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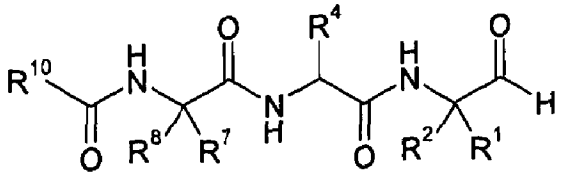

(A)

(57) Abstract: The present invention pertains generally to the field of therapeutic compounds, and more specifically to certain aldehyde compounds of the following formula (A) (for convenience, collectively referred to herein as "ALD compounds"), which, *inter alia*, inhibit a dust mite Group 1 peptidase allergen (*e.g.*, Der p 1, Der f 1, Eur m 1). The present invention also pertains to pharmaceutical compositions comprising such compounds, and the use of such compounds and compositions, both *in vitro* and *in vivo*, to inhibit a dust mite Group 1 peptidase allergen, and in the treatment of diseases and disorders that are mediated by a dust mite Group 1 peptidase allergen; that are ameliorated by the inhibition of a dust mite Group 1 peptidase allergen; asthma; rhinitis; allergic conjunctivitis; atopic dermatitis; an allergic condition which is triggered by dust mites; an allergic condition which is triggered by a dust mite Group 1 peptidase allergen; and canine atopy.

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ALDEHYDE COMPOUNDS AS INHIBITORS OF DUST MITE GROUP 1 PEPTIDASE ALLERGEN AND THEIR USE

RELATED APPLICATION

This application is related to United Kingdom patent application number 1011411.4 filed 06 July 2010, the contents of which are incorporated herein by reference in their entirety.

TECHNICAL FIELD

The present invention pertains generally to the field of therapeutic compounds, and more specifically to certain aldehyde compounds (for convenience, collectively referred to herein as "ALD compounds"), which, *inter alia*, inhibit a dust mite Group 1 peptidase allergen (e.g., Der p 1, Der f 1, Eur m 1). The present invention also pertains to pharmaceutical compositions comprising such compounds, and the use of such compounds and compositions, both *in vitro* and *in vivo*, to inhibit a dust mite Group 1 peptidase allergen, and in the treatment of diseases and disorders that are mediated by a dust mite Group 1 peptidase allergen; that are ameliorated by the inhibition of a dust mite Group 1 peptidase allergen; asthma; rhinitis; allergic conjunctivitis; atopic dermatitis; an allergic condition which is triggered by dust mites; an allergic condition which is triggered by a dust mite Group 1 peptidase allergen; and canine atopy.

BACKGROUND

A number of patents and publications are cited herein in order to describe and disclose the invention more fully and the state of the art to which the invention pertains. Each of these references is incorporated herein by reference in its entirety into the present disclosure, to the same extent as if each individual reference was specifically and individually indicated to be incorporated by reference.

Throughout this specification, including the claims that follow, unless the context requires otherwise, the word "comprise," and variations such as "comprises" and "comprising," will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

It must be noted that, as used in the specification and the appended claims, the singular forms "a," "an," and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a pharmaceutical carrier" includes mixtures of two or more such carriers, and the like.

Ranges are often expressed herein as from "about" one particular value, and/or to "about" another particular value. When such a range is expressed, another embodiment includes from the one particular value and/or to the other particular value. Similarly, when values are expressed as approximations, by the use of the antecedent "about," it will be understood that the particular value forms another embodiment.

This disclosure includes information that may be useful in understanding the present invention. It is not an admission that any of the information provided herein is prior art or relevant to the presently claimed invention, or that any publication specifically or implicitly referenced is prior art.

Allergic Diseases

Allergic diseases, such as asthma, rhinitis, conjunctivitis and eczema, are escalating global healthcare problems that have not been contained by existing medications. These clinical conditions are initiated and triggered in genetically susceptible individuals by exposure to a diverse range of substances known as allergens. Numerous sources of allergen exist, but those associated with domestic environments are especially important as disease triggers because people are exposed to them for long periods. Amongst domestic allergens, those derived from house dust mites (HDM) are globally the most significant cause of allergic disease. These mites are found abundantly in homes, in workplaces, in entertainment venues, and in public and private transport vehicles. Chronic sensitization to HDM allergens can occur at any time of life and subsequent exacerbations triggered by repeated allergen exposure increase the probability that minor conditions such as allergic rhinitis will escalate into asthma, which is more serious. In addition, house dust mites create health problems for animals that co-habit with humans. For example, the condition of canine atopy is an inherited condition that gives rise to a miscellany of allergic conditions of the skin, nose and eyes (Sture et al., 1995). Perennial symptoms are commonly associated with sensitization and subsequent re-exposure to dust mite allergens. It is well-described with house dust mites recognised as significant triggers of perennial allergic symptoms in dogs, resulting in a need for veterinary treatment to alleviate disease symptoms. The symptoms seen in dogs largely resemble those seen in human atopic dermatitis and conjunctivitis.

The pre-eminence of house dust mite allergens as triggers of allergic conditions has resulted in a need to understand why they are allergenic. Studies into the molecular basis of allergenicity have revealed that the HDM allergen of greatest clinical significance is a cysteine peptidase. Surprisingly, this peptidase activity contributes decisively to the development of allergy to HDM allergens generally and to other by-stander allergens unrelated to HDM.

Several species of dust mite are known (e.g., Dermatophagoides pteronyssinus, Dermatophagoides farinae, Dermatophagoides siboney and Euroglyphus maynei) and each of these produce numerous allergenic proteins. The allergens from the different species can be categorized into distinct groups which show immunological cross-reactivity because they are extremely similar proteins with highly conserved amino acid sequences. In the case of HDM, the Group 1 allergens (e.g., Der p 1, Der f 1, Eur m 1) underlie > 95% of HDM allergy and are a highly conserved family of cysteine peptidases. The normal function of these cysteine peptidases in mites is as digestive enzymes that have the capability of digesting the resilient structural proteins in dried flakes of exfoliated skin which form a significant component of the HDM diet. The degree of amino acid sequence conservation in HDM Group 1 cysteine peptidase allergens (>90%) is such that they may be regarded as functionally identical and, for drug discovery purposes, a single therapeutic target. It is also now known that a clinically significant allergen from another mite, Blomia tropicalis, of more restricted geographical distribution is a related cysteine peptidase and shows immunological reactivity with the Group 1 allergens from house dust mites. This suggests that an inhibitor of Gropup 1 HDM allergens may be more generally applicable as inhibitors of related molecules in all species of mite that cause allergy.

The Group 1 HDM allergens are major triggers of asthma and other allergic conditions. When inhaled, their peptidase activity cleaves proteins and thus (i) increases the permeability of the airway epithelium allowing access for them and other, non-peptidase allergens to dendritic antigen presenting cells, and (ii) triggers signalling events that skew immunological responses to the Th2 phenotype. Both of these events initiate allergy and must be recapitulated to maintain it. Blocking these essential, initial steps in allergic sensitization by inhibiting the cysteine peptidase activity of the Group 1 allergens could therefore provide the basis for a unique approach to the treatment and prevention of allergy.

Group 1 HDM allergens as a therapeutic target

People are exposed to house dust mite (HDM) allergens for up to 23 hours each day; consequently these allergens are of major significance in a range of clinical conditions that share elevated IgE as a molecular marker of disease. Population-based cross-sectional and longitudinal studies demonstrate that a positive skin test reaction for IgE antibody to HDM allergens is associated with asthma, persistent rhinitis, allergic conjunctivitis or atopic dermatitis (Arruda et al., 1991; Gelber et al., 1993; Miyamoto et al., 1968; Peat et al., 1996; Peat et al., 1991; Pollart et al.,1989; Smith et al., 1969; Sporik et al., 1990) In genetically predisposed individuals, first encounters with these allergens can trigger the onset of disease at any time and, with repeated exposures through life, minor conditions can evolve into serious disease. Thus, the probability of developing asthma is

increased 10-20 fold after rhinitis has been established. Furthermore, the largest ever study of adult-onset asthma demonstrated, contrary to previous beliefs, that HDM allergy is as important to adults as children (Jaakkola et al., 2006).

Allergy risk and severity both show dose-response relationships with allergen exposure. This increases the attraction of pharmacological intervention aimed at Group 1 HDM allergens. Clinical evidence strongly supports a threshold level of exposure above which sensitization of at-risk individuals becomes probable. Furthermore, a dose-response relationship exists between concentrations of these allergens in homes (and thus human exposure) and the importance of this sensitization to asthma (Gelber et al., 1993; Peat et al., 1991; Platts-Mills et al., 1997; Platts-Mills et al., 1987; Dowse et al., 1985; Charpin et al., 1991). These observations imply that avoidance or inactivation of these key allergens (i.e., by reducing the dose of functional allergen to which an individual is exposed) is likely to decrease sensitization, causing symptoms to wane and clinical prognosis to improve. Reducing exposure to these allergens is the basis of physical allergen avoidance strategies which have been investigated as a means of controlling allergy. The benefits of physical allergen avoidance are supported by controlled trials in which people have been moved to environments (e.g., alpine sanatoria) where allergen avoidance can be managed rigorously (Dowse et al., 1985; Platts-Mills et al., 2000; Vervloet et al., 1982; Peroni et al., 1994). The effect of a strict regime of allergen avoidance is rapid in onset, with patients showing a significant decrease in markers of inflammation or medicine usage within 2 to 4 weeks (van Velzen et al., 1996; Schultze-Werninghaus, 2006; Bodini et al., 2004; Gourgoulianis et al., 2001; Piacentini et al., 1999; Piacentini et al., 1998). However, such physical avoidance measures are generally impractical and the benefits wane upon a return to everyday life.

Given the contribution of proteolytic activity to allergic sensitization, the development of a means to inhibit the peptidase activity of Group 1 allergens would provide pharmacological allergen inactivation that would mimic the effects of physical allergen avoidance. It is envisaged that the optimum means to achieve this objective would be to treat patients with such inhibitors, either topically or systemically. One advantage of this approach is that pharmacological allergen inactivation would travel with the person being treated (i.e., it would be "portable") to achieve the benefits of continuous allergen avoidance, something which is not achievable with physical allergen avoidance measures. In addition to their use as medicines, it is likely that inhibitors of Group 1 peptidase allergens would have additional value as acaricides applied as environmental treatments. By inactivating key enzymes involved in the digestion of food by HDM, such inhibitors would deprive mites of a source of nutrition causing them to fail to thrive.

Allergens and peptidase activity

Two observations are relevant to an appreciation of the contribution of peptidase activity to allergic sensitization. The first is the demonstration that the proteolytic activity of a small cadre of enzymatic allergens is vital to allergic sensitization via the airways. The second is the ability of peptidases is to drive allergic sensitization to by-stander allergens that lack proteolytic activity. When administered alone and without adjuvants, such non-enzymatic bystanders fail to evoke responses, induce tolerance or show only weak IgG-mediated reactions, even with systemic immunisation (Seymour et al., 1998; van Halteren et al., 1997; McMillan et al., 2004; McCusker et al., 2002; Hellings et al., 2001). Since the majority of allergens are non-proteolytic, the ability of individual peptidases to exert a marked influence on the development of sensitization to by-stander allergens creates an interesting therapeutic opportunity which inhibitors of Group 1 mite allergens could exploit.

Previous studies have shown that the proteolytic activity of Group 1 HDM allergens makes an essential contribution to allergy through two general mechanisms that are central to the initiation and maintenance of the allergic state. These are:

- Facilitating allergen delivery across mucosal surfaces, thus gaining access to antigen presenting cells (e.g., in the lungs, dendritic cells) (Holt et al., 1990; Holt, 2002; Huh et al., 2003; Lambrecht et al., 2003a; Lambrecht et al., 2002; Lambrecht et al., 2003b; Wan et al., 2000).
- Activating signal transduction pathways that favour development of allergy in the genetically predisposed (Hellings et al., 2001; Comoy et al., 1998; Stewart et al., 2003).

HDM peptidase allergens therefore exert significant effects that are independent of IgE, but which have an essential bearing on IgE sensitization and allergic responses (King et al., 1998; Asokananthan et al., 2002). These actions serve to promote sensitization to the inciting peptidase allergen but, as described above, because the effects of the general mechanisms are essentially allergen non-specific, sensitization to non-enzymatic bystander allergens also occurs (Stewart et al., 2003; Wan et al., 1999).

Allergen delivery

Dendritic cells are the primary antigen presenting cells of the respiratory tract (Holt et al., 1990; Holt, 2002; Huh et al., 2003; Lambrecht et al., 2003a; Lambrecht et al., 2002; Lambrecht et al., 2003b). However, for effective IgE responses to develop and be maintained, the probability of contact with antigens must be increased (Lambrecht et al., 2003b). This essential step in the detection of allergen is facilitated by the cysteine peptidase activity of Group 1 mite allergens which cleaves the transmembrane adhesion

proteins of epithelial tight junctions, facilitating paracellular delivery of any allergen to dendritic cells (Wan et al., 1999; Wan et al., 2000; Winton et al., 1998).

IgE-independent cell activation

Peptidase allergens are thought to contribute to innate immunity and activate a variety of cells by numerous IgE-independent mechanisms. Signalling pathways activated by cleavage of tethered ligand receptors on epithelial cells is one such mechanism contributing to the chronic release of GM-CSF and IL-6. These cytokines are present in increased amounts in the airways in allergic asthma and rhinitis (Broide et al., 1992; Fahy et al., 1995; Muraguchi et al., 1988; Vercelli., 1989). They promote a Th2 allergic bias via several actions. For example, IL-6 is essential to B cell maturation and in the IL-4-dependent synthesis of IgE (Muraguchi et al., 1988; Vercelli., 1989). GM-CSF generates signals that cause dendritic cells to migrate from the airway epithelium to present captured antigens at regional lymph nodes (Stick et al., 2003). Proteolytic activity that cleaves tethered ligand receptors is thus associated with a chain of events central to both the initiation of allergic sensitization and its maintenance. Peptidase allergens activate mast cells by IgE-independent mechanisms and it follows, therefore, that a contribution to the acute bronchoconstriction resulting from allergen challenge must be due to this peptidase-dependent activation. This suggests that inhibitors of Group 1 peptidase allergens should attenuate acute allergic bronchoconstriction. Other IgE-independent mechanisms involve a cleavage of cytokine and IgE receptors that are associated with an augmentation of allergy (Ghaemmaghami et al., 2002), cleavage of antipeptidase defences (which may already be defective in allergy) and cleavage of other protective factors such as surfactant proteins (Deb et al., 2007).

Demonstrations of proteolytic allergen contributions to allergy

The potential importance of peptidase allergens as a target in allergy is demonstrated by the ease and directness with which they evoke IgE sensitization and by studies with generic inhibitors of cysteine peptidases in experimental animals.

Strong allergen-specific IgE sensitization can be achieved by non-invasive exposure of mice to Der p 1 of high specific proteolytic activity in the absence of adjuvants (Zhang et al., 2009). In Brown Norway rats, development of Der p 1-specific IgE and allergic responsiveness also occurs without the need for additional adjuvants. In contrast, the difficulties in raising high titre antibodies to recombinant Der p 1 that lacks high enzyme activity (and which therefore behaves like a by-stander allergen) are well known. The proteolytic nature of Der p 1 also augments the sensitization to non-peptidase by-stander allergens from HDM and other sources (Gough et al., 2001).

The promotion of allergen delivery by peptidase allergens may be augmented by their inactivation of antipeptidase defences (Kalsheker et al., 1996). Of related significance is that the loss of functional polymorphisms in endogenous enzyme inhibitors (e.g., chromosome 5q32 LETK1, chromosome 7 PAI-I, chromosome 11 C1 esterase inhibitor, chromosome 14 serpin cluster, chromosome 18q21) predisposes the subject to allergic disease. This recent evidence supplements functional associations between allergy and protease inhibitor deficiency that have accrued over the past 25 years (Rudolph et al., 1978; Hyde et al., 1979; Eden et al., 2003; Sigsgaard et al., 2000).

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a bar graph showing the magnitude of the acute bronchoconstrictor response to house dust mite allergen following Challenge 1 (left) and Challenge 2 (right). The response to Challenge 2 is expressed as a percentage of the magnitude of the mean response following Challenge 1 (data for challenge 2 shown as mean and standard error of the mean).

Figure 2 is a bar graph showing the percentage inhibition of the control acute bronchoconstrictor response to house dust mite allergen (Challenge 1) following a subsequent allergen challenge (Challenge 2) administered 15, 30 and 60 minutes after treatment with compound ALD-035 (data reported as mean and standard error of the mean).

