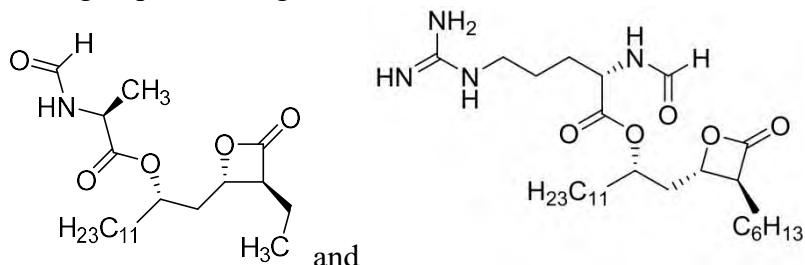
or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating sepsis in a subject in need thereof. Further provided herein is a method of treating sepsis in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound provided herein or a pharmaceutically acceptable salt thereof. In some examples, the sepsis is culture negative sepsis.

In another example, the present disclosure refers to use of a compound selected from the group consisting of:



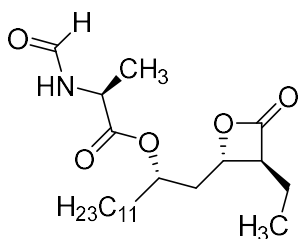
or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating burns in a subject in need thereof. This disclosure also provides methods of treating burns in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound provided herein or a pharmaceutically acceptable salt thereof.

In another example, the present disclosure refers to use of a compound selected from the group consisting of:

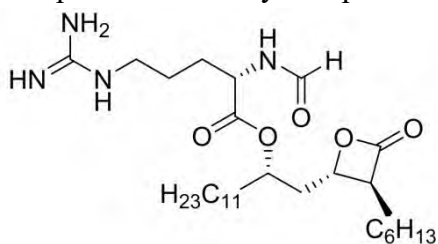


or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating infections in a subject in need thereof. Also provided herein is a method for treating infections in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound provided herein or a pharmaceutically acceptable salt thereof. In some examples, the infection is caused by one or more organisms selected from the group consisting of *P. auregenosa*, *S. aureus*, *B. subtilis*, and *B. cepecia*.

In some of the above examples, the compound is:



or a pharmaceutically acceptable salt thereof. In some examples, the compound is:



or a pharmaceutically acceptable salt thereof.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to

which this disclosure belongs. Methods and materials are described herein for use in the present disclosure; other, suitable methods and materials known in the art can also be used. The materials, methods, and examples are illustrative only and not intended to be limiting. All publications, patent applications, patents, sequences, database entries, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control.

Other features and advantages of the disclosure will be apparent from the following detailed description and figures, and from the claims.

## DESCRIPTION OF DRAWINGS

**FIG. 1** is a schematic of the structure of orlistat dividing the compound into three main regions.

**FIG. 2** is a scheme detailing a synthetic route to prepare amino-ester modifications to the orlistat core.

**FIG. 3** shows the structures of the various non-formylated amino ester modified analog compounds prepared.

**FIG. 4** provides line graphs showing the results of a lipase inhibition assay testing the non-formylated amino ester modified analog compounds. **FIG. 4A** provides the results of freshly prepared solutions of the compounds while **FIG. 4B** provides the results of solutions stored overnight.

**FIG. 5** is a scheme detailing a synthetic route to prepare formulated amino ester modified analogs.

**FIG. 6** shows the structures of the various formyl amino ester modified analog compounds prepared.

**FIG. 7** provides line graphs showing the results of a lipase inhibition assay testing the formyl amino ester modified analog compounds. **FIG. 7A** provides the results of freshly prepared solutions of the compounds while **FIG. 7B** provides the results of solutions stored overnight.

**FIG. 8** provides bar graphs detailing the efficacy of selected analog compounds in reducing lipotoxic damage to acinar cells in acinar-adipocyte co-culture (**FIG. 8A**) while also assessing the toxicity of the compounds to these cells (**FIG. 8B**).

**FIG. 9** is a scheme detailing the metastasis reaction used to prepare the  $\beta$ -chain analogs.

**FIG. 10** is a scheme detailing a synthetic route to the  $\beta$ -chain analogs.

**FIG. 11** is a scheme detailing a synthetic route to the  $\beta$ -chain analogs.

5 **FIG. 12** is a scheme detailing a synthetic route to the  $\beta$ -chain analogs.

**FIG. 13** is a scheme detailing a synthetic route to the  $\beta$ -chain analogs.

**FIG. 14** shows the structures of the various  $\beta$ -chain analogs prepared.

**FIG. 15** provides a line graph showing the results of a lipase inhibition assay testing the  $\beta$ -chain analogs in freshly prepared solutions.

10 **FIG. 16** is a scheme detailing a synthetic route to the  $\alpha$ -chain analogs.

**FIG. 17** provides line graphs showing the results of a lipase inhibition assay testing the  $\alpha$ -chain analogs. **FIG. 17A** provides the results of freshly prepared solutions of the compounds while **FIG. 17B** provides the results of solutions stored overnight.

15 **FIG. 18** provides line graphs showing the results of an assay exploring % free fatty acid (FFA) generation. **FIG. 18A** provides the results of freshly prepared solutions of the compounds while **FIG. 18B** provides the results of solutions stored overnight.

20 **FIG. 19** shows tables of values obtained from toxicity studies in mouse pancreatic cells.

**FIG. 20** provides line graphs showing the results of an assay exploring % FFA generation. **FIG. 20A** provides the results with hPLRP2 lipase while **FIG. 20B** provides the results with hCEL lipase.

**FIG. 21** provides a tabular summary of the in vitro studies described herein.

25 **FIG. 22** provides a summary of the use of orlistat in reducing severe pancreatitis.

**FIG. 23** provides the results of in vivo testing of compound 767. **FIG. 23A** provides the study timeline; **FIG. 23B** provides a bar graph of the serum lipase concentration; **FIG. 23C** provides a graph showing serum blood urea nitrogen levels at various time points; **FIG. 23D** provides a graph showing serum calcium levels at various time points; and **FIG. 23E** provides a graph showing protection against systemic inflammatory response syndrome (SIRS); **FIG. 23F** provides a graph

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showing protection against shock and **FIG. 23G** provides a graph showing improved survival

**FIG. 24** provides photographs of treated mice.

**FIG. 25** provides a tabular summary of the in vivo studies with compound 767 and orlistat.

**FIG. 26** provides a line graph showing % FFA generation in a medium of *P. acnes*.

**FIG. 27** provides pictures of spirit blue agar inoculated with *P. acnes* and exposed to both orlistat and compound 767.

**FIG. 28** shows efficacy of 10mM agents in reducing LDH leakage from acinar cells incubated with 600 mM GTL

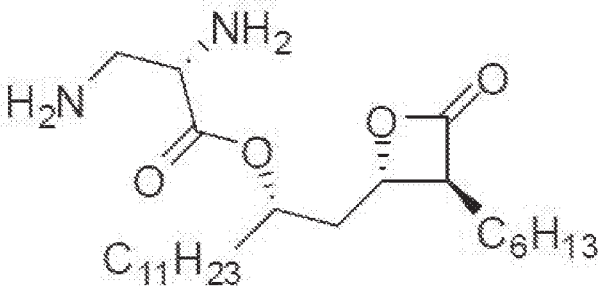
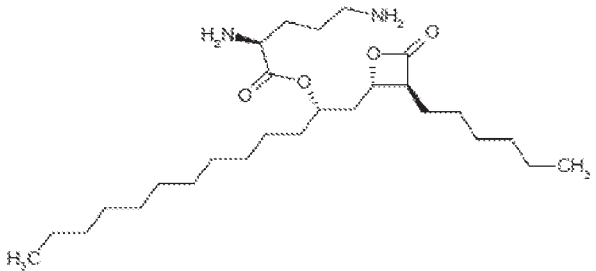
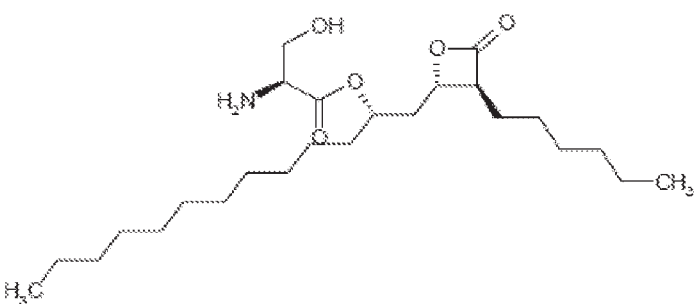
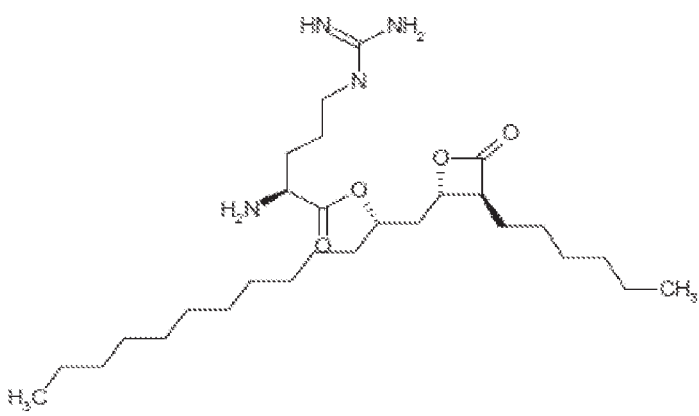
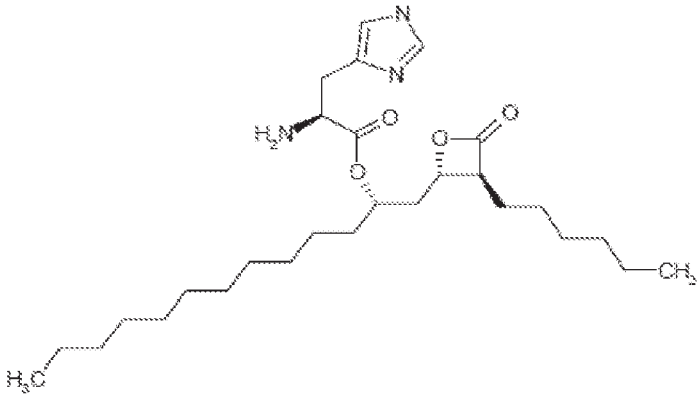
### DETAILED DESCRIPTION

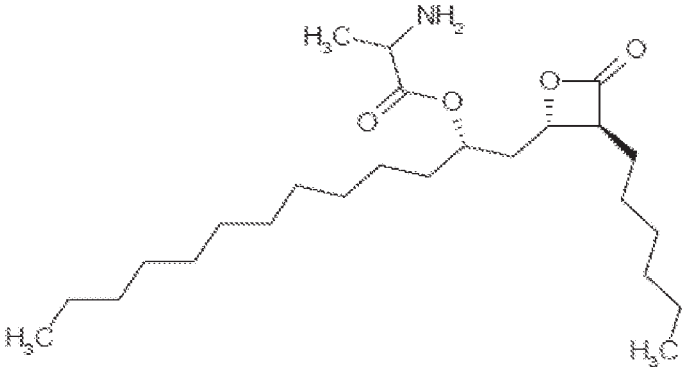
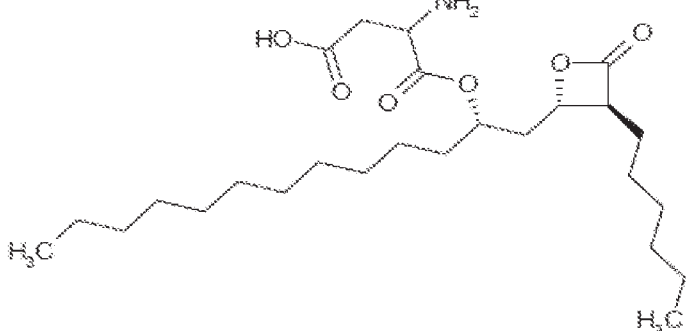
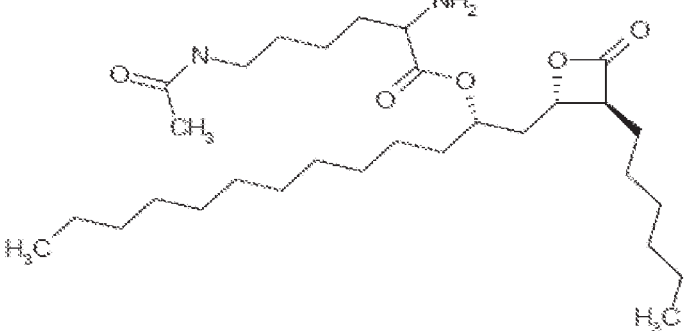
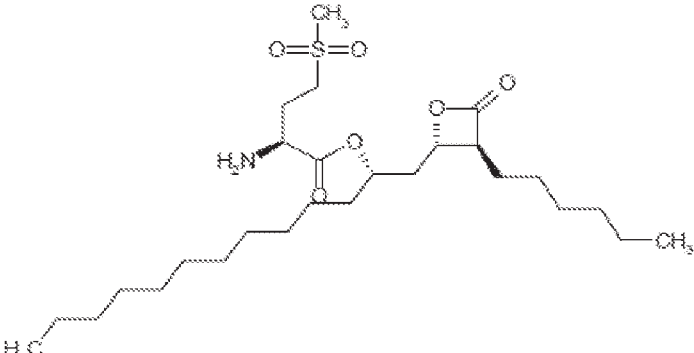
Presently, severe pancreatitis is often treated through administration of the FDA approved lipase inhibitor, orlistat. While lipase inhibition reduces the severity of pancreatitis, the use of orlistat is complicated by the need of repeated dosing (e.g., 50 mg/kg BID for two days) during pancreatitis, and the hypertriglyceridemia associated with the use of this compound. Provided herein are compounds that provide therapeutic benefits in pancreatitis, without the need of repeated dosing or the complications associated with orlistat.

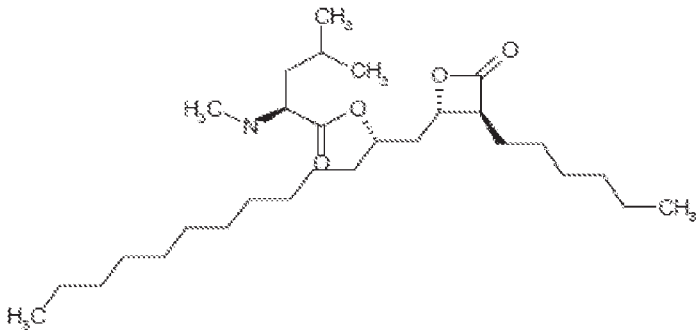
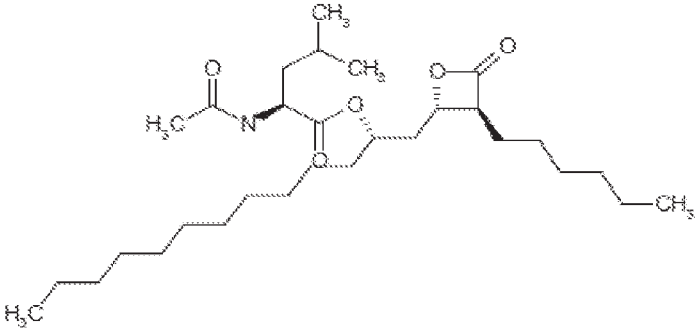
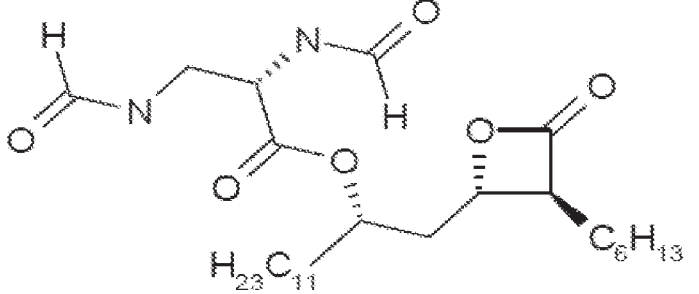
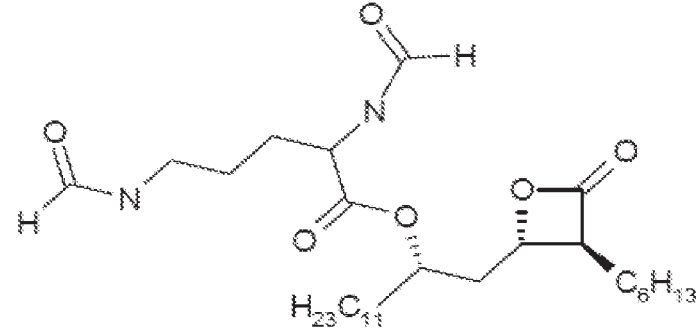
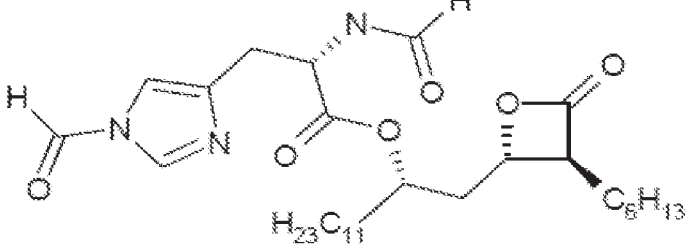
Compounds provided herein include those described in Table 1.