SUMMARY OF THE INVENTION

One aspect of the invention pertains to certain aldehyde compounds (for convenience, collectively referred to herein as "ALD compounds"), as described herein.

Another aspect of the invention pertains to a composition (e.g., a pharmaceutical composition) comprising an ALD compound, as described herein, and a pharmaceutically acceptable carrier or diluent.

Another aspect of the invention pertains to a method of preparing a composition (e.g., a pharmaceutical composition) comprising the step of admixing an ALD compound, as described herein, and a pharmaceutically acceptable carrier or diluent.

Another aspect of the present invention pertains to a method of inhibiting a dust mite Group 1 peptidase allergen (e.g., Der p 1, Der f 1, Eur m 1), *in vitro* or *in vivo,* comprising contacting a dust mite Group 1 peptidase allergen with an effective amount of an ALD compound, as described herein.

Another aspect of the present invention pertains to a method of inhibiting a dust mite Group 1 peptidase allergen in a cell, *in vitro* or *in vivo,* comprising contacting the cell with an effective amount of an ALD compound, as described herein.

Another aspect of the present invention pertains to a method of treatment comprising administering to a subject in need of treatment a therapeutically-effective amount of an ALD compound, as described herein, preferably in the form of a pharmaceutical composition.

Another aspect of the present invention pertains to an ALD compound as described herein for use in a method of treatment of the human or animal body by therapy.

Another aspect of the present invention pertains to use of an ALD compound, as described herein, in the manufacture of a medicament for use in treatment.

In one embodiment, the treatment is treatment of a disease or condition that is mediated by a dust mite Group 1 peptidase allergen.

In one embodiment, the treatment is treatment of a disease or condition that is ameliorated by the inhibition of a dust mite Group 1 peptidase allergen.

In one embodiment, the treatment is treatment of: asthma, for example, atopic asthma; allergic asthma; atopic bronchial IgE-mediated asthma; bronchial asthma; extrinsic

asthma; allergen-induced asthma; allergic asthma exacerbated by respiratory virus infection; infective asthma; infective asthma caused by bacterial infection; infective asthma caused by fungal infection; infective asthma caused by protozoal infection; or infective asthma caused by viral infection.

In one embodiment, the treatment is treatment of: bronchial hyperreactivity associated with asthma; or bronchial hyperresponsiveness associated with asthma.

In one embodiment, the treatment is treatment of: airway remodelling associated with an allergic lung disease, for example, airway remodelling associated with asthma.

In one embodiment, the treatment is treatment of: asthma co-presented with a chronic obstructive lung disease, for example, asthma co-presented with emphysema; or asthma co-presented with chronic bronchitis.

In one embodiment, the treatment is treatment of: rhinitis, for example, allergic rhinitis; *perennial rhinitis*; *persistent rhinitis*; or IgE-mediated *rhinitis*.

In one embodiment, the treatment is treatment of: allergic conjunctivitis, including, for example, IgE-mediated conjunctivitis.

In one embodiment, the treatment is treatment of: atopic dermatitis.

In one embodiment, the treatment is treatment of: an allergic condition which is triggered by dust mites.

In one embodiment, the treatment is treatment of: an allergic condition which is triggered by a dust mite Group 1 peptidase allergen (e.g., Der p 1, Der f 1, Eur m 1).

In one embodiment, the treatment is treatment of: canine atopy.

In one embodiment, the treatment further comprises treatment with one or more additional therapeutic agents, for example, one or more additional therapeutic agents selected from agents used, or likely to be used, in the treatment of a respiratory disease.

Another aspect of the present invention pertains to an ALD compound, as described herein, for use as an acaricide.

Another aspect of the present invention pertains to a composition comprising an ALD compound, as described herein, for use as an acaricide.

Another aspect of the present invention pertains to an acaricide composition comprising an ALD compound, as described herein.

Another aspect of the present invention pertains to the use of an ALD compound, as described herein, as an acaricide.

Another aspect of the present invention pertains a method of killing mites (e.g., dust mites), comprising exposing said mites to an effective amount of an ALD compound, as described herein.

Another aspect of the present invention pertains a method of controlling (e.g., limiting) a mite (e.g., dust mite) population comprising exposing mites to an effective amount of an ALD compound, as described herein.

Another aspect of the present invention pertains to a kit comprising (a) an ALD compound, as described herein, preferably provided as a pharmaceutical composition and in a suitable container and/or with suitable packaging; and (b) instructions for use, for example, written instructions on how to administer the compound.

Another aspect of the present invention pertains to an ALD compound *obtainable* by a method of synthesis as described herein, or a method comprising a method of synthesis as described herein.

Another aspect of the present invention pertains to an ALD compound *obtained* by a method of synthesis as described herein, or a method comprising a method of synthesis as described herein.

Another aspect of the present invention pertains to novel intermediates, as described herein, which are suitable for use in the methods of synthesis described herein.

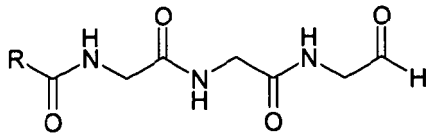
Another aspect of the present invention pertains to the use of such novel intermediates, as described herein, in the methods of synthesis described herein.

As will be appreciated by one of skill in the art, features and preferred embodiments of one aspect of the invention will also pertain to other aspect of the invention.

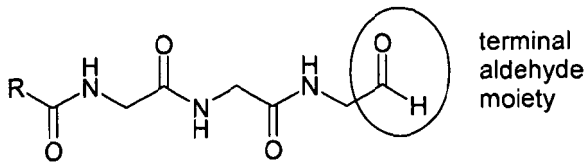
DETAILED DESCRIPTION OF THE INVENTION

Compounds

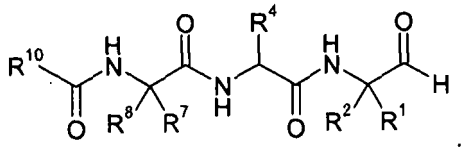
One aspect of the present invention relates to certain aldehyde compounds which are related to N-({[(2-Oxo-ethylcarbamoyl)-methyl]-carbamoyl}-methyl)-acylamide:



All of the compounds of the present invention have a terminal aldehyde moiety (i.e., -C(=O)H).



Thus, one aspect of the present invention pertains to compounds selected from compounds of the following formula, and salts, hydrates, and solvates thereof (e.g., pharmaceutically acceptable salts, hydrates, and solvates thereof), wherein R^1, R^2, R^4, R^7, R^8, and R^{10} are as defined herein (for convenience, collectively referred to herein as "ALD compounds"):



Depending upon the values of $-R^1$ and $-R^2$, the carbon atom to which they are attached may be chiral, and if so, may independently be in the (R) or (S) configuration. Unless otherwise indicated, it is intended that both configurations are encompassed. In a preferred embodiment, the configuration is (S).

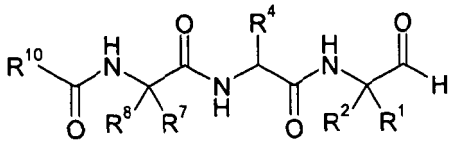
Depending upon the values of $-R^4$, the carbon atom to which it is attached may be chiral, and if so, may independently be in the (R) or (S) configuration. Unless otherwise indicated, it is intended that both configurations are encompassed. In a preferred embodiment, the configuration is (S).

Depending upon the values of $-R^7$ and $-R^8$, the carbon atom to which they are attached may be chiral, and if so, may independently be in the (R) or (S) configuration. Unless otherwise indicated, it is intended that both configuations are encompassed.

Depending upon the values of $-R^1$, $-R^2$, $-R^4$, $-R^7$, and $-R^8$, the compound may have one or two, or three chiral centres, giving rise to enantiomers or diastereoisomers. Unless otherwise indicated, it is intended that all such enantiomers and diastereoisomers are encompassed.

Some embodiments of the invention include the following:

(1) A compound selected from compounds of the following formulae, and pharmaceutically acceptable salts, hydrates, and solvates thereof:



wherein:

$-R^1$ is independently -H or $-R^{1A}$;
$-R^{1A}$ is independently saturated aliphatic C_{1-6}alkyl, phenyl, or benzyl, and is optionally substituted;

$-R^2$ is independently -H or $-R^{2A}$;
$-R^{2A}$ is independently saturated aliphatic C_{1-3}alkyl, and is optionally substituted;

or $-R^1$ and $-R^2$, taken together with the carbon atom to which they are attached, form a saturated C_{3-7}cycloalkyl ring or a saturated C_{3-7}heterocyclic ring, which is optionally substituted;

$-R^4$ is independently -H or $-R^{4A}$;
$-R^{4A}$ is independently saturated aliphatic C_{1-3}alkyl;

$-R^7$ is independently -H, $-R^{7A}$, or $-R^{7B}$;

$-R^{7A}$ is independently saturated aliphatic C_{1-6}alkyl, and is optionally substituted;

$-R^{7B}$ is independently $-L^{7B1}-R^{7BB}$, $-R^{7BB}$, $-L^{7B2}-O-R^{7BB}$, or $-L^{7B2}-O-L^{7B1}-R^{7BB}$;
$-L^{7B1}-$ is independently saturated aliphatic C_{1-3}alkylene;
$-L^{7B2}-$ is independently saturated aliphatic C_{1-3}alkylene;
$-R^{7BB}$ is independently $-R^{7BB1}$, $-R^{7BB2}$, $-R^{7BB3}$, or $-R^{7BB4}$;
$-R^{7BB1}$ is independently phenyl or naphthyl, and is optionally substituted;

$-R^{7BB2}$ is independently C_{5-10}heteroaryl, and is optionally substituted;
$-R^{7BB3}$ is independently C_{3-7}cycloalkyl, and is optionally substituted, or is optionally fused to a benzene ring;
$-R^{7BB4}$ is independently saturated bridged C_{5-10}cycloalkyl, and is optionally substituted;

$-R^{8}$ is independently -H or $-R^{8A}$;
$-R^{8A}$ is independently saturated aliphatic C_{1-6}alkyl, and is optionally substituted;

or $-R^{7}$ and $-R^{8}$, taken together with the carbon atom to which they are attached, form a saturated C_{3-7}cycloalkyl ring, a saturated bridged C_{5-10}cycloalkyl ring, or a non-aromatic C_{3-7}heterocyclic ring, which is optionally substituted;

$-R^{10}$ is independently $-R^{10A}$, $-R^{10B}$, $-R^{10C}$, or $-R^{10D}$;
$-R^{10A}$ is independently phenyl or naphthyl, and is optionally substituted;
$-R^{10B}$ is independently C_{5-10}heteroaryl, and is optionally substituted;
$-R^{10C}$ is independently saturated C_{3-7}cycloalkyl, and is optionally substituted; and
$-R^{10D}$ is independently non-aromatic C_{3-10}heterocyclyl, and is optionally substituted.

For the avoidance of doubt, the term "aliphatic alkyl" refers to linear and branched alkyl groups, but not alicyclic alkyl (e.g., cycloalkyl) groups. For example, -nBu is an example of a linear C_4alkyl group, and -iBu is an example of a branched C_4alkyl group; in this way, both -nBu and -iBu are examples are aliphatic C_4alkyl groups.

For the avoidance of doubt, the index "C_{x-y}" in terms such as "C_{5-10}heteroaryl", "C_{3-7}heterocyclic ring", "C_{3-7}heterocyclyl", and the like, refers to the number of ring atoms, which may be carbon atoms or heteroatoms (e.g., N, O, S). For example, pyridyl is an example of a C_6heteroaryl group, and piperidino is an example of a C_6heterocycyl group.

For the avoidance of doubt, the index "C_{x-y}" in terms such as "C_{5-10}heteroaryl", "C_{3-7}heterocyclic ring", "C_{3-7}heterocyclyl", and the like, refers to the number of ring atoms, which may be carbon atoms or heteroatoms (e.g., N, O, S).

For the avoidance of doubt, "heteroaryl" refers to a group that is attached to the rest of the molecule by an atom that is part of an aromatic ring, and which has one or more heteroatoms (e.g., N, O, S) forming part of the aromatic ring system. For example, pyridyl is an example of a C_6heteroaryl group, and quinolyl is an example of a C_{10}heteroaryl group. In contrast, "heterocyclyl" refers to a group that is attached to the rest of the molecule by a ring atom that is not part of an aromatic ring (i.e., the ring is fully or partially saturated), and the ring system contains one or more heteroatoms (e.g., N, O, S). For example, piperidino is an example of a C_6heterocycyl group.

The Group -R^1

(2) A compound according to (1), wherein -R^1 is independently -H or -R^{1A}.

(3) A compound according to (1), wherein -R^1 is independently -R^{1A}.

(4) A compound according to (1), wherein -R^1 is independently -H.

The Group -R^2

(5) A compound according to any one of (1) to (4), wherein -R^2 is independently -H or -R^{2A}.

(6) A compound according to any one of (1) to (4), wherein -R^2 is independently -R^{2A}.

(7) A compound according to any one of (1) to (4), wherein -R^2 is independently -H.

The Groups -R^1 and -R^2

(8) A compound according to (1), wherein:
-R^1 is independently -H or -R^{1A}; and
-R^2 is independently -H or -R^{2A}.

(9) A compound according to (1), wherein:
-R^1 is independently -H or -R^{1A}; and
-R^2 is independently -H.

(10) A compound according to (1), wherein:
-R^1 is independently -R^{1A}; and
-R^2 is independently -H.

(11) A compound according to (1), wherein:
-R^1 is independently -H; and
-R^2 is independently -H.

The Group -R^{1A}

(12) A compound according to any one of (1) to (11), wherein -R^{1A} is independently saturated aliphatic C_{1-6}alkyl, phenyl, or benzyl, and is optionally substituted, for example, with one or more substituents -R^{X1}.

(13) A compound according to any one of (1) to (11), wherein $-R^{1A}$, if present, is independently saturated aliphatic C_{1-6}alkyl, phenyl, or benzyl.

(14) A compound according to any one of (1) to (11), wherein $-R^{1A}$, if present, is independently saturated aliphatic C_{1-6}alkyl, and is optionally substituted, for example, with one or more substituents $-R^{X1}$.

(15) A compound according to any one of (1) to (11), wherein $-R^{1A}$, if present, is independently saturated aliphatic C_{1-6}alkyl.

(16) A compound according to any one of (1) to (11), wherein $-R^{1A}$, if present, is independently saturated aliphatic C_{1-4}alkyl, and is optionally substituted, for example, with one or more substituents $-R^{X1}$.

(17) A compound according to any one of (1) to (11), wherein $-R^{1A}$, if present, is independently saturated aliphatic C_{1-4}alkyl.

(18) A compound according to any one of (1) to (11), wherein $-R^{1A}$, if present, is independently -Me, -Et, -nPr, -iPr, -nBu, -iBu, -sBu, or -tBu.

(19) A compound according to any one of (1) to (11), wherein $-R^{1A}$, if present, is independently saturated aliphatic C_{3-4}alkyl.

(20) A compound according to any one of (1) to (11), wherein $-R^{1A}$, if present, is independently -nPr, -iPr, -nBu, -iBu, -sBu, or -tBu.

(21) A compound according to any one of (1) to (11), wherein $-R^{1A}$, if present, is independently -iPr, -nBu, -iBu, or -tBu.

(22) A compound according to any one of (1) to (11), wherein $-R^{1A}$, if present, is independently -nPr, -iPr, -nBu, -iBu, or -sBu.

(23) A compound according to any one of (1) to (11), wherein $-R^{1A}$, if present, is independently -iPr or -nBu.

(24) A compound according to any one of (1) to (11), wherein $-R^{1A}$, if present, is independently -iPr.

(25) A compound according to any one of (1) to (11), wherein $-R^{1A}$, if present, is independently -nBu.

The Group -R^{2A}

(26) A compound according to any one of (1) to (25), wherein -R^{2A}, if present, is independently saturated aliphatic C_{1-3}alkyl, and is optionally substituted, for example, with one or more substituents -R^{X1}.

(27) A compound according to any one of (1) to (25), wherein -R^{2A}, if present, is independently saturated aliphatic C_{1-3}alkyl.

(28) A compound according to any one of (1) to (25), wherein -R^{2A}, if present, is independently -Me, -Et, -nPr, or -iPr.

(29) A compound according to any one of (1) to (25), wherein -R^{2A}, if present, is independently -Me or -Et.

(30) A compound according to any one of (1) to (25), wherein -R^{2A}, if present, is independently -Me.

The Group -C(R^1)(R^2)-

(31) A compound according to (1), wherein -R^1 and -R^2, taken together with the carbon atom to which they are attached, form a saturated C_{3-7}cycloalkyl ring or a non-aromatic C_{3-7}heterocyclic ring, which is optionally substituted, for example, with one or more substituents -R^{X2}.

(32) A compound according to (1), wherein -R^1 and -R^2, taken together with the carbon atom to which they are attached, form a saturated C_{3-7}cycloalkyl ring or a non-aromatic C_{3-7}heterocyclic ring.

(33) A compound according to (1), wherein -R^1 and -R^2, taken together with the carbon atom to which they are attached, form a saturated C_{3-7}cycloalkyl ring, which is optionally substituted, for example, with one or more substituents -R^{X2}.

(34) A compound according to (1), wherein -R^1 and -R^2, taken together with the carbon atom to which they are attached, form a saturated C_{3-7}cycloalkyl ring.

(35) A compound according to (1), wherein -R^1 and -R^2, taken together with the carbon atom to which they are attached, form cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl, and is optionally substituted, for example, with one or more substituents -R^{X2}.

(36) A compound according to (1), wherein $-R^1$ and $-R^2$, taken together with the carbon atom to which they are attached, form cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.

(37) A compound according to (1), wherein $-R^1$ and $-R^2$, taken together with the carbon atom to which they are attached, form cyclopentyl.

(38) A compound according to (1), wherein $-R^1$ and $-R^2$, taken together with the carbon atom to which they are attached, form a non-aromatic C_{3-7}heterocyclic ring, which is optionally substituted, for example, with one or more substituents $-R^{X2}$.

(39) A compound according to (1), wherein $-R^1$ and $-R^2$, taken together with the carbon atom to which they are attached, form a non-aromatic C_{3-7}heterocyclic ring.

The Group $-R^4$

(40) A compound according to any one of (1) to (39), wherein $-R^4$ is independently $-R^{4A}$.

(41) A compound according to any one of (1) to (39), wherein $-R^4$ is independently -H.

The Group $-R^{4A}$

(42) A compound according to any one of (1) to (41), wherein $-R^{4A}$, if present, is independently -Me, -Et, -nPr, or -iPr.

(43) A compound according to any one of (1) to (41), wherein $-R^{4A}$, if present, is independently -Me or -nPr.

(44) A compound according to any one of (1) to (41), wherein $-R^{4A}$, if present, is independently -Me.

The Group $-R^7$

(45) A compound according to any one of (1) to (44), wherein $-R^7$ is independently $-R^{7A}$ or $-R^{7B}$.

(46) A compound according to any one of (1) to (44), wherein $-R^7$ is independently $-R^{7A}$.

(47) A compound according to any one of (1) to (44), wherein $-R^7$ is independently $-R^{7B}$.

(48) A compound according to any one of (1) to (44), wherein $-R^7$ is independently -H.

The Group -R^{7A}

(49) A compound according to any one of (1) to (48), wherein -R^{7A}, if present, is independently saturated aliphatic C_{1-6}alkyl, and is optionally substituted, for example, with one or more substituents -R^{X1}.

(50) A compound according to any one of (1) to (48), wherein -R^{7A}, if present, is independently saturated aliphatic C_{1-6}alkyl.

(51) A compound according to any one of (1) to (48), wherein -R^{7A}, if present, is independently saturated aliphatic C_{1-4}alkyl, and is optionally substituted, for example, with one or more substituents -R^{X1}.

(52) A compound according to any one of (1) to (48), wherein -R^{7A}, if present, is independently saturated aliphatic C_{1-4}alkyl.

(53) A compound according to any one of (1) to (48), wherein -R^{7A}, if present, is independently -Me, -Et, -nPr, -iPr, -nBu, -sBu, -iBu, or -tBu.

(54) A compound according to any one of (1) to (48), wherein -R^{7A}, if present, is independently saturated aliphatic C_{3-4}alkyl.

(55) A compound according to any one of (1) to (48), wherein -R^{7A}, if present, is independently -nPr, -iPr, -nBu, -sBu, -iBu, or -tBu.

(56) A compound according to any one of (1) to (48), wherein -R^{7A}, if present, is independently -tBu.

The Group -R^{7B}

(57) A compound according to any one of (1) to (56), wherein -R^{7B}, if present, is independently -L^{7B1}-R^{7BB}, -L^{7B2}-O-R^{7BB}, or -L^{7B2}-O-L^{7B1}-R^{7BB}.

(58) A compound according to any one of (1) to (56), wherein -R^{7B}, if present, is independently -L^{7B1}-R^{7BB} or -L^{7B2}-O-L^{7B1}-R^{7BB}.

(59) A compound according to any one of (1) to (56), wherein -R^{7B}, if present, is independently -L^{7B1}-R^{7BB}.

(60) A compound according to any one of (1) to (56), wherein -R^{7B}, if present, is independently -L^{7B2}-O-L^{7B1}-R^{7BB}.

(61) A compound according to any one of (1) to (56), wherein $-R^{7B}$, if present, is independently $-L^{7B2}-O-R^{7BB}$.

(62) A compound according to any one of (1) to (56), wherein $-R^{7B}$, if present, is independently $-R^{7BB}$.

The Group $-L^{7B1}-$

(63) A compound according to any one of (1) to (62), wherein $-L^{7B1}-$, if present, is independently $-CH_2-$, $-CH(Me)-$, $-C(Me)_2-$, $-CH_2CH_2-$, or $-CH_2CH_2CH_2-$.

(64) A compound according to any one of (1) to (62), wherein $-L^{7B1}-$, if present, is independently $-CH_2-$ or $-CH_2CH_2-$.

(65) A compound according to any one of (1) to (62), wherein $-L^{7B1}-$, if present, is independently $-CH_2-$.

The Group $-L^{7B2}-$

(66) A compound according to any one of (1) to (65), wherein $-L^{7B2}-$, if present, is independently $-CH_2-$, $-CH(Me)-$, $-C(Me)_2-$, $-CH_2CH_2-$, or $-CH_2CH_2CH_2-$.

(67) A compound according to any one of (1) to (65), wherein $-L^{7B2}-$, if present, is independently $-CH_2-$ or $-CH_2CH_2-$.

(68) A compound according to any one of (1) to (65), wherein $-L^{7B2}-$, if present, is independently $-CH_2-$.

The Group $-R^{7BB}$

(69) A compound according to any one of (1) to (68), wherein $-R^{7BB}$, if present, is independently $-R^{7BB1}$, $-R^{7BB2}$, or $-R^{7BB3}$.

(70) A compound according to any one of (1) to (68), wherein $-R^{7BB}$, if present, is independently $-R^{7BB1}$.

(71) A compound according to any one of (1) to (68), wherein $-R^{7BB}$, if present, is independently $-R^{7BB2}$.

(72) A compound according to any one of (1) to (68), wherein -R^{7BB}, if present, is independently -R^{7BB3}.

(73) A compound according to any one of (1) to (68), wherein -R^{7BB}, if present, is independently -R^{7BB4}.

The Group -R^{7BB1}

(74) A compound according to any one of (1) to (73), wherein -R^{7BB1}, if present, is independently phenyl or naphthyl, and is optionally substituted, for example, with one or more substituents -R^{X3}.

(75) A compound according to any one of (1) to (73), wherein -R^{7BB1}, if present, is independently phenyl or naphthyl, and is optionally substituted, for example, with one or more substituents independently selected from -F, -Cl, -Br, -I, -Me, and -Ph.

(76) A compound according to any one of (1) to (73), wherein -R^{7BB1}, if present, is independently phenyl or naphthyl.

(77) A compound according to any one of (1) to (73), wherein -R^{7BB1}, if present, is independently phenyl, and is optionally substituted, for example, with one or more substituents -R^{X3}.

(78) A compound according to any one of (1) to (73), wherein -R^{7BB1}, if present, is independently phenyl, and is optionally substituted, for example, with one or more substituents independently selected from -F, -Cl, -Br, -I, -Me, and -Ph.

(79) A compound according to any one of (1) to (73), wherein -R^{7BB1}, if present, is independently phenyl.

(80) A compound according to any one of (1) to (73), wherein -R^{7BB1}, if present, is independently naphthyl, and is optionally substituted, for example, with one or more substituents -R^{X3}.

(81) A compound according to any one of (1) to (73), wherein -R^{7BB1}, if present, is independently naphthyl, and is optionally substituted, for example, with one or more substituents independently selected from -F, -Cl, -Br, -I, -Me, and -Ph.

(82) A compound according to any one of (1) to (73), wherein -R^{7BB1}, if present, is independently naphthyl.

The Group -R^{7BB2}

(83) A compound according to any one of (1) to (82), wherein -R^{7BB2}, if present, is independently C_{5-10}heteroaryl, and is optionally substituted, for example, with one or more substituents -R^{X3}.

(84) A compound according to any one of (1) to (82), wherein -R^{7BB2}, if present, is independently C_{5-10}heteroaryl.

(85) A compound according to any one of (1) to (82), wherein -R^{7BB2}, if present, is independently C_{5-6}heteroaryl, and is optionally substituted, for example, with one or more substituents -R^{X3}.

(86) A compound according to any one of (1) to (82), wherein -R^{7BB2}, if present, is independently C_{5-6}heteroaryl.

(87) A compound according to any one of (1) to (82), wherein -R^{7BB2}, if present, is independently furanyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl (e.g., 1H-[1,2,3]triazolyl, 2H-[1,2,3]triazolyl, 4H-[1,2,4]triazolyl, 1H-[1,2,4]triazolyl), oxadiazolyl (e.g., [1,2,3]oxadiazolyl, furazanyl, [1,3,4]oxadiazolyl, [1,2,4]oxadiazolyl), thiadiazolyl (e.g., [1,2,3]thiadiazolyl, [1,2,5]thiadiazolyl, [1,3,4]thiadiazolyl, [1,2,4]thiadiazolyl), pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, or triazinyl (e.g., [1,3,5]-triazinyl), and is optionally substituted, for example, with one or more substituents -R^{X3}.

(88) A compound according to any one of (1) to (82), wherein -R^{7BB2}, if present, is independently furanyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridyl, pyrimidinyl, pyrazinyl, or pyridazinyl, and is optionally substituted, for example, with one or more substituents -R^{X3}.

(89) A compound according to any one of (1) to (82), wherein -R^{7BB2}, if present, is independently furanyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridyl, pyrimidinyl, pyrazinyl, or pyridazinyl.

(90) A compound according to any one of (1) to (82), wherein -R^{7BB2}, if present, is independently pyridyl, and is optionally substituted, for example, with one or more substituents -R^{X3}.

(91) A compound according to any one of (1) to (82), wherein -R^{7BB2}, if present, is independently pyridyl.

(92) A compound according to any one of (1) to (82), wherein -R^{7BB2}, if present, is independently C_{9-10}heteroaryl, and is optionally substituted, for example, with one or more substituents -R^{X3}.

(93) A compound according to any one of (1) to (82), wherein -R^{7BB2}, if present, is independently C_{9-10}heteroaryl.

(94) A compound according to any one of (1) to (82), wherein -R^{7BB2}, if present, is independently quinolinyl, isoquinolinyl, or indolyl, and is optionally substituted, for example, with one or more substituents -R^{X3}.

(95) A compound according to any one of (1) to (82), wherein -R^{7BB2}, if present, is independently quinolinyl, isoquinolinyl, or indolyl.

The Group -R^{7BB3}

(96) A compound according to any one of (1) to (95), wherein -R^{7BB3}, if present, is independently C_{3-7}cycloalkyl, and is optionally substituted, for example, with one or more substituents -R^{X2}, or is optionally fused to a benzene ring.

(97) A compound according to any one of (1) to (95), wherein -R^{7BB3}, if present, is independently C_{3-7}cycloalkyl, and is optionally substituted, for example, with one or more substituents -R^{X2}.

(98) A compound according to any one of (1) to (95), wherein -R^{7BB3}, if present, is independently cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or cycloheptyl, and is optionally substituted, for example, with one or more substituents -R^{X2}.

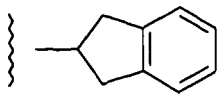
(99) A compound according to any one of (1) to (95), wherein -R^{7BB3}, if present, is independently cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or cycloheptyl.

(100) A compound according to any one of (1) to (95), wherein -R^{7BB3}, if present, is independently cyclohexyl.

(101) A compound according to any one of (1) to (95), wherein -R^{7BB3}, if present, is independently C_{3-6}cycloalkyl, and is optionally fused to a benzene ring.

(102) A compound according to any one of (1) to (95), wherein -R^{7BB3}, if present, is independently cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or cycloheptyl, and is optionally fused to a benzene ring.

(103) A compound according to any one of (1) to (95), wherein -R^{7BB3}, if present, is independently cyclopentyl fused to a benzene ring; as in, for example, indan-2-yl:



(indan-2-yl)

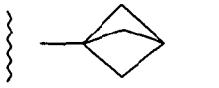
The Group -R^{7BB4}

(104) A compound according to any one of (1) to (103), wherein -R^{7BB4}, if present, is independently saturated bridged C_{5-10}cycloalkyl, and is optionally substituted, for example, with one or more substituents -R^{X2}.

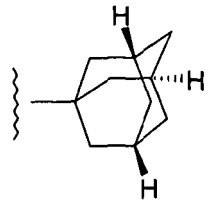
(105) A compound according to any one of (1) to (103), wherein -R^{7BB4}, if present, is independently saturated bridged C_{5-10}cycloalkyl.

(106) A compound according to any one of (1) to (103), wherein -R^{7BB4}, if present, is independently bicyclo[1.1.1]pentyl or adamantyl, and is optionally substituted, for example, with one or more substituents -R^{X2}.

(107) A compound according to any one of (1) to (103), wherein -R^{7BB4}, if present, is independently bicyclo[1.1.1]pentyl (an example of a saturated bridged C_5cycloalkyl group) or adamantyl (an example of a saturated bridged C_{10}cycloalkyl group).



(bicyclo[1.1.1]pent-1-yl)



(adamant-1-yl)

(108) A compound according to any one of (1) to (103), wherein -R^{7BB4}, if present, is independently adamantyl.

The Group -R^{8}

(109) A compound according to any one of (1) to (108), wherein -R^{8} is independently -H.

(110) A compound according to any one of (1) to (108), wherein -R^{8} is independently -R^{8A}.

The Group -R^{8A}

(111) A compound according to any one of (1) to (110), wherein -R^{8A}, if present, is independently saturated aliphatic C_{1-6}alkyl, and is optionally substituted, for example, with one or more substituents -R^{X1}.

(112) A compound according to any one of (1) to (110), wherein -R^{8A}, if present, is independently saturated aliphatic C_{1-6}alkyl.

(113) A compound according to any one of (1) to (110), wherein -R^{8A}, if present, is independently saturated aliphatic C_{1-4}alkyl, and is optionally substituted, for example, with one or more substituents -R^{X1}.

(114) A compound according to any one of (1) to (110), wherein -R^{8A}, if present, is independently saturated aliphatic C_{1-4}alkyl.

(115) A compound according to any one of (1) to (110), wherein -R^{8A}, if present, is independently -Me, -Et, -nPr, -iPr, -nBu, -sBu, -iBu, or -tBu.

(116) A compound according to any one of (1) to (110), wherein -R^{8A}, if present, is independently -Me, -Et, -nPr, or -iPr.

(117) A compound according to any one of (1) to (110), wherein -R^{8A}, if present, is independently -Me.

The Group -$C(R^7)(R^8)$-

(118) A compound according to any one of (1) to (44), wherein -R^7 and -R^8, taken together with the carbon atom to which they are attached, form a saturated C_{3-7}cycloalkyl ring, a saturated bridged C_{5-10}cycloalkyl ring, or a non-aromatic C_{3-7}heterocyclic ring, which is optionally substituted, for example, with one or more substituents -R^{X2}.

(119) A compound according to any one of (1) to (44), wherein -R^7 and -R^8, taken together with the carbon atom to which they are attached, form a saturated C_{3-7}cycloalkyl ring, which is optionally substituted, for example, with one or more substituents -R^{X2}.

(120) A compound according to any one of (1) to (44), wherein -R^7 and -R^8, taken together with the carbon atom to which they are attached, form a saturated C_{3-7}cycloalkyl ring.

(121) A compound according to any one of (1) to (44), wherein $-R^7$ and $-R^8$, taken together with the carbon atom to which they are attached, form cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl, and is optionally substituted, for example, with one or more substituents $-R^{X2}$.

(122) A compound according to any one of (1) to (44), wherein $-R^7$ and $-R^8$, taken together with the carbon atom to which they are attached, form cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.