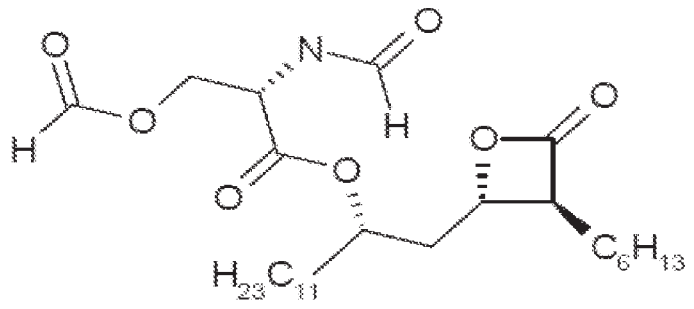
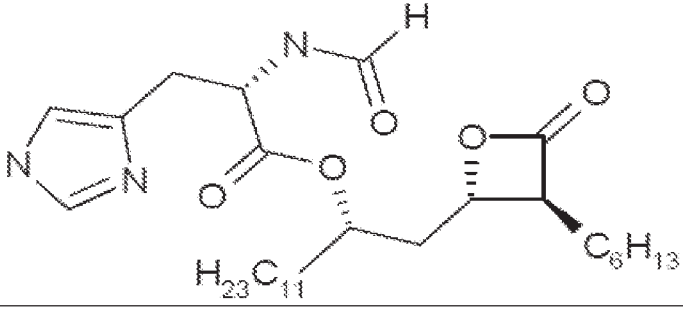
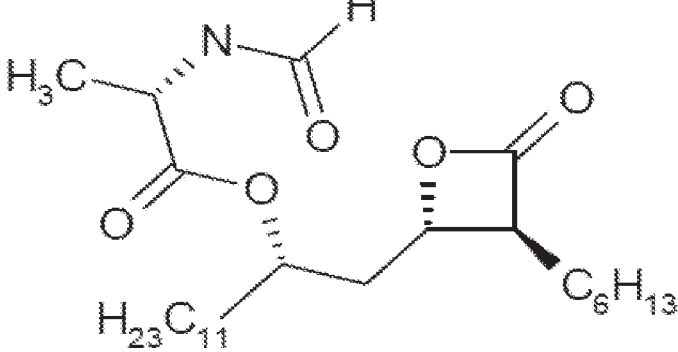
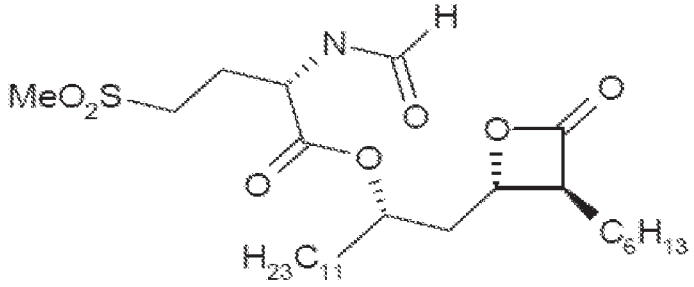
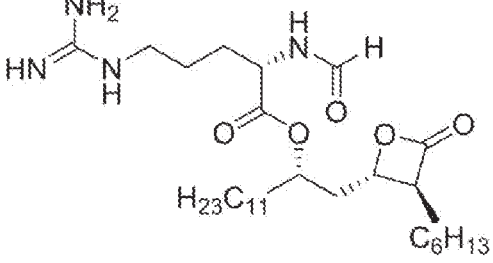
Table 1.

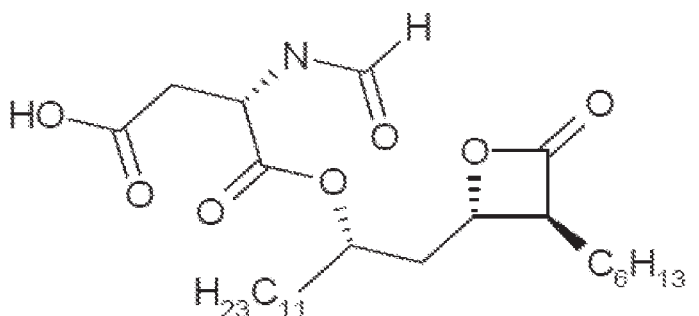
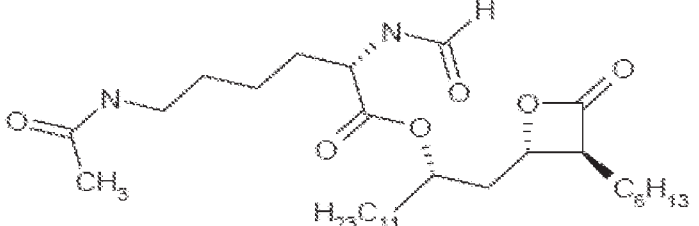
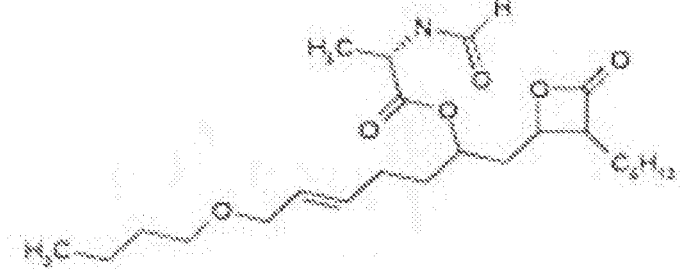
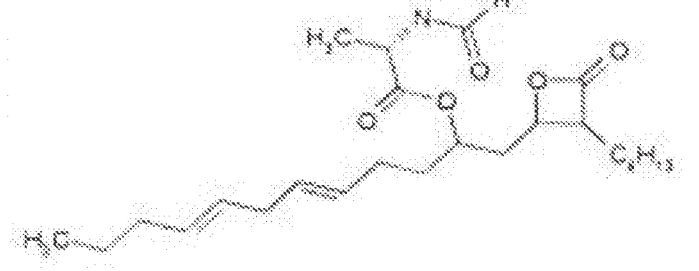
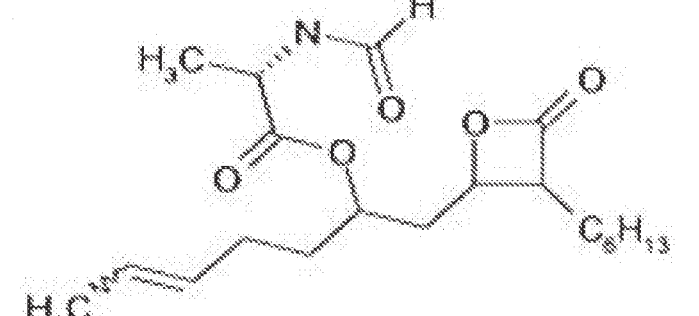
| Compound Number | Structure |
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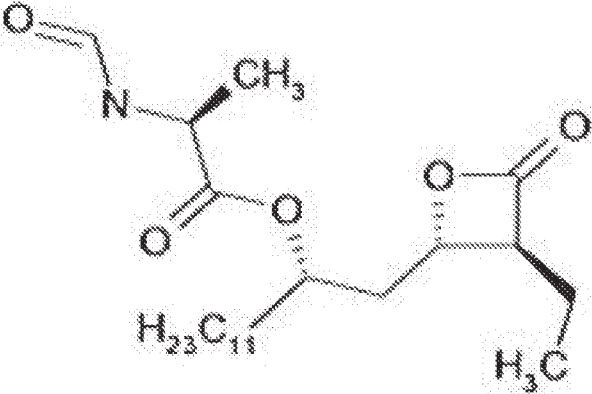
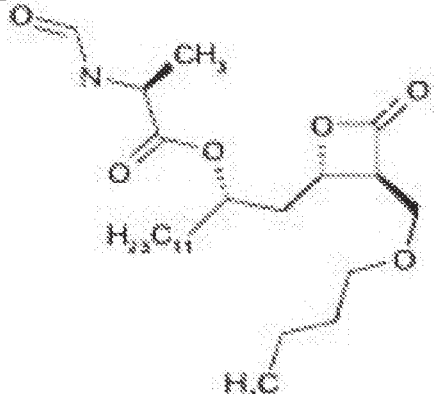
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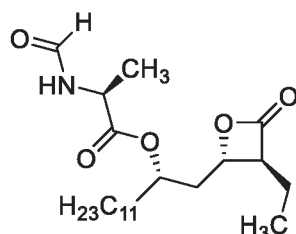
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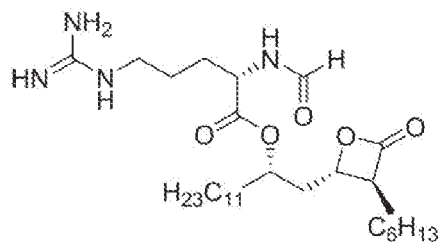
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| 767 |  |
| 768 |  |