(123) A compound according to any one of (1) to (44), wherein $-R^7$ and $-R^8$, taken together with the carbon atom to which they are attached, form cyclohexyl.

(124) A compound according to any one of (1) to (44), wherein $-R^7$ and $-R^8$, taken together with the carbon atom to which they are attached, form a saturated bridged C_{5-10}cycloalkyl ring, which is optionally substituted, for example, with one or more substituents $-R^{X2}$.

(125) A compound according to any one of (1) to (44), wherein $-R^7$ and $-R^8$, taken together with the carbon atom to which they are attached, form a saturated bridged C_{5-10}cycloalkyl ring.

(126) A compound according to any one of (1) to (44), wherein $-R^7$ and $-R^8$, taken together with the carbon atom to which they are attached, form a non-aromatic C_{3-7}heterocyclic ring, which is optionally substituted, for example, with one or more substituents $-R^{X2}$.

(127) A compound according to any one of (1) to (44), wherein $-R^7$ and $-R^8$, taken together with the carbon atom to which they are attached, form a non-aromatic C_{3-7}heterocyclic ring.

(128) A compound according to any one of (1) to (44), wherein $-R^7$ and $-R^8$, taken together with the carbon atom to which they are attached, form a non-aromatic C_{5-7}heterocyclic ring, which is optionally substituted, for example, with one or more substituents $-R^{X2}$.

(129) A compound according to any one of (1) to (44), wherein $-R^7$ and $-R^8$, taken together with the carbon atom to which they are attached, form a non-aromatic C_{5-7}heterocyclic ring.

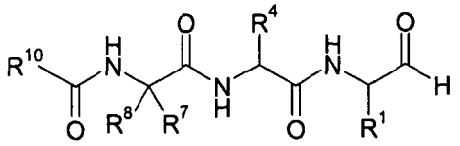
(130) A compound according to any one of (1) to (44), wherein $-R^7$ and $-R^8$, taken together with the carbon atom to which they are attached, form a non-aromatic

C_6heterocyclic ring, which is optionally substituted, for example, with one or more substituents $-R^{X2}$.

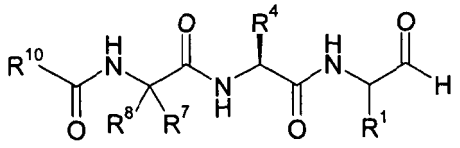
(131) A compound according to any one of (1) to (44), wherein $-R^7$ and $-R^8$, taken together with the carbon atom to which they are attached, form a non-aromatic C_6heterocyclic ring.

Some Preferred Combinations

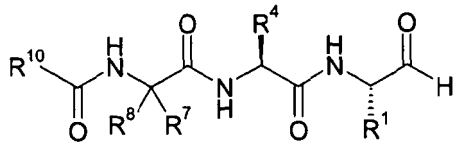
(132) A compound according to (1), wherein: $-R^2$ is -H; for example, as shown below:



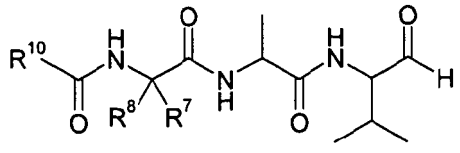
(133) A compound according to (132), wherein the carbon atom to which $-R^4$ is attached has the configuration shown in the following formula:



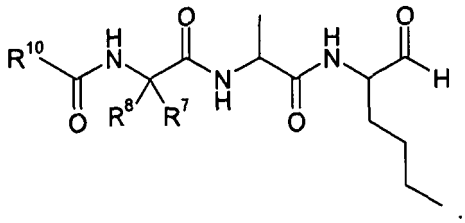
(134) A compound according to (132), wherein the carbon atom to which $-R^4$ is attached, and the carbon atom to which $-R^1$ and $-R^2$ is attached, have the configurations shown in the following formula:



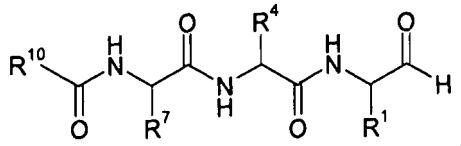
(135) A compound according to any one of (132) to (134), wherein: $-R^1$ is -iPr and $-R^4$ is -Me; for example, as shown below:



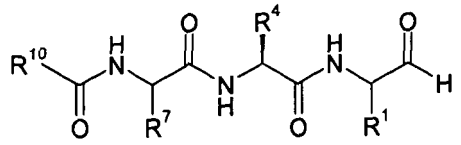
(136) A compound according to any one of (130) to (132), wherein: -R^1 is -nBu and -R^4 is -Me; for example, as shown below:



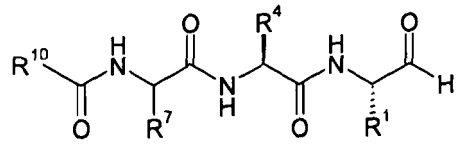
(137) A compound according to (1), wherein: -R^2 is -H; and -R^8 is -H; for example, as shown below:



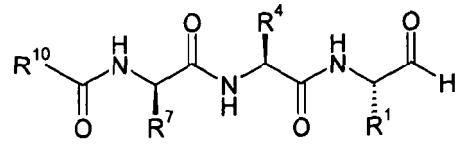
(138) A compound according to (137), wherein the carbon atom to which -R^4 is attached has the configuration shown in the following formula:



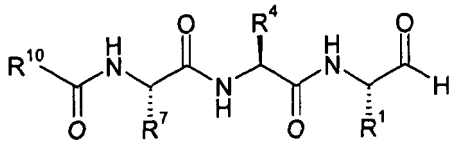
(139) A compound according to (137), wherein the carbon atom to which -R^4 is attached, and the carbon atom to which -R^1 and -R^2 is attached, have the configurations shown in the following formula:



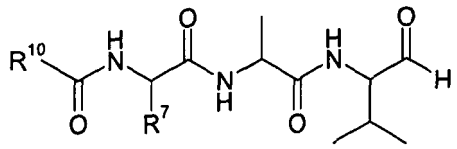
(140) A compound according to (137), wherein the carbon atom to which -R^4 is attached, the carbon atom to which -R^1 and -R^2 is attached, and the carbon atom to which -R^7 and -R^8 are attached, have the configurations shown in the following formula:



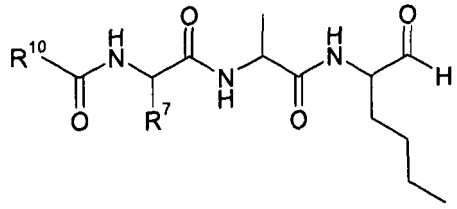
(141) A compound according to (137), wherein the carbon atom to which -R^4 is attached, the carbon atom to which -R^1 and -R^2 is attached, and the carbon atom to which -R^7 and -R^8 are attached, have the configurations shown in the following formula:



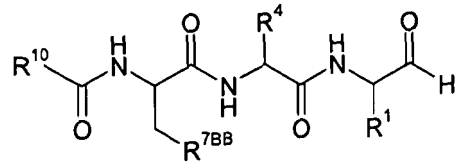
(142) A compound according to any one of (137) to (141), wherein: -R^1 is -iPr and -R^4 is -Me; for example, as shown below:



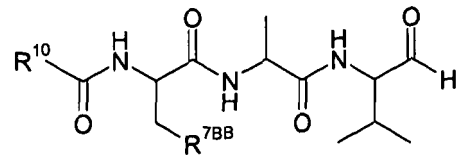
(143) A compound according to any one of (137) to (141), wherein: -R^1 is -nBu and -R^4 is -Me; for example, as shown below:



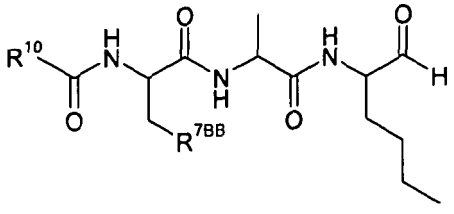
(144) A compound according to any one of (137) to (141), wherein -R^7 is -CH_2-R^{7BB}; for example, as shown below:



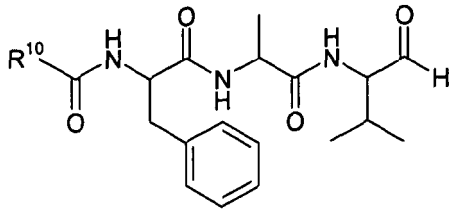
(145) A compound according to any one of (137) to (141), wherein -R^1 is -iPr, -R^4 is -Me, and -R^7 is -CH_2-R^{7BB}; for example, as shown below:



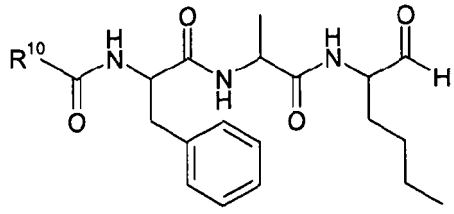
(146) A compound according to any one of (137) to (141), wherein -R^1 is -nBu, -R^4 is -Me, and -R^7 is -CH_2-R^{7BB}; for example, as shown below:



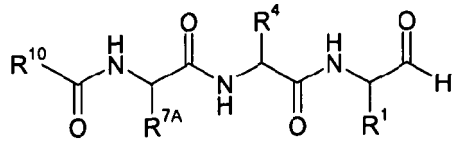
(147) A compound according to any one of (137) to (141), wherein -R^1 is -iPr, -R^4 is -Me, and -R^7 is -CH_2-Ph; for example, as shown below:



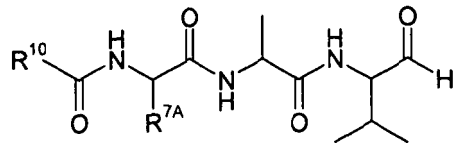
(148) A compound according to any one of (137) to (141), wherein -R^1 is -nBu, -R^4 is -Me, and -R^7 is -CH_2-Ph; for example, as shown below:



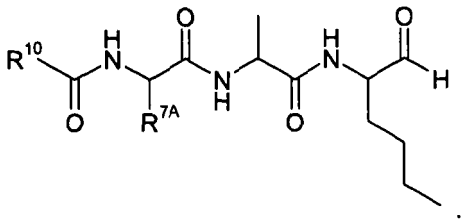
(149) A compound according to any one of (137) to (141), wherein -R^7 is -R^{7A}; for example, as shown below:



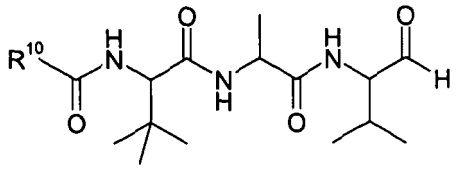
(150) A compound according to any one of (137) to (141), wherein R^1 is -iPr, -R^4 is -Me, and -R^7 is -R^{7A}; for example, as shown below:



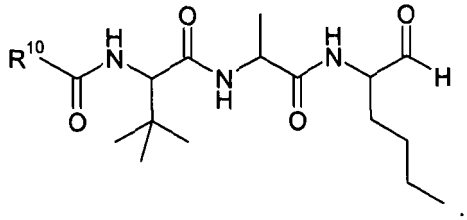
(151) A compound according to any one of (137) to (141), wherein R^1 is -nBu, $-R^4$ is -Me, and $-R^7$ is $-R^{7A}$; for example, as shown below:



(152) A compound according to any one of (137) to (141), wherein R^1 is -iPr, $-R^4$ is -Me, and $-R^7$ is -tBu; for example, as shown below:



(153) A compound according to any one of (137) to (141), wherein R^1 is -nBu, $-R^4$ is -Me, and $-R^7$ is -tBu; for example, as shown below:



The Group $-R^{10}$

(154) A compound according to any one of (1) to (153), wherein $-R^{10}$ is independently $-R^{10A}$, $-R^{10B}$, or $-R^{10C}$.

(155) A compound according to any one of (1) to (153), wherein $-R^{10}$ is independently $-R^{10A}$ or $-R^{10B}$.

(156) A compound according to any one of (1) to (153), wherein $-R^{10}$ is independently $-R^{10A}$.

(157) A compound according to any one of (1) to (153), wherein $-R^{10}$ is independently $-R^{10B}$.

(158) A compound according to any one of (1) to (153), wherein $-R^{10}$ is independently $-R^{10C}$.

(159) A compound according to any one of (1) to (153), wherein $-R^{10}$ is independently $-R^{10D}$.

The Group $-R^{10A}$

(160) A compound according to any one of (1) to (159), wherein $-R^{10A}$, if present, is independently phenyl or naphthyl, and is optionally substituted, for example, with one or more substituents $-R^{X3}$.

(161) A compound according to any one of (1) to (159), wherein $-R^{10A}$, if present, is independently phenyl or naphthyl, and is optionally substituted, for example, with one or more substituents independently selected from:

-F, -Cl, -Br, -I,
C_{1-4}alkyl, -O-C_{1-4}alkyl,
$-CF_3$, $-OCF_3$,
phenyl, -O-phenyl,
$-NH_2$, $-NH(C_{1-4}alkyl)$, $-N(C_{1-4}alkyl)_2$,
$-NH(C=O)(C_{1-4}alkyl)$,
pyrrolidino, piperidino, morpholino, piperizino, N-(C_{1-4}alkyl)-piperizino,
$-O-CH_2CH_2-NH_2$, $-O-CH_2CH_2-NH(C_{1-4}alkyl)$, $-O-CH_2CH_2-N(C_{1-4}alkyl)_2$,
$-O-CH_2CH_2$-pyrrolidino, $-O-CH_2CH_2$-piperidino, $-O-CH_2CH_2$-morpholino,
$-O-CH_2CH_2$-piperizino, $-O-CH_2CH_2$-{N-(C_{1-4}alkyl)-piperizino},
$-O-CH_2$-imidazol-2-yl, $-O-CH_2$-{N-(C_{1-4}alkyl)-imidazol-2-yl}, and
=O.

(162) A compound according to any one of (1) to (159), wherein $-R^{10A}$, if present, is independently phenyl or naphthyl, and is optionally substituted, for example, with one or more substituents independently selected from:

phenyl, -O-phenyl,
$-NH_2$, $-NH(C_{1-4}alkyl)$, $-N(C_{1-4}alkyl)_2$,
pyrrolidino, piperidino, morpholino, piperizino, N-(C_{1-4}alkyl)-piperizino,
$-O-CH_2CH_2-NH_2$, $-O-CH_2CH_2-NH(C_{1-4}alkyl)$, $-O-CH_2CH_2-N(C_{1-4}alkyl)_2$,
$-O-CH_2CH_2$-pyrrolidino, $-O-CH_2CH_2$-piperidino, $-O-CH_2CH_2$-morpholino,
$-O-CH_2CH_2$-piperizino, $-O-CH_2CH_2$-{N-(C_{1-4}alkyl)-piperizino},
$-O-CH_2$-imidazol-2-yl, and $-O-CH_2$-{N-(C_{1-4}alkyl)-imidazol-2-yl}.

(163) A compound according to any one of (1) to (159), wherein $-R^{10A}$, if present, is independently phenyl, and is optionally substituted, for example, with one or more substituents $-R^{X3}$.

(164) A compound according to any one of (1) to (159), wherein $-R^{10A}$, if present, is independently phenyl, and is optionally substituted, for example, with one or more substituents independently selected from:

-F, -Cl, -Br, -I,
C_{1-4}alkyl, -O-C_{1-4}alkyl,
$-CF_3$, $-OCF_3$,
phenyl, -O-phenyl,
$-NH_2$, -NH(C_{1-4}alkyl), -N(C_{1-4}alkyl)$_2$,
-NH(C=O)(C_{1-4}alkyl),
pyrrolidino, piperidino, morpholino, piperizino, N-(C_{1-4}alkyl)-piperizino,
$-O-CH_2CH_2-NH_2$, -O-CH_2CH_2-NH(C_{1-4}alkyl), -O-CH_2CH_2-N(C_{1-4}alkyl)$_2$,
-O-CH_2CH_2-pyrrolidino, -O-CH_2CH_2-piperidino, -O-CH_2CH_2-morpholino,
-O-CH_2CH_2-piperizino, -O-CH_2CH_2-{N-(C_{1-4}alkyl)-piperizino},
$-O-CH_2$-imidazol-2-yl, and $-O-CH_2$-{N-(C_{1-4}alkyl)-imidazol-2-yl}.

(165) A compound according to any one of (1) to (159), wherein $-R^{10A}$, if present, is independently phenyl, and is optionally substituted, for example, with one or more substituents independently selected from:

phenyl, -O-phenyl,
$-NH_2$, -NH(C_{1-4}alkyl), -N(C_{1-4}alkyl)$_2$,
pyrrolidino, piperidino, morpholino, piperizino, N-(C_{1-4}alkyl)-piperizino,
$-O-CH_2CH_2-NH_2$, -O-CH_2CH_2-NH(C_{1-4}alkyl), -O-CH_2CH_2-N(C_{1-4}alkyl)$_2$,
-O-CH_2CH_2-pyrrolidino, -O-CH_2CH_2-piperidino, -O-CH_2CH_2-morpholino,
-O-CH_2CH_2-piperizino, -O-CH_2CH_2-{N-(C_{1-4}alkyl)-piperizino},
$-O-CH_2$-imidazol-2-yl, and $-O-CH_2$-{N-(C_{1-4}alkyl)-imidazol-2-yl}.

(166) A compound according to any one of (1) to (159), wherein $-R^{10A}$, if present, is independently phenyl.

(167) A compound according to any one of (1) to (159), wherein $-R^{10A}$, if present, is independently naphthyl, and is optionally substituted, for example, with one or more substituents $-R^{X3}$.

(168) A compound according to any one of (1) to (159), wherein $-R^{10A}$, if present, is independently naphthyl.

The Group $-R^{10B}$

(169) A compound according to any one of (1) to (168), wherein $-R^{10B}$, if present, is independently C_{5-10}heteroaryl, and is optionally substituted, for example, with one or more substituents $-R^{X3}$.

(170) A compound according to any one of (1) to (168), wherein $-R^{10B}$, if present, is independently furanyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl (e.g., 1H-[1,2,3]triazolyl, 2H-[1,2,3]triazolyl, 4H-[1,2,4]triazolyl, 1H-[1,2,4]triazolyl), oxadiazolyl (e.g., [1,2,3]oxadiazolyl, furazanyl, [1,3,4]oxadiazolyl, [1,2,4]oxadiazolyl), thiadiazolyl (e.g., [1,2,3]thiadiazolyl, [1,2,5]thiadiazolyl, [1,3,4]thiadiazolyl, [1,2,4]thiadiazolyl), pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl (e.g., [1,3,5]-triazinyl), indolyl, isoindolyl, indazolyl, benzofuranyl, isobenzofuranyl, benzothienyl, isobenzothienyl, benzimidazolyl, benzothiazolyl, benzoxazolyl, benzoisoxazolyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, phthalazinyl, or quinoxalinyl, and is optionally substituted, for example, with one or more substituents $-R^{X3}$.

(171) A compound according to any one of (1) to (168), wherein $-R^{10B}$, if present, is independently C_{5-6}heteroaryl, and is optionally substituted, for example, with one or more substituents $-R^{X3}$.

(172) A compound according to any one of (1) to (168), wherein $-R^{10B}$, if present, is independently C_{5-6}heteroaryl, and is optionally substituted, for example, with one or more substituents independently selected from:

$-NH_2$, $-NH(C_{1-4}alkyl)$, $-N(C_{1-4}alkyl)_2$,
pyrrolidino, piperidino, morpholino, piperizino, N-(C_{1-4}alkyl)-piperizino,
$-NHC(=O)(C_{1-4}alkyl)$, and
=O.

(173) A compound according to any one of (1) to (168), wherein $-R^{10B}$, if present, is independently furanyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridyl, pyrimidinyl, pyrazinyl, or pyridazinyl, and is optionally substituted, for example, with one or more substituents $-R^{X3}$.

(174) A compound according to any one of (1) to (168), wherein $-R^{10B}$, if present, is independently pyridyl, pyrimidinyl, pyrazinyl, or pyridazinyl, and is optionally substituted, for example, with one or more substituents $-R^{X3}$.

(175) A compound according to any one of (1) to (168), wherein $-R^{10B}$, if present, is independently pyridyl, pyrimidinyl, or pyrazinyl, and is optionally substituted, for example, with one or more substituents $-R^{X3}$.

(176) A compound according to any one of (1) to (168), wherein $-R^{10B}$, if present, is independently pyridyl, pyrimidinyl, or pyrazinyl, and is optionally substituted, for example, with one or more substituents independently selected from:

$-NH_2$, $-NH(C_{1-4}alkyl)$, $-N(C_{1-4}alkyl)_2$,
pyrrolidino, piperidino, morpholino, piperizino, $N-(C_{1-4}alkyl)$-piperizino,
$-NHC(=O)(C_{1-4}alkyl)$, and
=O.

(177) A compound according to any one of (1) to (168), wherein $-R^{10B}$, if present, is independently pyridyl, and is optionally substituted, for example, with one or more substituents $-R^{X3}$.

(178) A compound according to any one of (1) to (168), wherein $-R^{10B}$, if present, is independently pyridyl, and is optionally substituted, for example, with one or more substituents independently selected from:
$-NH_2$, $-NH(C_{1-4}alkyl)$, $-N(C_{1-4}alkyl)_2$,
pyrrolidino, piperidino, morpholino, piperizino, $N-(C_{1-4}alkyl)$-piperizino,
$-NHC(=O)(C_{1-4}alkyl)$, and
=O.

(179) A compound according to any one of (1) to (168), wherein $-R^{10B}$, if present, is independently C_{9-10}heteroaryl, and is optionally substituted, for example, with one or more substituents $-R^{X3}$.

(180) A compound according to any one of (1) to (168), wherein $-R^{10B}$, if present, is independently indolyl, isoindolyl, indazolyl, benzofuranyl, isobenzofuranyl, benzothienyl, isobenzothienyl, benzimidazolyl, benzothiazolyl, benzoxazolyl, benzoisoxazolyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, phthalazinyl, or quinoxalinyl, and is optionally substituted, for example, with one or more substituents $-R^{X3}$.

(181) A compound according to any one of (1) to (168), wherein $-R^{10B}$, if present, is independently benzothiazolyl, quinolinyl, or isoquinolinyl, and is optionally substituted, for example, with one or more substituents $-R^{X3}$.

(182) A compound according to any one of (1) to (168), wherein $-R^{10B}$, if present, is independently benzothiazolyl, quinolinyl, or isoquinolinyl.

(183) A compound according to any one of (1) to (168), wherein $-R^{10B}$, if present, is independently benzothiazolyl, and is optionally substituted, for example, with one or more substituents $-R^{X3}$.

(184) A compound according to any one of (1) to (168), wherein $-R^{10B}$, if present, is independently benzothiazolyl.

(185) A compound according to any one of (1) to (168), wherein $-R^{10B}$, if present, is independently quinolinyl or isoquinolinyl, and is optionally substituted, for example, with one or more substituents $-R^{X3}$.

(186) A compound according to any one of (1) to (168), wherein $-R^{10B}$, if present, is independently quinolinyl or isoquinolinyl.

The Group $-R^{10C}$

(187) A compound according to any one of (1) to (186), wherein $-R^{10C}$, if present, is independently saturated C_{3-7}cycloalkyl, and is optionally substituted, for example, with one or more substituents $-R^{X2}$.

(188) A compound according to any one of (1) to (186), wherein $-R^{10C}$, if present, is independently cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl, and is optionally substituted, for example, with one or more substituents $-R^{X2}$.

(189) A compound according to any one of (1) to (186), wherein $-R^{10C}$, if present, is independently cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.

(190) A compound according to any one of (1) to (186), wherein $-R^{10C}$, if present, is independently cyclopentyl or cyclohexyl, and is optionally substituted, for example, with one or more substituents $-R^{X2}$.

(191) A compound according to any one of (1) to (186), wherein $-R^{10C}$, if present, is independently cyclopentyl or cyclohexyl.

The Group $-R^{10D}$

(192) A compound according to any one of (1) to (191), wherein $-R^{10D}$, if present, is independently non-aromatic C_{3-10}heterocyclyl, and is optionally substituted, for example, with one or more substituents $-R^{X2}$.

(193) A compound according to any one of (1) to (191), wherein $-R^{10D}$, if present, is independently non-aromatic C_{3-10}heterocyclyl, and is optionally substituted, for example, with one or more substituents independently selected from C_{1-4}alkyl.

(194) A compound according to any one of (1) to (191), wherein $-R^{10D}$, if present, is independently non-aromatic C_{3-10}heterocyclyl.

(195) A compound according to any one of (1) to (191), wherein $-R^{10D}$, if present, is independently non-aromatic C_{5-7}heterocyclyl, and is optionally substituted, for example, with one or more substituents $-R^{X2}$.

(196) A compound according to any one of (1) to (191), wherein $-R^{10D}$, if present, is independently non-aromatic C_{5-7}heterocyclyl, and is optionally substituted, for example, with one or more substituents independently selected from C_{1-4}alkyl.

(197) A compound according to any one of (1) to (191), wherein $-R^{10D}$, if present, is independently non-aromatic C_{5-7}heterocyclyl.

(198) A compound according to any one of (1) to (191), wherein $-R^{10D}$ is independently pyrrolidinyl, piperidinyl, morpholinyl, piperizinyl, tetrahydrofuranyl, tetrahydropyranyl, dixoanyl, azepanyl, or diazepanyl, and is optionally substituted, for example, with one or more substituents $-R^{X2}$.

(199) A compound according to any one of (1) to (191), wherein $-R^{10D}$ is independently pyrrolidinyl, piperidinyl, morpholinyl, piperizinyl, tetrahydrofuranyl, tetrahydropyranyl, dixoanyl, azepanyl, or diazepanyl, and is optionally substituted, for example, with one or more substituents independently selected from C_{1-4}alkyl.

(200) A compound according to any one of (1) to (191), wherein $-R^{10D}$ is independently pyrrolidinyl, piperidinyl, morpholinyl, piperizinyl, tetrahydrofuranyl, tetrahydropyranyl, dixoanyl, azepanyl, or diazepanyl.

(201) A compound according to any one of (1) to (191), wherein $-R^{10D}$ is independently pyrrolidinyl, piperidinyl, morpholinyl, piperizinyl, tetrahydrofuranyl, tetrahydropyranyl, or dixoanyl, and is optionally substituted, for example, with one or more substituents $-R^{X2}$.

(202) A compound according to any one of (1) to (191), wherein $-R^{10D}$ is independently pyrrolidinyl, piperidinyl, morpholinyl, piperizinyl, tetrahydrofuranyl, tetrahydropyranyl, or dixoanyl, and is optionally substituted, for example, with one or more substituents independently selected from C_{1-4}alkyl.

(203) A compound according to any one of (1) to (191), wherein $-R^{10D}$ is independently pyrrolidinyl, piperidinyl, morpholinyl, piperizinyl, tetrahydrofuranyl, tetrahydropyranyl, or dixoanyl.

(204) A compound according to any one of (1) to (191), wherein $-R^{10D}$ is independently piperidinyl, morpholinyl, or piperizinyl, and is optionally substituted, for example, with one or more substituents $-R^{X2}$.

(205) A compound according to any one of (1) to (191), wherein $-R^{10D}$ is independently piperidinyl, morpholinyl, or piperizinyl, and is optionally substituted, for example, with one or more subsituents independently selected from C_{1-4}alkyl.

(206) A compound according to any one of (1) to (191), wherein $-R^{10D}$ is independently piperidinyl, morpholinyl, or piperizinyl.

(207) A compound according to any one of (1) to (191), wherein $-R^{10D}$ is independently piperidinyl, and is optionally substituted, for example, with one or more substituents $-R^{X2}$.

(208) A compound according to any one of (1) to (191), wherein $-R^{10D}$ is independently piperidinyl, and is optionally substituted, for example, with one or more substituents independently selected from C_{1-4}alkyl.

(209) A compound according to any one of (1) to (191), wherein $-R^{10D}$ is independently piperidin-4-yl, and is optionally substituted, for example, with one or more substituents $-R^{X2}$.

(210) A compound according to any one of (1) to (191), wherein $-R^{10D}$ is independently piperidin-4-yl, and is optionally substituted, for example, with one or more substituents independently selected from C_{1-4}alkyl.

The Optional Substituents $-R^{X1}$

(211) A compound according to any one of (1) to (210), wherein each $-R^{X1}$, if present, is independently selected from:

-F, -Cl, -Br, -I, phenyl, $-CF_3$, -OH, $-OR^S$, $-OCF_3$, $-NH_2$, $-NHR^S$, $-NR^S_2$, pyrrolidino, piperidino, morpholino, piperizino, N-(C_{1-4}alkyl)-piperizino, $-NHC(=O)R^S$, $-NR^SC(=O)R^S$, $-C(=O)R^S$, -C(=O)OH, $-C(=O)OR^S$, $-C(=O)NH_2$, $-C(=O)NHR^S$, $-C(=O)NR^S_2$, -C(=O)-pyrrolidino, -C(=O)-piperidino, -C(=O)-morpholino, -C(=O)-piperizino, -C(=O)-{N-(C_{1-4}alkyl)-piperizino}-, $-SR^S$, $-S(=O)R^S$, and $-S(=O)_2R^S$;

wherein each $-R^S$ is independently saturated aliphatic C_{1-6}alkyl, phenyl, or $-CH_2$-phenyl;

wherein each phenyl is optionally substituted with one or more groups selected from: -F, -Cl, -Br, -I, $-R^{SS}$, $-CF_3$, -OH, $-OR^{SS}$, or $-OCF_3$, wherein each $-R^{SS}$ is independently saturated aliphatic C_{1-4}alkyl.

(212) A compound according to (211), wherein each $-R^{X1}$, if present, is independently selected from:

-F, -Cl, -Br, -I, -OH, -OR^S, -NH_2, -NHR^S, -NR^S_2, pyrrolidino, piperidino, morpholino, piperizino, N-(C_{1-4}alkyl)-piperizino, -$NHC(=O)R^S$, -$NR^SC(=O)R^S$, -$C(=O)NH_2$, -$C(=O)NHR^S$, -$C(=O)NR^S_2$, -C(=O)-pyrrolidino, -C(=O)-piperidino, -C(=O)-morpholino, -C(=O)-piperizino, and -C(=O)-{N-(C_{1-4}alkyl)-piperizino}-.

(213) A compound according to (211), wherein each -R^{X1}, if present, is independently selected from:

-OH, -OR^S, -NH_2, -NHR^S, -NR^S_2, pyrrolidino, piperidino, morpholino, piperizino, N-(C_{1-4}alkyl)-piperizino, -$NHC(=O)R^S$, -$NR^SC(=O)R^S$, -$C(=O)NH_2$, -$C(=O)NHR^S$, -$C(=O)NR^S_2$, -C(=O)-pyrrolidino, -C(=O)-piperidino, -C(=O)-morpholino, -C(=O)-piperizino, and -C(=O)-{N-(C_{1-4}alkyl)-piperizino}-.

(214) A compound according to any one of (211) to (213), wherein each -R^S is independently saturated aliphatic C_{1-6}alkyl.

(215) A compound according to any one of (211) to (213), wherein each -R^S is independently saturated aliphatic C_{1-4}alkyl.

The Optional Substituents -R^{X2}

(216) A compound according to any one of (1) to (210), wherein each -R^{X2}, if present, is independently selected from:

-F, -Cl, -Br, -I, -R^T, phenyl, -OH, -OR^T, -$C(=O)R^T$, -NH_2, -NHR^T, -NR^T_2, pyrrolidino, piperidino, morpholino, piperizino, N-(C_{1-4}alkyl)-piperizino, -$NHC(=O)R^T$, and -$NR^TC(=O)R^T$;

wherein each -R^T is independently saturated aliphatic C_{1-6}alkyl, phenyl, or -CH_2-phenyl;

wherein each phenyl is optionally substituted with one or more groups selected from: -F, -Cl, -Br, -I, -R^{TT}, -CF_3, -OH, -OR^{TT}, or -OCF_3, wherein each -R^{TT} is independently saturated aliphatic C_{1-4}alkyl.

(217) A compound according to (216), wherein each -R^{X2}, if present, is independently selected from:

-R^T, -OH, -OR^T, -$C(=O)R^T$, -NH_2, -NHR^T, -NR^T_2, pyrrolidino, piperidino, morpholino, piperizino, N-(C_{1-4}alkyl)-piperizino, -$NHC(=O)R^T$, and -$NR^TC(=O)R^T$.

(218) A compound according to (216), wherein each -R^{X2}, if present, is independently selected from:

-R^T, -$C(=O)R^T$, -NH_2, -NHR^T, -NR^T_2, pyrrolidino, piperidino, morpholino, piperizino, N-(C_{1-4}alkyl)-piperizino, -$NHC(=O)R^T$, and -$NR^TC(=O)R^T$.