or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is



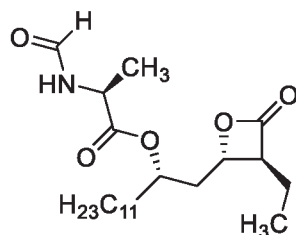
or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is



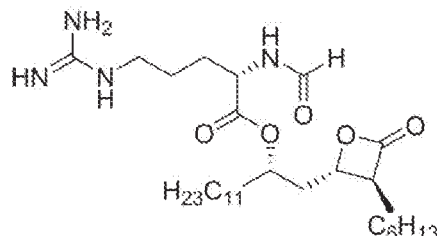
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or a pharmaceutically acceptable salt thereof.

In some embodiments, a compound provided herein is stable in aqueous solution. For example, a compound provided herein can be more stable than orlistat in aqueous solution. In some embodiments, the compound is



or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is



or a pharmaceutically acceptable salt thereof.

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### Synthesis

The compounds described herein can be prepared, for example, according to the procedures described in the Examples and associated figures.

It will be appreciated by one skilled in the art that the processes described are not the exclusive means by which compounds provided herein may be synthesized and that a broad repertoire of synthetic organic reactions is available to be potentially employed in synthesizing compounds provided herein. The person skilled in the art knows how to select and implement appropriate synthetic routes. Suitable synthetic methods of starting materials, intermediates and products may be identified by reference to the literature, including reference sources such as: *Advances in Heterocyclic Chemistry*, Vols. 1-107 (Elsevier, 1963-2012); *Journal of Heterocyclic Chemistry* Vols. 1-49 (Journal of Heterocyclic Chemistry, 1964-2012); Carreira, *et al.* (Ed.) *Science of Synthesis*, Vols. 1-48 (2001-2010) and Knowledge Updates KU2010/1-4; 2011/1-4; 2012/1-2 (Thieme, 2001-2012); Katritzky, *et al.* (Ed.) *Comprehensive Organic Functional Group Transformations*, (Pergamon Press, 1996); Katritzky *et al.* (Ed.); *Comprehensive Organic Functional Group Transformations II* (Elsevier, 2<sup>nd</sup> Edition, 2004); Katritzky *et al.* (Ed.), *Comprehensive Heterocyclic Chemistry* (Pergamon Press, 1984); Katritzky *et al.*, *Comprehensive Heterocyclic Chemistry II*, (Pergamon Press, 1996); Smith *et al.*, *March's Advanced Organic*

*Chemistry: Reactions, Mechanisms, and Structure*, 6<sup>th</sup> Ed. (Wiley, 2007); Trost *et al.* (Ed.), *Comprehensive Organic Synthesis* (Pergamon Press, 1991).

The reactions for preparing compounds described herein can be carried out in suitable solvents which can be readily selected by one of skill in the art of organic synthesis. Suitable solvents can be substantially non-reactive with the starting materials (reactants), the intermediates, or products at the temperatures at which the reactions are carried out, (e.g., temperatures which can range from the solvent's freezing temperature to the solvent's boiling temperature). A given reaction can be carried out in one solvent or a mixture of more than one solvent. Depending on the particular reaction step, suitable solvents for a particular reaction step can be selected by the skilled artisan.

Preparation of compounds described herein can involve the protection and deprotection of various chemical groups. The need for protection and deprotection, and the selection of appropriate protecting groups, can be readily determined by one skilled in the art. The chemistry of protecting groups can be found, for example, in T. W. Greene and P. G. M. Wuts, *Protective Groups in Organic Synthesis*, 3<sup>rd</sup> Ed., Wiley & Sons, Inc., New York (1999).

Reactions can be monitored according to any suitable method known in the art. For example, product formation can be monitored by spectroscopic means, such as nuclear magnetic resonance spectroscopy (e.g., <sup>1</sup>H or <sup>13</sup>C), infrared spectroscopy, spectrophotometry (e.g., UV-visible), mass spectrometry, or by chromatographic methods such as high performance liquid chromatography (HPLC), liquid chromatography-mass spectroscopy (LCMS), or thin layer chromatography (TLC). Compounds can be purified by those skilled in the art by a variety of methods, including high performance liquid chromatography (HPLC) and normal phase silica chromatography.

The term "compound" as used herein is meant to include all stereoisomers, geometric isomers, tautomers, and isotopes of the structures depicted. Compounds herein identified by name or structure as one particular tautomeric form are intended to include other tautomeric forms unless otherwise specified.

Compounds provided herein also include tautomeric forms. Tautomeric forms result from the swapping of a single bond with an adjacent double bond together with

the concomitant migration of a proton. Tautomeric forms include prototropic tautomers which are isomeric protonation states having the same empirical formula and total charge. Example prototropic tautomers include ketone – enol pairs, amide – imidic acid pairs, lactam – lactim pairs, enamine – imine pairs, and annular forms where a proton can occupy two or more positions of a heterocyclic system, for example, 1H- and 3H-imidazole, 1H-, 2H- and 4H- 1,2,4-triazole, 1H- and 2H- isoindole, and 1H- and 2H-pyrazole. Tautomeric forms can be in equilibrium or sterically locked into one form by appropriate substitution.

In some embodiments, the compounds described herein can contain one or more asymmetric centers and thus occur as racemates and racemic mixtures, enantiomerically enriched mixtures, single enantiomers, individual diastereomers and diastereomeric mixtures (e.g., including (*R*)- and (*S*)-enantiomers, diastereomers, (*D*)-isomers, (*L*)-isomers, (+) (*dextrorotatory*) forms, (-) (*levorotatory*) forms, the racemic mixtures thereof, and other mixtures thereof). Additional asymmetric carbon atoms can be present in a substituent, such as an alkyl group. All such isomeric forms, as well as mixtures thereof, of these compounds are expressly included in the present description. The compounds described herein can also or further contain linkages wherein bond rotation is restricted about that particular linkage, e.g. restriction resulting from the presence of a ring or double bond (e.g., carbon-carbon bonds, carbon-nitrogen bonds such as amide bonds). Accordingly, all *cis/trans* and *E/Z* isomers and rotational isomers are expressly included in the present description. Unless otherwise mentioned or indicated, the chemical designation of a compound encompasses the mixture of all possible stereochemically isomeric forms of that compound.