(219) A compound according to (216), wherein each $-R^{X2}$, if present, is independently selected from:

$-R^T$, $-NH_2$, $-NHR^T$, $-NR^T_2$, pyrrolidino, piperidino, morpholino, piperizino, N-(C_{1-4}alkyl)-piperizino, $-NHC(=O)R^T$, and $-NR^TC(=O)R^T$.

(220) A compound according to (216), wherein each $-R^{X2}$, if present, is independently selected from:

$-R^T$, $-NH_2$, $-NHR^T$, $-NR^T_2$, pyrrolidino, piperidino, morpholino, piperizino, and N-(C_{1-4}alkyl)-piperizino.

(221) A compound according to (216), wherein each $-R^{X2}$, if present, is independently $-R^T$.

(222) A compound according to any one of (216) to (221), wherein each $-R^T$ is independently saturated aliphatic C_{1-6}alkyl.

(223) A compound according to any one of (216) to (221), wherein each $-R^T$ is independently saturated aliphatic C_{1-4}alkyl.

The Optional Substituents $-R^{X3}$

(224) A compound according to any one of (1) to (223), wherein each $-R^{X3}$, if present, is independently selected from:

-F, -Cl, -Br, -I,
$-R^V$,
$-CH=CH_2$, $-C\equiv CH$, cyclopropyl,
$-CF_3$, $-CHF_2$, $-OCF_3$, $-OCHF_2$,
-CN,
$-NO_2$,
$-OH$, $-OR^V$,
$-L^V-OH$, $-L^V-OR^V$,
$-O-L^V-OH$, $-O-L^V-OR^V$,
$-NH_2$, $-NHR^V$, $-NR^V_2$,
pyrrolidino, piperidino, morpholino,
piperizino, N-(C_{1-4}alkyl)-piperizino,
$-L^V-NH_2$, $-L^V-NHR^V$, $-L^V-NR^V_2$,
$-L^V$-pyrrolidino, $-L^V$-piperidino, $-L^V$-morpholino,
$-L^V$-piperizino, $-L^V$-{N-(C_{1-4}alkyl)-piperizino},
$-L^V$-imidazol-2-yl, $-L^V$-{N-(C_{1-4}alkyl)-imidazol-2-yl},
$-O-L^V-NH_2$, $-O-L^V-NHR^V$, $-O-L^V-NR^V_2$,
$-O-L^V$-pyrrolidino, $-O-L^V$-piperidino, $-O-L^V$-morpholino,
$-O-L^V$-piperizino, $-O-L^V$-{N-(C_{1-4}alkyl)-piperizino},

-O-L^V-imidazol-2-yl, -O-L^V-{N-(C_{1-4}alkyl)-imidazol-2-yl},
-NHC(=O)R^V, -NR^VC(=O)R^V,
-C(=O)R^V,
-C(=O)OH, -C(=O)OR^V,
-C(=O)NH_2, -C(=O)NHR^V, -C(=O)NR^V_2,
-C(=O)-pyrrolidino, -C(=O)-piperidino, -C(=O)-morpholino,
-C(=O)-piperizino, -C(=O)-{N-(C_{1-4}alkyl)-piperizino}-,
-NHC(=O)NH_2, -NHC(=O)NHR^V, -NHC(=O)NR^V_2,
-NHC(=O)-pyrrolidino, -NHC(=O)-piperidino, -NHC(=O)-morpholino,
-NHC(=O)-piperizino, -NHC(=O)-{N-(C_{1-4}alkyl)-piperizino}-,
-S(=O)$_2R^V$,
-S(=O)$_2NH_2$, -S(=O)$_2$NHR^V, -S(=O)$_2$NR^V_2, and
=O;

wherein each -L^V- is independently saturated aliphatic C_{2-4}alkylene;

wherein each -R^V is independently saturated aliphatic C_{1-6}alkyl, phenyl, -CH_2-phenyl, C_{5-6}heteroaryl, or -CH_2-C_{5-6}heteroaryl;

wherein each phenyl is optionally substituted with one or more groups selected from: -F, -Cl, -Br, -I, -R^{VV}, -CF_3, -OH, -OR^{VV}, or -OCF_3;

wherein each C_{5-6}heteroaryl is optionally substituted with one or more groups selected from: -F, -Cl, -Br, -I, -R^{VV}, -CF_3, -OH, -OR^{VV}, or -OCF_3;

wherein each -R^{VV} is independently saturated aliphatic C_{1-4}alkyl;

and additionally, two adjacent groups -R^{X3} may together form -OCH_2O-, -OCH_2CH_2O-, -CH_2OCH_2- or -OCH_2CH_2-;

and additionally, two adjacent groups -R^{X3} may, together with the ring atoms to which they are attached, form a C_{5-7}carbocyclic ring or a C_{5-7}heterocyclic ring.

(225) A compound according to (224), wherein each -R^{X3}, if present, is independently selected from:

-F, -Cl, -Br, -I,
-R^V,
-CH=CH_2, -C≡CH, cyclopropyl,
-CF_3, -CHF_2, -OCF_3, -$OCHF_2$,
-CN,
-NO_2,
-OH, -OR^V,
-L^V-OH, -L^V-OR^V,
-O-L^V-OH, -O-L^V-OR^V,
-NH_2, -NHR^V, -NR^V_2,
pyrrolidino, piperidino, morpholino,
piperizino, N-(C_{1-4}alkyl)-piperizino,
-L^V-NH_2, -L^V-NHR^V, -L^V-NR^V_2,

-L^V-pyrrolidino, -L^V-piperidino, -L^V-morpholino,
-L^V-piperizino, -L^V-{N-(C_{1-4}alkyl)-piperizino},
-L^V-imidazol-2-yl, -L^V-{N-(C_{1-4}alkyl)-imidazol-2-yl},
-O-L^V-NH_2, -O-L^V-NHR^V, -O-L^V-NR^V_2,
-O-L^V-pyrrolidino, -O-L^V-piperidino, -O-L^V-morpholino,
-O-L^V-piperizino, -O-L^V-{N-(C_{1-4}alkyl)-piperizino},
-O-L^V-imidazol-2-yl, -O-L^V-{N-(C_{1-4}alkyl)-imidazol-2-yl},
-$NHC(=O)R^V$, -$NR^VC(=O)R^V$,
-$C(=O)R^V$,
-C(=O)OH, -$C(=O)OR^V$,
-$C(=O)NH_2$, -$C(=O)NHR^V$, -$C(=O)NR^V_2$,
-C(=O)-pyrrolidino, -C(=O)-piperidino, -C(=O)-morpholino,
-C(=O)-piperizino, -C(=O)-{N-(C_{1-4}alkyl)-piperizino}-,
-$NHC(=O)NH_2$, -$NHC(=O)NHR^V$, -$NHC(=O)NR^V_2$,
-NHC(=O)-pyrrolidino, -NHC(=O)-piperidino, -NHC(=O)-morpholino,
-NHC(=O)-piperizino, -NHC(=O)-{N-(C_{1-4}alkyl)-piperizino}-,
-$S(=O)_2R^V$,
-$S(=O)_2NH_2$, -$S(=O)_2NHR^V$, -$S(=O)_2NR^V_2$, and
=O;
and additionally, two adjacent groups -R^{X3} may together form -OCH_2O-, -OCH_2CH_2O-, -CH_2OCH_2- or -OCH_2CH_2-.

(226) A compound according to (224), wherein each -R^{X3}, if present, is independently selected from:
-F, -Cl, -Br, -I,
-R^V,
-OH, -OR^V,
-NH_2, -NHR^V, -NR^V_2,
pyrrolidino, piperidino, morpholino,
piperizino, and N-(C_{1-4}alkyl)-piperizino.

(227) A compound according to (224), wherein each -R^{X3}, if present, is independently selected from:
-F, -Cl, -Br, -I,
-R^V,
-OH, -OR^V,
-NH_2, -NHR^V, and -NR^V_2.

(228) A compound according to any one of (224) to (226), wherein each -L^V- is independently -CH_2CH_2-, -$CH_2CH_2CH_2$-, or -$CH_2CH_2CH_2CH_2$-.

(229) A compound according to any one of (224) to (228), wherein each $-R^V$ is independently saturated aliphatic C_{1-6}alkyl.

(230) A compound according to any one of (224) to (228), wherein each $-R^V$ is independently saturated aliphatic C_{1-4}alkyl.

Molecular Weight

(231) A compound according to any one of (1) to (230), wherein the compound has a molecular weight of from 241 to 1200.

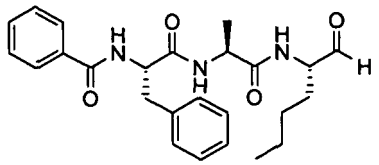
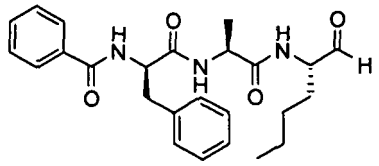
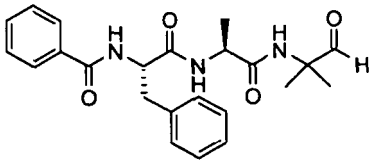
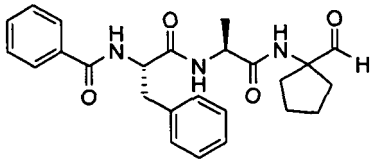
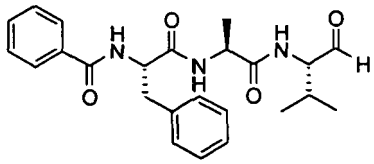
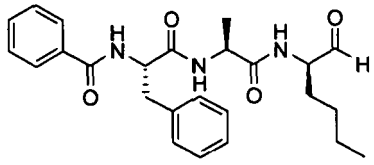
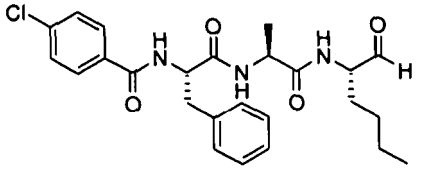
(232) A compound according to (231), wherein the bottom of range is 250, 275, 300, 325, 350, 375, 400, or 500.

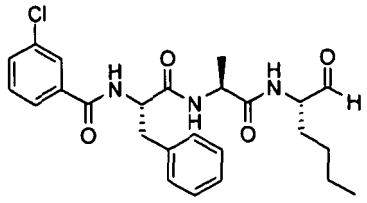
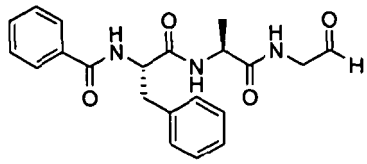
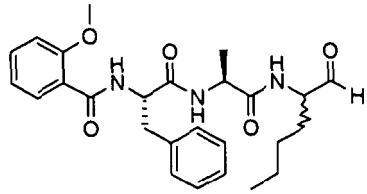
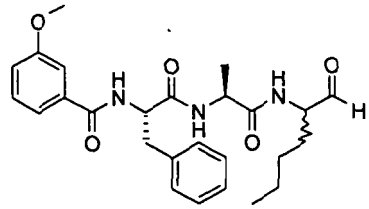
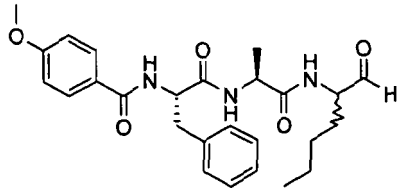
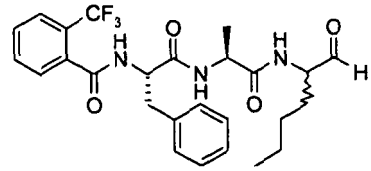
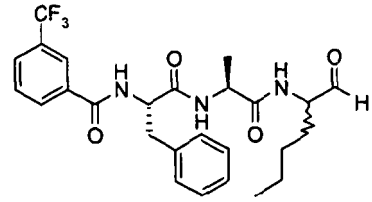
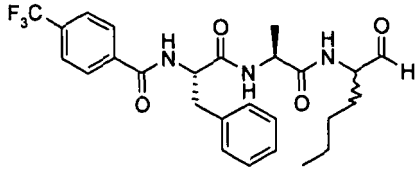
(233) A compound according to (231) or (232), wherein the top of range is 1100, 1000, 900, 800, 700, or 600.

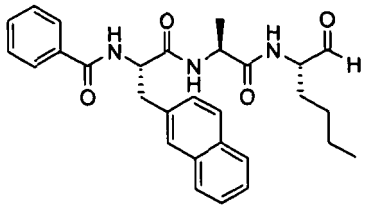
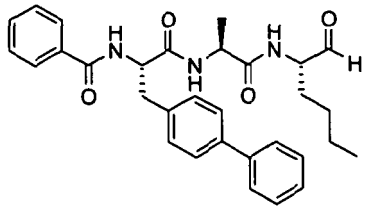
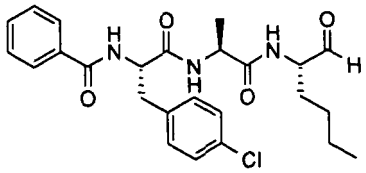
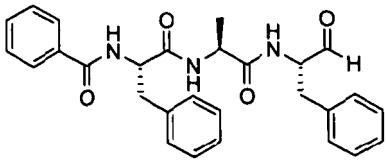
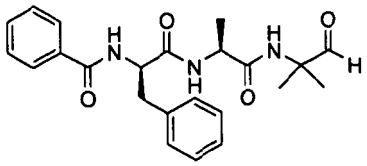
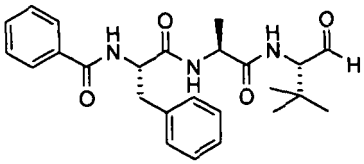
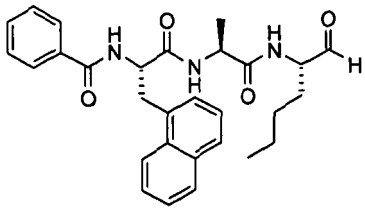
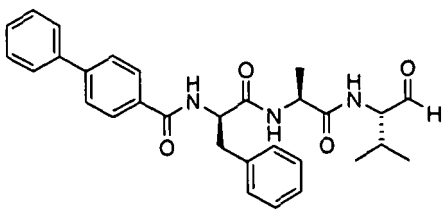
(234) A compound according to any one of (1) to (230), wherein the compound has a molecular weight of range from 375 to 700.