Optical isomers can be obtained in pure form by standard procedures known to those skilled in the art, and include, but are not limited to, diastereomeric salt formation, kinetic resolution, and asymmetric synthesis. See, for example, Jacques, et al., *Enantiomers, Racemates and Resolutions* (Wiley Interscience, New York, 1981); Wilen, S.H., et al., *Tetrahedron* 33:2725 (1977); Eliel, E.L. *Stereochemistry of Carbon Compounds* (McGraw-Hill, NY, 1962); Wilen, S.H. *Tables of Resolving Agents and Optical Resolutions* p. 268 (E.L. Eliel, Ed., Univ. of Notre Dame Press, Notre Dame, IN 1972), each of which is incorporated herein by reference in their

entireties. It is also understood that the compounds described herein include all possible regioisomers, and mixtures thereof, which can be obtained in pure form by standard separation procedures known to those skilled in the art, and include, but are not limited to, column chromatography, thin-layer chromatography, and high-performance liquid chromatography.

Unless specifically defined, compounds provided herein can also include all isotopes of atoms occurring in the intermediates or final compounds. Isotopes include those atoms having the same atomic number but different mass numbers. Unless otherwise stated, when an atom is designated as an isotope or radioisotope (e.g., deuterium, [ $^{11}\text{C}$ ], [ $^{18}\text{F}$ ]), the atom is understood to comprise the isotope or radioisotope in an amount at least greater than the natural abundance of the isotope or radioisotope. For example, when an atom is designated as “D” or “deuterium”, the position is understood to have deuterium at an abundance that is at least 3000 times greater than the natural abundance of deuterium, which is 0.015% (i.e., at least 45% incorporation of deuterium).

All compounds, and pharmaceutically acceptable salts thereof, can be found together with other substances such as water and solvents (e.g. hydrates and solvates) or can be isolated.

In some embodiments, preparation of compounds can involve the addition of acids or bases to affect, for example, catalysis of a desired reaction or formation of salt forms such as acid addition salts.

Example acids can be inorganic or organic acids and include, but are not limited to, strong and weak acids. Some example acids include hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, *p*-toluenesulfonic acid, 4-nitrobenzoic acid, methanesulfonic acid, benzenesulfonic acid, trifluoroacetic acid, and nitric acid. Some weak acids include, but are not limited to acetic acid, propionic acid, butanoic acid, benzoic acid, tartaric acid, pentanoic acid, hexanoic acid, heptanoic acid, octanoic acid, nonanoic acid, and decanoic acid.

Example bases include lithium hydroxide, sodium hydroxide, potassium hydroxide, lithium carbonate, sodium carbonate, potassium carbonate, and sodium bicarbonate. Some example strong bases include, but are not limited to, hydroxide, alkoxides, metal amides, metal hydrides, metal dialkylamides and arylamines,

wherein; alkoxides include lithium, sodium and potassium salts of methyl, ethyl and t-butyl oxides; metal amides include sodium amide, potassium amide and lithium amide; metal hydrides include sodium hydride, potassium hydride and lithium hydride; and metal dialkylamides include lithium, sodium, and potassium salts of methyl, ethyl, n-propyl, *iso*-propyl, n-butyl, *tert*-butyl, trimethylsilyl and cyclohexyl substituted amides.

The phrase “pharmaceutically acceptable” is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

The present application also includes pharmaceutically acceptable salts of the compounds described herein. As used herein, “pharmaceutically acceptable salts” refers to derivatives of the disclosed compounds wherein the parent compound is modified by converting an existing acid or base moiety to its salt form. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts of the present application include the conventional non-toxic salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. The pharmaceutically acceptable salts of the present application can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, non-aqueous media like ether, ethyl acetate, alcohols (e.g., methanol, ethanol, *iso*-propanol, or butanol) or acetonitrile (MeCN) are preferred. Lists of suitable salts are found in *Remington's Pharmaceutical Sciences*, 17th ed., Mack Publishing Company, Easton, Pa., 1985, p. 1418 and *Journal of Pharmaceutical Science*, 66, 2 (1977). Conventional methods for preparing salt forms are described, for example, in *Handbook of Pharmaceutical Salts: Properties, Selection, and Use*, Wiley-VCH, 2002.

*Pharmaceutical Compositions*

When employed as pharmaceuticals, the compounds provided herein and pharmaceutically acceptable salts thereof can be administered in the form of pharmaceutical compositions. These compositions can be prepared as described herein or elsewhere, and can be administered by a variety of routes, depending upon whether local or systemic treatment is desired and upon the area to be treated. Administration may be topical (including transdermal, epidermal, ophthalmic and to mucous membranes including intranasal, vaginal and rectal delivery), pulmonary (e.g., by inhalation or insufflation of powders or aerosols, including by nebulizer; intratracheal or intranasal), oral, or parenteral. Parenteral administration includes intravenous, intraarterial, subcutaneous, intraperitoneal intramuscular or injection or infusion; or intracranial, (e.g., intrathecal or intraventricular, administration). Parenteral administration can be in the form of a single bolus dose, or may be, for example, by a continuous perfusion pump. In some embodiments, the compounds provided herein, or a pharmaceutically acceptable salt thereof, are suitable for parenteral administration. In some embodiments, the compounds provided herein are suitable for intravenous administration. In some embodiments, the compounds provided herein are suitable for oral administration. In some embodiments, the compounds provided herein are suitable for topical administration.

Pharmaceutical compositions and formulations for topical administration may include, but are not limited to, transdermal patches, ointments, lotions, creams, gels, drops, suppositories, sprays, liquids and powders. Conventional pharmaceutical carriers, aqueous, powder or oily bases, thickeners and the like may be necessary or desirable. In some embodiments, the pharmaceutical compositions provided herein are suitable for parenteral administration. In some embodiments, the compounds provided herein can be formulated for topical delivery (e.g., for the treatment of acne). An exemplary formulation includes:

about 10 to about 50 mM of a compound provided herein (e.g., a compound 767)

about 50% (v/v) 99.5 – 100% ethanol or isopropanol

about 0.25 to about 2% (w/v) carbomer (e.g., carbomer 934 or carbomer 940)

about 0.5 to about 1% (w/v) trolamine

water (to 100%).

In some embodiments, the pharmaceutical compositions provided herein are suitable for intravenous administration. In some embodiments, the pharmaceutical compositions provided herein are suitable for oral administration. In some  
5       embodiments, the pharmaceutical compositions provided herein are suitable for topical administration.

Also provided are pharmaceutical compositions which contain, as the active ingredient, a compound provided herein, or a pharmaceutically acceptable salt thereof, in combination with one or more pharmaceutically acceptable carriers (*e.g.*  
10       excipients). In making the pharmaceutical compositions provided herein, the active ingredient is typically mixed with an excipient, diluted by an excipient or enclosed within such a carrier in the form of, for example, a capsule, sachet, paper, or other container. When the excipient serves as a diluent, it can be a solid, semi-solid, or liquid material, which acts as a vehicle, carrier or medium for the active ingredient.  
15       Thus, the compositions can be, for example, in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), ointments, soft and hard gelatin capsules, suppositories, sterile injectable solutions, and sterile packaged powders.

Some examples of suitable excipients include, without limitation, lactose,  
20       dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, water, syrup, and methyl cellulose. The formulations can additionally include, without limitation, lubricating agents such as talc, magnesium stearate, and mineral oil; wetting agents; emulsifying and suspending  
25       agents; preserving agents such as methyl- and propylhydroxy-benzoates; sweetening agents; flavoring agents, or combinations thereof.

The active compound can be effective over a wide dosage range and is generally administered in an effective amount. It will be understood, however, that the amount of the compound actually administered will usually be determined by a  
30       physician, according to the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound administered, the

age, weight, and response of the individual subject, the severity of the subject's symptoms, and the like.

The compositions provided herein can be administered one from one or more times per day to one or more times per week; including once every other day. The skilled artisan will appreciate that certain factors can influence the dosage and timing required to effectively treat a subject, including, but not limited to, the severity of the disease or disorder, previous treatments, the general health and/or age of the subject, and other diseases present. Moreover, treatment of a subject with a therapeutically effective amount of a compound described herein can include a single treatment or a series of treatments. In some embodiments, the compositions provided herein are administered as a single dose.

Dosage, toxicity and therapeutic efficacy of the compounds provided herein can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., for determining the LD<sub>50</sub> (the dose lethal to 50% of the population) and the ED<sub>50</sub> (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio LD<sub>50</sub>/ED<sub>50</sub>. Compounds exhibiting high therapeutic indices are preferred. While compounds that exhibit toxic side effects can be used, care should be taken to design a delivery system that targets such compounds to the site of affected tissue in order to minimize potential damage to uninfected cells and, thereby, reduce side effects. In some embodiments, the compounds provided herein exhibit lower toxicity as compared to similar dosages of orlistat. Evaluation of toxicity may be determined, for example, using methods such as those described herein.

#### *Methods of treatment*

The present disclosure further provides methods for the treatment of disorders associated with elevated lipid concentrations (e.g., lipotoxicity). A number of such disorders are known in the art and can be readily identified by one of skill in the art. In some embodiments, the methods include a method for inhibiting serum lipases in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound provided herein, or a

pharmaceutically acceptable salt thereof. In some embodiments, the compounds provided herein decrease serum lipase concentrations. In some embodiments, the lipase is a pancreatic lipase such as human pancreatic tri-acyl glycerol lipase (hPNLIP), human pancreatic lipase related protein 2 (hPLRP2) and human colipase (hCEL). In some embodiments, the compounds provided herein can reduce or inhibit generation of free fatty acids. For example, the compounds provided herein can decrease serum concentrations of free fatty acids.

As used herein, the term “subject,” refers to any animal, including mammals. For example, the term “subject” includes, but is not limited to, mice, rats, other rodents, rabbits, dogs, cats, swine, cattle, sheep, horses, primates, and humans. In some embodiments, the subject is a human. In some embodiments, the subject is obese. The term “obese” as used herein refers to a subject having a body mass index of greater than 23, 25 and particularly greater than or equal to 30. Alternatively it could an increase in abdominal fat or girth more than normal for the race, ethnicity, sex or nationality of the individual.

In some embodiments, the methods described herein can include *in vitro* methods, e.g., contacting a sample (e.g., a cell or tissue) with a compound provided herein, or a pharmaceutically acceptable salt thereof.

In some embodiments, the disorder is acute pancreatitis. For example, the acute pancreatitis can be severe. In some embodiments, the methods provided herein can be useful in downgrading a severe case of acute pancreatitis to a mild case of pancreatitis. The disclosure provides methods of treating one or more symptoms of pancreatitis in a subject in need thereof by administering a therapeutically effective amount of a compound provided herein, or a pharmaceutically acceptable salt thereof, to treat one or more symptoms of acute pancreatitis. Exemplary symptoms of acute pancreatitis include abdominal pain, back pain, swollen abdomen, nausea, vomiting, fever, rapid pulse, shortness of breath, low body temperature and the like. .

Non-limiting embodiments of the invention provide for a method of reducing the risk of organ failure in a subject suffering from acute pancreatitis comprising administering, to the subject, an effective amount of a pancreatic lipase inhibitor. Organs for which the risk of organ failure may be reduced include the kidney (where failure is referred to as renal failure), the lung (where failure is referred to as

pulmonary failure), Shock with low blood pressure or an increase in heart rate or the appearance of pulmonary edema (noted as crackles on auscultation, or CXR, or CT scan) as well as multisystem organ failure (e.g. multiple organ dysfunction syndrome involving at least these two organs). The status of these organs may be determined using clinical methods well known in the art. For example, and not by way of limitation, kidney function (and the development of renal failure) may be assessed via increased blood urea nitrogen levels, increased creatinine, decreased urine output, and/or histologic findings; lung function and the development of pulmonary failure may be assessed using pulmonary function tests, blood gases (oxygen and carbon dioxide levels), oxygen supplementation requirements (e.g. nasal cannula or face mask or ventilator, with different percentages and flow rates of oxygen) and/or histologic findings; (for indices of organ failure, see J. Wallach, 1978, Interpretation of Diagnostic Tests, Third Edition, Little, Brown and Co., Boston, and/or J. Wallach, 2006, Interpretation of Diagnostic Tests, Eighth Edition, Lippincott Williams & Wilkins, both incorporated by reference in their entireties). Likewise, an index of systemic inflammation is an increase in levels of one or more inflammatory mediators, including but not limited to CRP, or parts of systemic inflammatory response syndrome (SIRS) criteria, tumor necrosis factor alpha, monocyte chemotactic protein 1 and/or interleukin 6. These embodiments are supported, at least in part, by working examples below, which show the effectiveness of pancreatic lipase inhibitors in decreasing the risk of multisystem organ failure.

In some embodiments, the compounds provided herein are useful for reducing the risk of secondary effects of acute pancreatitis in a subject in need thereof. For example, the risk of developing shock can be reduced. In some embodiments, the risk of developing renal failure is reduced. In some embodiments, the risk of developing pulmonary failure is reduced.

In some embodiments, the disorder is acne. In other embodiments, the disorder is trauma, hemorrhage, critical illness, or sepsis. For example, the sepsis is culture negative sepsis. In some embodiments, the disorder is a burn. In other embodiments, the disorder is an infection. For example, the infection may be caused by one or more organisms selected from the group consisting of *P. auregenosa*, *S. aureus*, *B. subtilis*, and *B. cepecia*. See, for example, Ryan CM, Sheridan RL, Schoenfeld DA, Warshaw

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## EXAMPLES

### Example 1. Preparation and testing of non-formylated amino acid analogs

A number of non-formylated amino acid analogs were prepared in which the  
 15 L- amino-ester leucine was replaced by alternates. The synthetic steps involved in this  
 process are outlined in **FIG. 2**. As shown in **FIG 3**, the compounds generated  
 included

compounds where the L-leucine (#723, which is also orlistat) amino-ester was  
 replaced by alternates such as N-methyl leucine (#724) or more polar or shorter  
 20 alternates, including L-alanine (#716), N-acetyl-L-cystine (#717), L-aspartate (#718),  
 L-histidine (#725), L-methionine sulfone (#726), L-arginine (727), L-diaminopimelic  
 acid (#728), L-serine (#729), L-ornithine (#731), or N-acetyl leucine (#732).

To test the efficacy of these compounds, the agents were dissolved as a 20 mM  
 stock in ethanol, and further diluted to in PBS as a 600 micromolar working stock  
 25 (3.3% ethanol). This was either used immediately or left at room temperature for 16-  
 20 hours overnight before retesting efficacy. The agents were incubated with a  
 pancreatic lysate in serial 1/3 dilutions spanning a range of 200 to 0.3 micromolars for  
 30 minutes. 5 microliters of these mixtures were then used to measure lipase activity  
 using a commercial lipase assay (Pointe scientific) containing a monoacyl glycerol  
 30 lipase in the reagent. The lipase assay was done using reagents in proportion to the  
 recommended protocol. Values were depicted as % maximal lipase activity of the well

without any inhibitor. As can be seen there was no increase in efficacy of the non-formylated orlistat analogs over that of orlistat (**FIG. 4**).

#### Example 2. Preparation and testing of formylated amino acid analogs

5 A number of formylated amino acid analogs were prepared in which the L-amino-ester leucine was replaced by alternates. The synthetic steps involved in this process are outlined in **FIG. 2** and **FIG. 5**.