Specific Compounds

(235) A compound according to (1), selected from compounds of the following formulae and pharmaceutically acceptable salts, hydrates, and solvates thereof:

Code	Compound
ALD-001	
ALD-002	
ALD-003	
ALD-004	
ALD-005	
ALD-006	
ALD-007	

Code	Compound
ALD-008	
ALD-009	
ALD-010	
ALD-011	
ALD-012	
ALD-013	
ALD-014	
ALD-015	

Code	Compound
ALD-016	
ALD-017	
ALD-018	
ALD-019	
ALD-020	
ALD-021	
ALD-022	
ALD-023	

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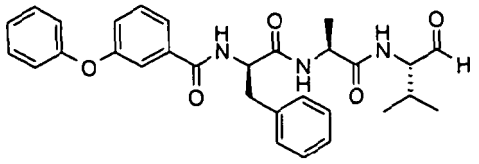
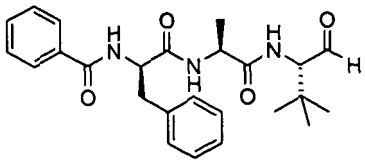
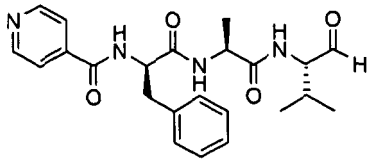
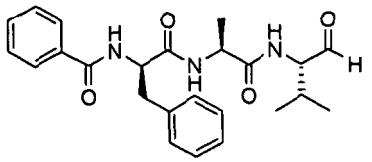
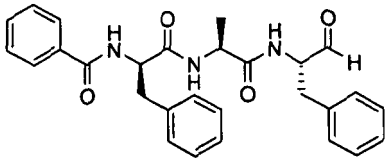
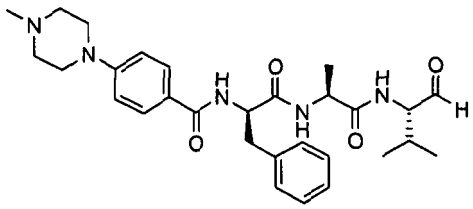
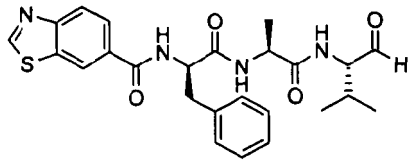
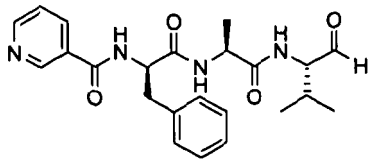
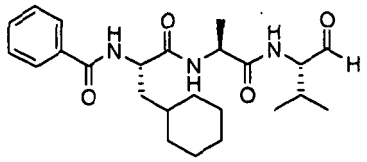
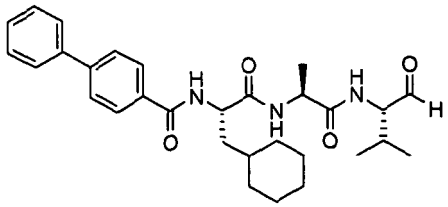
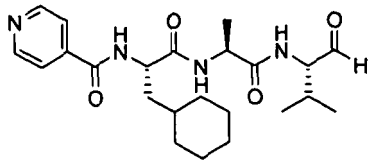
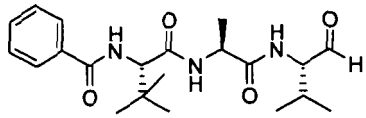
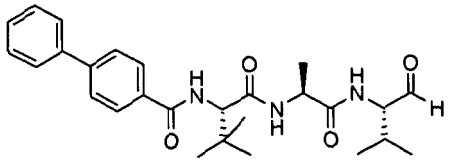
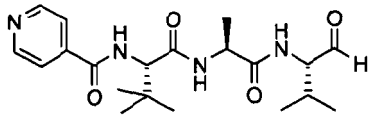
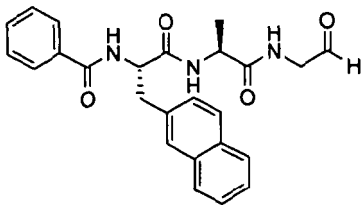
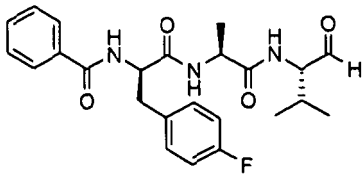
ALD-024	
ALD-025	
ALD-026	
ALD-027	
ALD-028	
ALD-029	
ALD-030	
ALD-031	

Code	Compound
ALD-032	
ALD-033	
ALD-034	
ALD-035	
ALD-036	
ALD-037	
ALD-038	
ALD-039	

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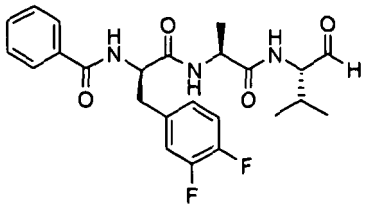
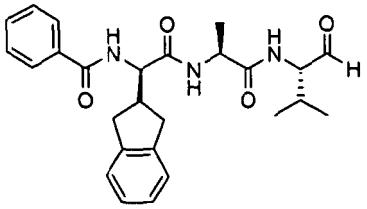
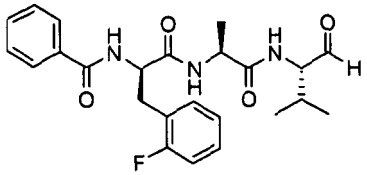
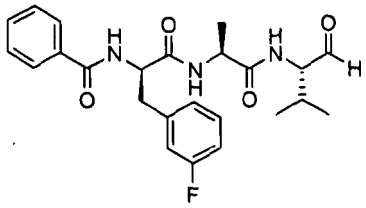
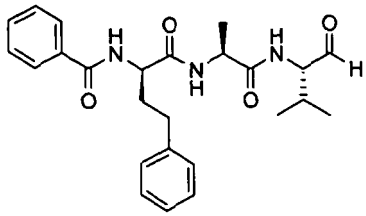
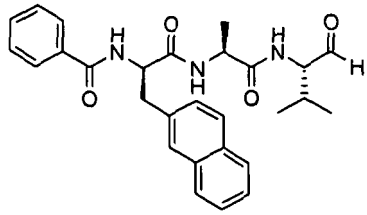
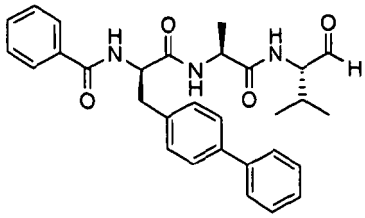
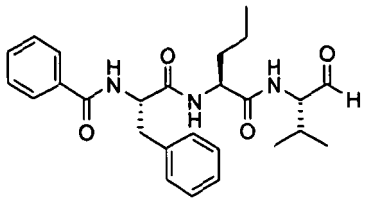
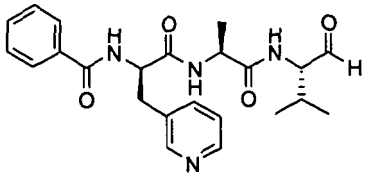
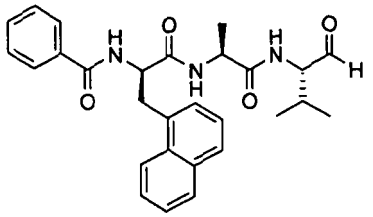
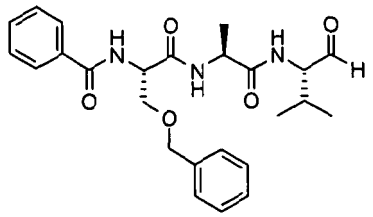
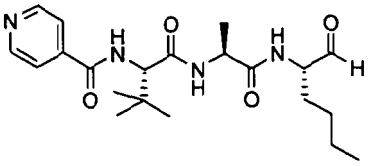
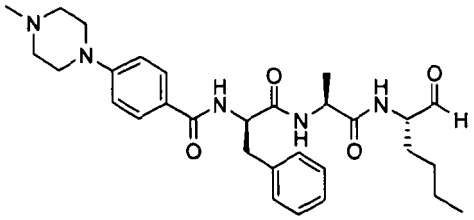
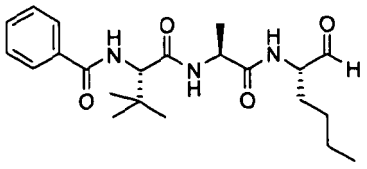
ALD-040	
ALD-041	
ALD-042	
ALD-043	
ALD-044	
ALD-045	
ALD-046	

Code	Compound
ALD-047	
ALD-048	
ALD-049	
ALD-050	
ALD-051	
ALD-052	
ALD-053	

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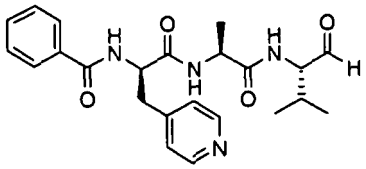
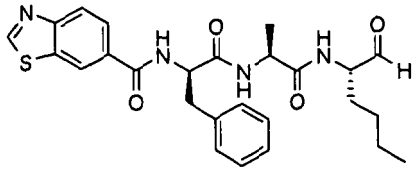
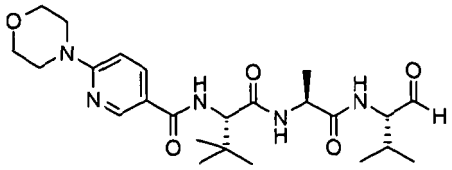
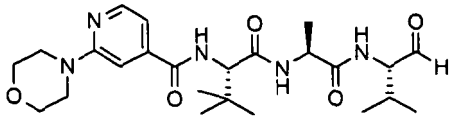
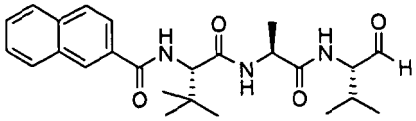
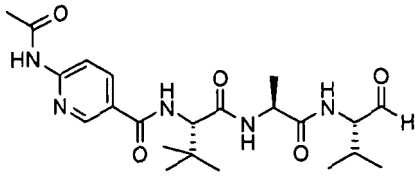
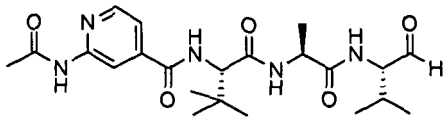
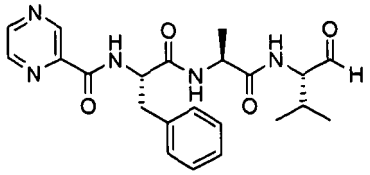
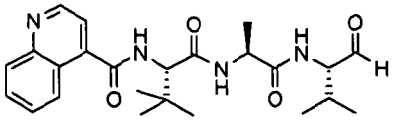
ALD-054	
ALD-055	
ALD-056	
ALD-057	
ALD-058	
ALD-059	
ALD-060	
ALD-061	
ALD-062	

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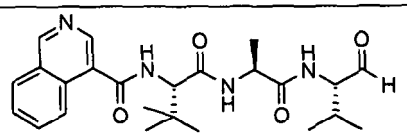
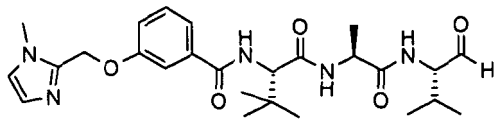
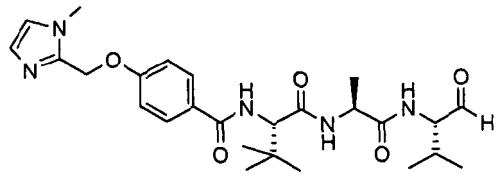
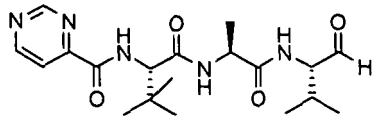
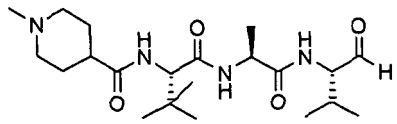
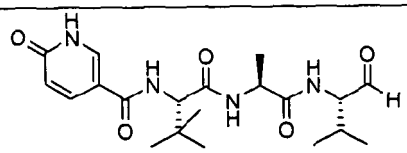
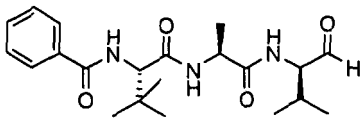
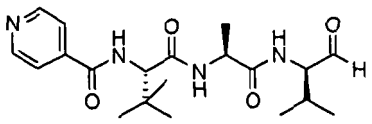
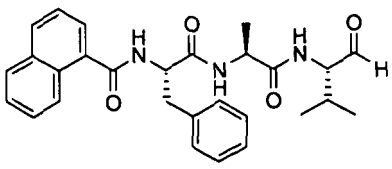
ALD-063	
ALD-064	
ALD-065	
ALD-066	
ALD-067	
ALD-068	
ALD-069	
ALD-070	
ALD-071	

Combinations

It is appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, may also be provided in combination in a single embodiment. Conversely, various features of the invention, which are, for brevity, described in the context of a single embodiment, may also be provided separately or in any suitable sub-combination. All combinations of the embodiments pertaining to the chemical groups represented by the variables (e.g., $-R^1$, $-R^2$, $-R^4$, $-R^7$, $-R^8$, $-R^{10}$, $-R^{1A}$, $-R^{2A}$, $-R^{4A}$, $-R^{7A}$, $-R^{7B}$, $-L^{7B1}-$, $-L^{7B2}-$, $-R^{7BB}$, $-R^{7BB1}$, $-R^{7BB2}$, $-R^{7BB3}$, $-R^{7BB4}$, $-R^{8A}$, $-R^{10A}$, $-R^{10B}$, $-R^{10C}$, $-R^{10D}$, $-R^{X1}$, $-R^{X2}$, $-R^{X3}$, etc.) are specifically embraced by the present invention and are disclosed herein just as if each and every combination was individually and explicitly disclosed, to the extent that such combinations embrace compounds that are stable compounds (i.e., compounds that can be isolated, characterised, and tested for biological activity). In addition, all sub-combinations of the chemical groups listed in the embodiments describing such variables are also specifically embraced by the present invention and are disclosed herein just as if each and every such sub-combination of chemical groups was individually and explicitly disclosed herein.

Substantially Purified Forms

One aspect of the present invention pertains to ALD compounds, as described herein, in substantially purified form and/or in a form substantially free from contaminants.

In one embodiment, the substantially purified form is at least 50% by weight, e.g., at least 60% by weight, e.g., at least 70% by weight, e.g., at least 80% by weight, e.g., at least 90% by weight, e.g., at least 95% by weight, e.g., at least 97% by weight, e.g., at least 98% by weight, e.g., at least 99% by weight.

Unless specified, the substantially purified form refers to the compound in any stereoisomeric or enantiomeric form. For example, in one embodiment, the substantially purified form refers to a mixture of stereoisomers, i.e., purified with respect to other compounds. In one embodiment, the substantially purified form refers to one stereoisomer, e.g., optically pure stereoisomer. In one embodiment, the substantially purified form refers to a mixture of enantiomers. In one embodiment, the substantially purified form refers to a equimolar mixture of enantiomers (i.e., a racemic mixture, a racemate). In one embodiment, the substantially purified form refers to one enantiomer, e.g., optically pure enantiomer.

In one embodiment, the contaminants represent no more than 50% by weight, e.g., no more than 40% by weight, e.g., no more than 30% by weight, e.g., no more than 20% by

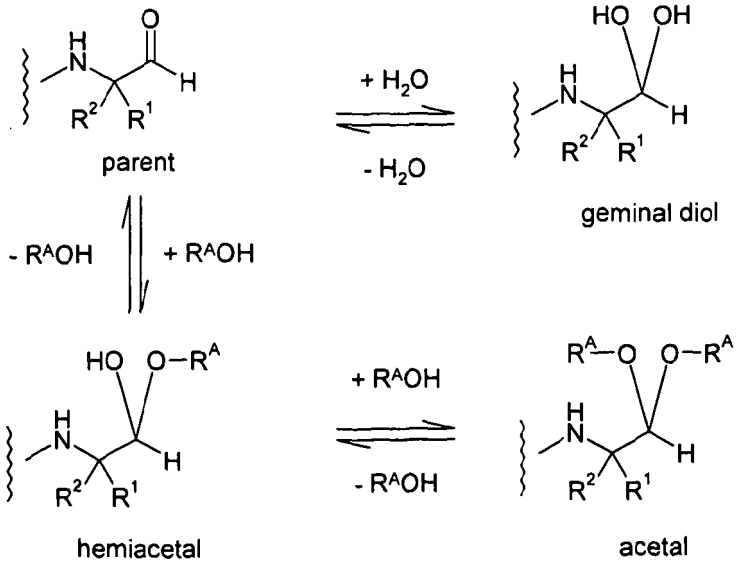
weight, e.g., no more than 10% by weight, e.g., no more than 5% by weight, e.g., no more than 3% by weight, e.g., no more than 2% by weight, e.g., no more than 1% by weight.

Unless specified, the contaminants refer to other compounds, that is, other than stereoisomers or enantiomers. In one embodiment, the contaminants refer to other compounds and other stereoisomers. In one embodiment, the contaminants refer to other compounds and the other enantiomer.

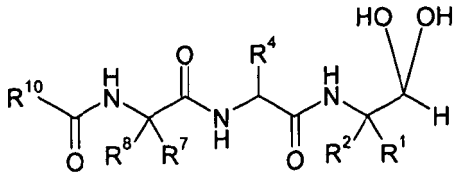
In one embodiment, the substantially purified form is at least 60% optically pure (i.e., 60% of the compound, on a molar basis, is the desired stereoisomer or enantiomer, and 40% is the undesired stereoisomer or enantiomer), e.g., at least 70% optically pure, e.g., at least 80% optically pure, e.g., at least 90% optically pure, e.g., at least 95% optically pure, e.g., at least 97% optically pure, e.g., at least 98% optically pure, e.g., at least 99% optically pure.

Geminal Diols, Hemiacetals, and Acetals

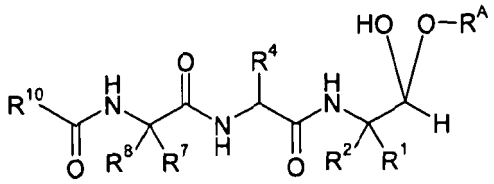
It is anticipated that the aldehyde (-C(=O)H) group of the ALD compounds may deliberately or inadvertently be converted entirely or partially to the corresponding geminal diol, hemi-acetal, or acetal upon contact with water, an alcohol, or a mixture of water and an alcohol. Such a transformation may occur, for example during purification (e.g., during recrystallisation from an aqueous or alcoholic solvent). This is illustrated below wherein, for example, each $-R^A$ is independently C_{1-4}alkyl, for example, -Me. Furthermore, a cyclic acetal may be formed if a diol is used, for example, ethylene glycol, to produce the corresponding 1,3-dioxolane.