These agents (#733, 734, 738, 739, 740, 742, 743, as shown in **FIG. 6**) were initially tested as described in Example 1. It was noted that compounds 741, 736, 743  
10 had an approximately 10-fold improvement in stability and efficacy over orlistat after overnight storage (**FIG. 7**). The compounds were further tested for efficacy in reducing lipotoxic damage to acinar cells in acinar-adipocyte co-culture as described in Navina S, Acharya C, DeLany JP, Orlichenko LS, Baty CJ, Shiva SS, Durgampudi C, Karlsson JM, Lee K, Bae KT et al: Lipotoxicity causes multisystem organ failure and exacerbates acute pancreatitis in obesity. *Sci Transl Med* 2011, 3(107):107ra110  
15 (**FIG. 8A**), and while all agents were effective at 66 micromolars (the nearest concentration to IC<sub>50</sub> of orlistat after overnight incubation), compound 743 was noted to be toxic to acinar cells (**FIG. 8B**) and compound 741 was the least toxic at this concentration, while retaining its efficacy. Compound 736 also retained its efficacy at  
20 low toxicities.

#### Example 3. Preparation and testing of $\beta$ -chain analogs

To further explore options for improving efficacy of the analogs, the beta chain of 741 was altered to make it more hydrophilic. For this, compounds 760, 762,  
25 763 were prepared as described in **FIGS. 9-14**. The modifications at this position were associated with no improvement in the lipase inhibition efficacy, and, in fact, a decrease in efficacy was observed. See **FIG. 15**.

#### Example 4. Preparation and testing of $\alpha$ -chain analogs

30 A series of analogs were prepared based on modifications to the alpha chain as shown in **FIG. 16**, generating compounds 767 and 768. While these agents had

equivalent efficacy in the lipase activity assay to orlistat when fresh, agent 767 significantly retained its efficacy as a solution when left overnight. See **FIG. 17**.

Example 5. Inhibition of free fatty acid (FFA) generation, toxicity, and efficacy in inhibiting recombinant human pancreatic tri-acyl glycerol lipase [hPNLIP], pancreatic lipase related protein 2 (hPLRP2) and carboxyester lipase (hCEL)

The efficacy of a selection of the prepared analogs was explored to determine their ability to inhibit free fatty acid (FFA) generation from recombinant human lipases while retaining stability. To test these features, the analogs were dissolved in ethanol (200 mM stock) and further diluted to a 600 micromolar (0.3% ethanol) working stock in PBS. The agents were incubated with the recombinant enzymes in serial 1/3 dilutions spanning a range of 200 to 0.3 micromolar for 30 minutes, and then added to the substrate 1 mM glyceryl trilinoleate (GTL) in PBS, pH 7.4 along with cofactor colipase (CLPS; 0.5mcg/ml). As seen in **FIG. 18**, agents 767, 733, 734, 740 and 743 had  $IC_{50}$ s against recombinant human pancreatic tri-acyl glycerol lipase [PNLIP; hPTL, in the presence of colipase (CLPS)] that were 50x lower than orlistat or 741, while retaining an  $IC_{50} < 2$  micromolar when stored overnight. In particular, compounds 767 and 740 displayed the best stability.

Toxicity studies of the relevant compounds were also performed using by diluting the original ethanol stock 200 mM into the incubation medium for acinar cells (HEPES buffer, pH 7.4, as described by Navina et al) 600 micromolar stock solutions of the compounds in 0.3% ethanol in PBS. These were added to acinar cells at 1/3 dilutions starting at 200 micromolar. Mouse pancreatic acinar ATP levels and LDH leakage were measured over 4 hours and compared to control. Any number positive over control indicates % injury greater than control acini. Agent 743 (See **FIG. 8B**), and 733 were, however, toxic to acinar cells, causing a drop in ATP and inducing LDH leakage (see **FIG. 19**) at concentrations in the 20-200 micromolar range—concentrations relevant to in vivo use.

These compounds were further tested for efficacy in reducing recombinant human pancreatic lipase related protein 2 (hPLRP2) and carboxyester lipase (hCEL) as shown in **FIG. 20**. These lipases form 15-30% of pancreatic lipases. Agents 740, 734 and 767 again exhibited  $IC_{50}$ s of 2 micromolars or less. The relative potency and

toxicities are summarized in the table in **FIG. 21**. Noting this, along with the strengths of 767, i.e., a) the higher efficacy against mouse pancreatic lysates (**FIGs. 7 and 17**), b) higher potency against the most prevalent lipase (hPTL) (**FIG. 18**), c) better stability in aqueous media (**FIGs. 17 and 18**), and d) lower toxicity (**FIG. 19**), compound 767 was elected to proceed on to in vivo studies. Furthermore, Agents 740 and 767 at 10 micromolar were less toxic and more efficacious in reducing GTL induced acinar injury than orlistat (**FIG. 28**)

#### Example 6. In vivo studies of compound 767

The goal of this in vivo study was to learn if the severity of lethal pancreatitis could be reduced in mice when compound 767 is administered as a single therapeutic dose, and whether the compound could avoid the limitations of orlistat, e.g., repeated high dosing and hypertriglyceridemia. See **FIG. 22**.

Compound 767 or orlistat was dissolved as 1 mg/10 microliter ethanol, which was diluted to 400 microliters with saline (final concentration 2.5% ethanol). Genetically obese male ob/ob mice (50-60 gm) were used and baseline tail vein blood draw was collected for serum lipase, triglycerides, and BUN (blood urea nitrogen). The time line is shown as in **FIG. 23A**. Severe pancreatitis was induced by implanting an alzet pump subcutaneously containing 2.5 mg/ml caerulein, which was administered at a dose of 50 mc/kg/hr. Six hours later a tail vein sample (50 microliters) was tested for serum lipase to verify an increase > 3 fold basal. As seen in **FIG. 23B**, this was achieved ( $P=0.003$ ).

The agents were then administered as an intraperitoneal dose (20 mg/kg single dose [n=8 for 767 or orlistat n=7]). Animals were given saline IP 1 mL BID, vitals were monitored daily focusing on severity (Temperature for fever or hypothermia and Pulse distention for shock). These are respectively part of SIRS and revised Atlanta criteria for severity (Classification of acute pancreatitis--2012: revision of the Atlanta classification and definitions by international consensus. Gut 2013, 62(1):102-111). tail vein samples were collected for severity parameters (Serum BUN, serum calcium and total white blood cell count) which are a part of Ranson's and Glasgow criteria) and triglycerides. Animals were sacrificed if they were moribund.

As can be seen in **FIG. 23**, *in vivo* all untreated mice developed renal failure (BUN  $85 \pm 18$  mg/dl) **FIG. 23C**, hypocalcemia (serum calcium  $4.9 \pm 0.2$  mg/dl) **FIG. 23D**, SIRS **FIG. 23E**, shock **FIG. 23F** and 100% mortality. **FIG. 23G**. 767 was more efficacious than orlistat in normalizing BUN (peak  $18.5 \pm 0.9$  vs. orlistat  $50 \pm 4.4$  mg/dl,  $p < 0.05$ ) **FIG. 23C**, serum calcium ( $8.8 \pm 1.0$  mg/dl vs.  $4.2 \pm 0.3$  mg/dl,  $p < 0.05$ ) **FIG. 23D**, UFAs ( $2.4 \pm 0.4$  mM vs.  $5.4 \pm 0.9$  mM), preventing shock (PD:  $290 \pm 20$   $\mu$ m vs.  $171 \pm 21$   $\mu$ m,  $p < 0.05$ ) **FIG. 23F**, leucopenia (in 0/8 mice vs. 4/7 mice,  $p < 0.03$ , see **FIG. 25**), hypothermia ( $94.1 \pm 0.8$  vs.  $86 \pm 0.9$  °F,  $p < 0.01$ ; **FIG. 23E**) and improving 5 day survival (8/8 vs. 2/7,  $p < 0.01$ ) **FIG. 23G**. There was 8/8 (meantime 44 hours) mortality in the vehicle group, 5/7 mortality in the orlistat group. The gross appearance with the two agents is compared in **FIG. 24**. As can be seen there is much more extensive fat necrosis in the orlistat treated animal. This protection from agent 767 was achieved without the hypertriglyceridemia associated with the dosing needed for orlistat to be protective (**Fig. 25**). The results are summarized in the table in **FIG 25**.

#### Example 7. FFA generation in a medium of *P. acnes*

The lipolysis by *P. acnes* was inhibited by 767 (**FIG. 26** and **FIG. 27**).

#### *P. acnes* BROTH culture:

For medium, 2.0 g of Casein hydrolysate enzymatic digest (Cat# 12855, Affymetrix Inc, Ohio, USA), 1.0 g of Yeast extract (Cat#61180-5000, Acros organics, New Jersey, USA) and 0.03 g of Victoria Blue B (Cat#sc-216055, Santa Cruz Biotechnology Inc, California, USA) were dissolved completely in 200 ml of double distilled water with mild heating. The mixed solution was sterilized by autoclaving at 15 lbs pressure (121°C) for 15 min. The autoclaved solution allowed to cool down to 50°C, then 6 ml of emulsified lipase substrate slowly added with continuous stirring to get an even distribution and stored at 4°C for *P. acnes* culture.

Lipase substrate preparation: Lipase substrate was prepared by mixing 200  $\mu$ l of Tween 80 (Cat#P4780, Sigma, St louis, USA) in 100 ml of warm double distilled water and 25 ml of Cotton seeds oil (Cat#C0145, Spectrum chemical, California, USA). The mixture was agitated vigorously followed by sonication (10 sec pulse x 5 times) to get an emulsion.

*P. acnes* culture-expansion medium, storage conditions, size of inoculum used in medium.

A small part of lyophilized *Propionibacterium acnes* (Strain VPI0389, ATCC) was added to the medium and allowed to grow at 37°C for 48 h in a BD GasPak EZ standard incubation container (Cat#260671, Beckton Dickinson, MD, USA) with two anaerobe Sachets (Cat#260683, Beckton Dickinson, MD, USA) which maintained the anaerobic condition within the container. After 48 h of culture, bacterial count was measured by turbidity (OD600nm) method. Amount of secreted lipase and produced FFA were measure in the culture supernatant.

For *P. acnes* storage, cultured bacteria in 1.5 ml autoclaved eppendorf microfuge (1 ml/microfuge) was span down at 5000 rpm for 5 min, removed the spent medium, pelleted bacteria was resuspended in 15% glycerol contained *P. acnes* culture medium (1 ml/microfuge) without substrate and stored at -80°C for future use.

For further *P. acnes* culture, one aliquoted *P. acnes* stock was taken out from -80°C and thawed in ice. Almost 30 µl of *P. acnes* stock ( $1 \times 10^6$ /30 µl) was added into 1 ml of culture medium with lipase substrate in each 2 ml Eppendorf microfuge and incubated at 37°C for 48 h in anaerobic condition.

Efficacy Testing or lipase inhibitors against *P. acnes*:

Orlistat or agent 767 (stocks 200mM in ethanol) added at the indicated concentrations at the beginning of the incubations. At the end of the incubation period, a portion of the well mixed medium was removed, and free fatty acid generation using the HR Series NEFA-HR(2) kit from Wako Diagnostics (Richmond Virginia).

#### *P. acnes* Agar culture

Spirit blue agar: Supplier, catalog #. Preparation, storage. Culture inoculum size, culture conditions.

For plate preparation, 3.215 g of Spirit blue agar (Cat#M445, HiMedia Laboratories Pvt Ltd, Mumbai, India) dissolved in 100 ml of double distilled water, autoclaved, allowed to cool to 55 °C, added 3 ml of warm lipase substrate and mixed well. In warm condition, the mixture was poured into tissue culture plates (6 well, 12 well plates) in aseptically. The solidified agar plates were wrapped with parafilm and kept at 37°C overnight to confirm no contamination. The extra plates were kept at 4°C

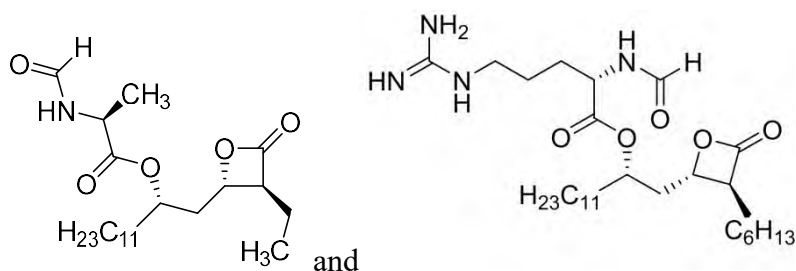
freezer for future use. Either thawed *P. acnes* -80°C stock was spread out (30 µl/well) in 6 well/12 well plates or inoculated throughout the well by means of inoculating loops. Then the plates were kept at 37°C in BD GasPak EZ chamber with one anaerobe sachets and waited for 5-7 days to see the bacterial colonies. These were then visualized and photographed on a trans illuminator.

### OTHER EMBODIMENTS

It is to be understood that while the invention has been described in conjunction with the detailed description thereof, the foregoing description is intended to illustrate and not limit the scope of the invention, which is defined by the scope of the appended claims. Other aspects, advantages, and modifications are within the scope of the following claims.

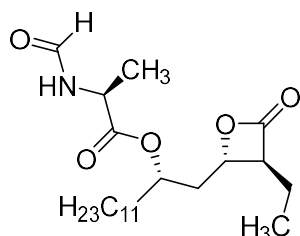
## WHAT IS CLAIMED IS:

1. A compound selected from the group consisting of:



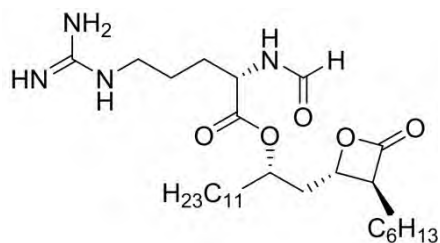
or a pharmaceutically acceptable salt thereof.

2. The compound of claim 1, wherein the compound is:



or a pharmaceutically acceptable salt thereof.

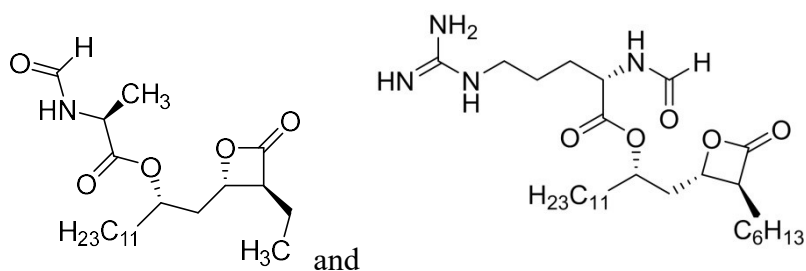
3. The compound of claim 1, wherein the compound is:



or a pharmaceutically acceptable salt thereof.

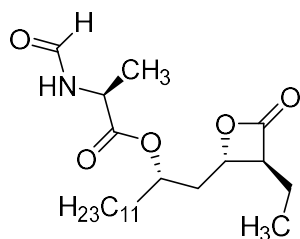
4. A pharmaceutical composition comprising a compound of any one of claims 1-3, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

5. Use of a compound selected from the group consisting of:



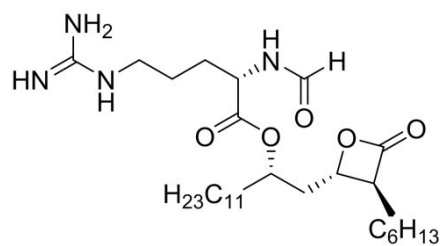
or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating acute pancreatitis in a subject in need thereof.

6. The use of claim 5, wherein the acute pancreatitis is severe.
7. The use of claim 5, wherein the acute pancreatitis is downgraded from severe to mild following administration.
8. The use of claim 5, wherein the subject is obese.
9. The use of claim 5, wherein the risk of developing shock is reduced.
10. The use of claim 5, wherein the risk of developing renal failure is reduced.
11. The use of claim 5, wherein the risk of developing pulmonary failure is reduced.
12. The use of any one of claims 5-11, wherein the compound is:



or a pharmaceutically acceptable salt thereof.

13. The use of any one of claims 5-11, wherein the compound is:



or a pharmaceutically acceptable salt thereof.