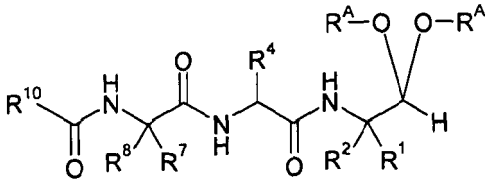
It is anticipated that in aqueous solution any such geminal diols, hemiacetals, and acetals would be present in equilibrium with the parent compound. For the avoidance of doubt, it is intended that, unless otherwise specified, references herein to the ALD compounds also encompass such geminal diol, hemi-acetal, and acetal forms.



geminal diol



hemiacetal



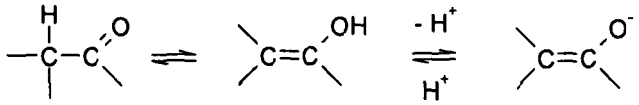
acetal

Isomers

Certain compounds may exist in one or more particular geometric, optical, enantiomeric, diastereoisomeric, epimeric, atropic, stereoisomeric, tautomeric, conformational, or anomeric forms, including but not limited to, cis- and trans-forms; E- and Z-forms; c-, t-, and r- forms; endo- and exo-forms; R-, S-, and meso-forms; D- and L-forms; d- and l-forms; (+) and (-) forms; keto-, enol-, and enolate-forms; syn- and anti-forms; synclinal- and anticlinal-forms; α- and β-forms; axial and equatorial forms; boat-, chair-, twist-, envelope-, and halfchair-forms; and combinations thereof, hereinafter collectively referred to as "isomers" (or "isomeric forms").

A reference to a class of structures may well include structurally isomeric forms falling within that class (e.g., C_{1-7}alkyl includes n-propyl and iso-propyl; butyl includes n-, iso-, sec-, and tert-butyl; methoxyphenyl includes ortho-, meta-, and para-methoxyphenyl). However, reference to a specifc group or substitution pattern is not intended to include other structural (or constitutional isomers) which differ with respect to the connections between atoms rather than by positions in space. For example, a reference to a methoxy group, $-OCH_3$, is not to be construed as a reference to its structural isomer, a hydroxymethyl group, $-CH_2OH$. Similarly, a reference to ortho-chlorophenyl is not to be construed as a reference to its structural isomer, meta-chlorophenyl.

The above exclusion does not pertain to tautomeric forms, for example, keto-, enol-, and enolate-forms, as in, for example, the following tautomeric pairs: keto/enol (illustrated below), imine/enamine, amide/imino alcohol, amidine/amidine, nitroso/oxime, thioketone/enethiol, N-nitroso/hydroxyazo, and nitro/aci-nitro.



keto enol enolate

For example, 1H-pyridin-2-one-5-yl and 2-hydroxyl-pyridin-5-yl (shown below) are tautomers of one another. A reference herein to one is intended to encompass both. See, for example, ALD-068.

1H-pyridin-2-one-5-yl 2-hydroxyl-pyridin-5-yl

Note that specifically included in the term "isomer" are compounds with one or more isotopic substitutions. For example, H may be in any isotopic form, including ^{1}H, ^{2}H (D), and ^{3}H (T); C may be in any isotopic form, including ^{12}C, ^{13}C, and ^{14}C; O may be in any isotopic form, including ^{16}O and ^{18}O; and the like.

Unless otherwise specified, a reference to a particular compound includes all such isomeric forms, including mixtures (e.g., racemic mixtures) thereof. Methods for the preparation (e.g., asymmetric synthesis) and separation (e.g., fractional crystallisation and chromatographic means) of such isomeric forms are either known in the art or are readily obtained by adapting the methods taught herein, or known methods, in a known manner.

Salts

It may be convenient or desirable to prepare, purify, and/or handle a corresponding salt of the compound, for example, a pharmaceutically-acceptable salt. Examples of pharmaceutically acceptable salts are discussed in Berge *et al.*, 1977, "Pharmaceutically Acceptable Salts," J. Pharm. Sci., Vol. 66, pp. 1-19.

For example, if the compound is anionic, or has a functional group which may be anionic (e.g., -COOH may be -COO^-), then a salt may be formed with a suitable cation. Examples of suitable inorganic cations include, but are not limited to, alkali metal ions

such as Na^+ and K^+, alkaline earth cations such as Ca^{2+} and Mg^{2+}, and other cations such as Al^{+3}. Examples of suitable organic cations include, but are not limited to, ammonium ion (i.e., NH_4^+) and substituted ammonium ions (e.g., NH_3R^+, $NH_2R_2^+$, NHR_3^+, NR_4^+). Examples of some suitable substituted ammonium ions are those derived from: ethylamine, diethylamine, dicyclohexylamine, triethylamine, butylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine, benzylamine, phenylbenzylamine, choline, meglumine, and tromethamine, as well as amino acids, such as lysine and arginine. An example of a common quaternary ammonium ion is $N(CH_3)_4^+$.

If the compound is cationic, or has a functional group which upon protonation may become cationic (e.g., $-NH_2$ may become $-NH_3^+$), then a salt may be formed with a suitable anion. Examples of suitable inorganic anions include, but are not limited to, those derived from the following inorganic acids: hydrochloric, hydrobromic, hydroiodic, sulfuric, sulfurous, nitric, nitrous, phosphoric, and phosphorous.

Examples of suitable organic anions include, but are not limited to, those derived from the following organic acids: 2-acetyoxybenzoic, acetic, trifluoroacetic, ascorbic, aspartic, benzoic, camphorsulfonic, cinnamic, citric, edetic, ethanedisulfonic, ethanesulfonic, fumaric, glucheptonic, gluconic, glutamic, glycolic, hydroxymaleic, hydroxynaphthalene carboxylic, isethionic, lactic, lactobionic, lauric, maleic, malic, methanesulfonic, mucic, oleic, oxalic, palmitic, pamoic, pantothenic, phenylacetic, phenylsulfonic, propionic, pyruvic, salicylic, stearic, succinic, sulfanilic, tartaric, toluenesulfonic, and valeric. Examples of suitable polymeric organic anions include, but are not limited to, those derived from the following polymeric acids: tannic acid, carboxymethyl cellulose.

Unless otherwise specified, a reference to a particular compound also includes salt forms thereof.

Solvates and Hydrates

It may be convenient or desirable to prepare, purify, and/or handle a corresponding solvate of the compound. The term "solvate" is used herein in the conventional sense to refer to a complex of solute (e.g., compound, salt of compound) and solvent. If the solvent is water, the solvate may be conveniently referred to as a hydrate, for example, a mono-hydrate, a di-hydrate, a tri-hydrate, etc.

Unless otherwise specified, a reference to a particular compound also includes solvate and hydrate forms thereof.

Chemically Protected Forms

It may be convenient or desirable to prepare, purify, and/or handle the compound in a chemically protected form. The term "chemically protected form" is used herein in the conventional chemical sense and pertains to a compound in which one or more reactive functional groups are protected from undesirable chemical reactions under specified conditions (e.g., pH, temperature, radiation, solvent, and the like). In practice, well known chemical methods are employed to reversibly render unreactive a functional group, which otherwise would be reactive, under specified conditions. In a chemically protected form, one or more reactive functional groups are in the form of a protected or protecting group (also known as a masked or masking group or a blocked or blocking group). By protecting a reactive functional group, reactions involving other unprotected reactive functional groups can be performed, without affecting the protected group; the protecting group may be removed, usually in a subsequent step, without substantially affecting the remainder of the molecule. See, for example, Protective Groups in Organic Synthesis (T. Green and P. Wuts; 4th Edition; John Wiley and Sons, 2006).

A wide variety of such "protecting," "blocking," or "masking" methods are widely used and well known in organic synthesis. For example, a compound which has two nonequivalent reactive functional groups, both of which would be reactive under specified conditions, may be derivatized to render one of the functional groups "protected," and therefore unreactive, under the specified conditions; so protected, the compound may be used as a reactant which has effectively only one reactive functional group. After the desired reaction (involving the other functional group) is complete, the protected group may be "deprotected" to return it to its original functionality.

For example, a hydroxy group may be protected as an ether (-OR) or an ester (-OC(=O)R), for example, as: a t-butyl ether; a benzyl, benzhydryl (diphenylmethyl), or trityl (triphenylmethyl) ether; a trimethylsilyl or t-butyldimethylsilyl ether; or an acetyl ester (-OC(=O)CH_3, -OAc).

For example, an aldehyde or ketone group may be protected as an acetal (R-CH$(OR)_2$) or ketal ($R_2C(OR)_2$), respectively, in which the carbonyl group (>C=O) is converted to a diether (>C$(OR)_2$), by reaction with, for example, a primary alcohol. The aldehyde or ketone group is readily regenerated, for example, by hydrolysis using water in the presence of acid.

For example, an amine group may be protected, for example, as an amide (-NRCO-R) or a urethane (-NRCO-OR), for example, as: a methyl amide (-NHCO-CH_3); a benzyloxy amide (-NHCO-$OCH_2C_6H_5$, -NH-Cbz); as a t-butoxy amide (-NHCO-$OC(CH_3)_3$, -NH-Boc); a 2-biphenyl-2-propoxy amide (-NHCO-$OC(CH_3)_2C_6H_4C_6H_5$, -NH-Bpoc), as a

9-fluorenylmethoxy amide (-NH-Fmoc), as a 6-nitroveratryloxy amide (-NH-Nvoc), as a 2-trimethylsilylethyloxy amide (-NH-Teoc), as a 2,2,2-trichloroethyloxy amide (-NH-Troc), as an allyloxy amide (-NH-Alloc), as a 2(-phenylsulfonyl)ethyloxy amide (-NH-Psec); or, in suitable cases (e.g., cyclic amines), as a nitroxide radical (>N-O•).

For example, a carboxylic acid group may be protected as an ester for example, as: an C_{1-7}alkyl ester (e.g., a methyl ester; a t-butyl ester); a C_{1-7}haloalkyl ester (e.g., a C_{1-7}trihaloalkyl ester); a triC_{1-7}alkylsilyl-C_{1-7}alkyl ester; or a C_{5-20}aryl-C_{1-7}alkyl ester (e.g., a benzyl ester; a nitrobenzyl ester); or as an amide, for example, as a methyl amide.

For example, a thiol group may be protected as a thioether (-SR), for example, as: a benzyl thioether; an acetamidomethyl ether (-S-CH_2NHC(=O)CH_3).

Prodrugs

It may be convenient or desirable to prepare, purify, and/or handle the compound in the form of a prodrug. The term "prodrug," as used herein, pertains to a compound which yields the desired active compound *in vivo*. Typically, the prodrug is inactive, or less active than the desired active compound, but may provide advantageous handling, administration, or metabolic properties.

For example, some prodrugs are esters of the active compound (e.g., a physiologically acceptable metabolically labile ester). During metabolism, the ester group (-C(=O)OR) is cleaved to yield the active drug. Such esters may be formed by esterification, for example, of any of the carboxylic acid groups (-C(=O)OH) in the parent compound, with, where appropriate, prior protection of any other reactive groups present in the parent compound, followed by deprotection if required.

Another form of prodrug of the ALD compounds may be one wherein the aldehyde (-C(=O)H) group of the ALD compound is protected, for example, as an acetal or hemiacetal, which is converted, *in vivo*, to the corresponding aldehyde.

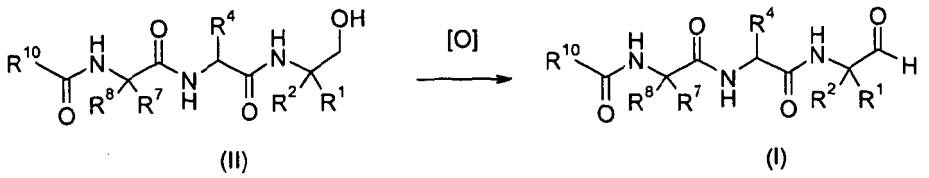
Also, some prodrugs are activated enzymatically to yield the active compound, or a compound which, upon further chemical reaction, yields the active compound (for example, as in antibody directed enzyme prodrug therapy (ADEPT), gene directed enzyme prodrug therapy (GDEPT), lipid directed enzyme prodrug therapy (LIDEPT), etc.). For example, the prodrug may be a sugar derivative or other glycoside conjugate, or may be an amino acid ester derivative.

Chemical Synthesis

Several methods for the chemical synthesis of ALD compounds of the present invention are described herein. These and/or other well known methods may be modified and/or adapted in known ways in order to facilitate the synthesis of additional compounds within the scope of the present invention.

Compounds of Formula (I) may be prepared, for example, by reacting an alcohol of Formula (II) with an appropriate oxidising agent, as illustrated in the following scheme. Suitable oxidising agents include, but are not limited to, Dess-Martin periodinane, pyridinium chlorochromate (PCC), tetrapropylammonium perruthenate (TPAP), and the use of Swern or modified Swern conditions, which use DMSO in conjunction with an activating agent such as oxalyl chloride.

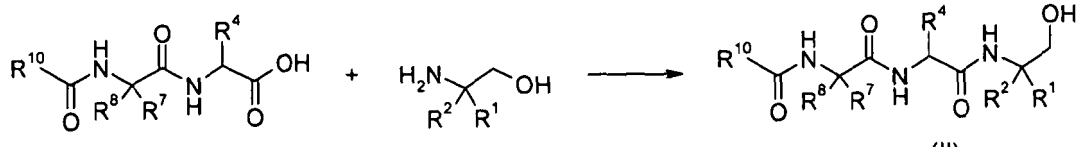
Scheme 1



(II) (I)

Alcohols of Formula (II) can be prepared by several different routes which are well known in the art. One such method involves reacting a compound of Formula (III) with a compound of Formula (IV) using standard acid-amine coupling conditions, as illustrated in the following scheme. Such conditions are known in the art. A potential side reaction under such conditions can be the epimerisation of the R^4 chiral centre. It is common to avoid such side reactions by carrying out low temperature coupling reactions using a mixed anhydride derived from Formula (III). Mixed anhydrides are commonly generated in situ using, for example, isobutylchloroformate or ethylchloroformate and a mild base, such as N-methylmorpholine. Such methods are in the art.

Scheme 2



(III) (IV) (II)

The alcohol group of compound (IV) may also be protected with for example a silyl protecting group in order to prevent side reactions during the coupling process. Compound (II) can then be generated following removal of the protecting group. Suitable alcohol protecting groups and conditions for their removal can be found for example in

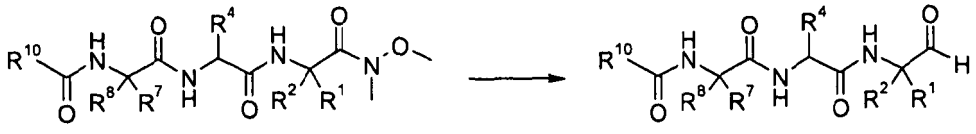
Protective Groups in Organic Synthesis, 3rd Ed., (T. Green and P. Wuts; 4th Edition; Wiley-Interscience, 1999), pp. 17-245.

Dipeptide and tripeptide derivatives may be synthesised on a polymeric (e.g., polystyrene) resin using standard resin-based Fmoc coupling methods. The first Fmoc protected amino acid is generally coupled to Wang or 2-chloro-trityl resin. Subsequent amino acids are coupled using standard acid-amine coupling conditions. Suitable conditions include the use of hydroxybenzotriazole (HOBt) with N,N'-diisopropylcarbodiimide (DIC) or 2-(1H-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate methanaminium (HATU), O-(Benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (TBTU), O-Benzotriazole-N,N,N',N'-tetramethyl-uronium-hexafluoro-phosphate (HBTU), or benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate (PyBop), with a suitable base such as N,N-diisopropylethylamine (DIPEA). Further information on the synthesis of peptides on resin may be found, for example, in: Chan and White, Fmoc Solid Phase Peptide Synthesis: A Practical Approach (Oxford University Press, 2000).

Alternatively, peptide derivatives can be built up in a sequential fashion using solution chemistry with appropriately protected amino acids using methods known in the art. The use of suitable nitrogen protecting groups coupled with low temperature mixed-anhydride coupling conditions is commonly used for this purpose. Suitable nitrogen protecting groups include, but are not limited to, carboxybenzyl (CBz), t-butoxycarbonyl (Boc), and fluorenylmethyloxycarbonyl (Fmoc). A review of amine protecting groups can be found, for example, Protective Groups in Organic Synthesis, 3rd Ed., (T. Green and P. Wuts; 4th Edition; Wiley-Interscience, 1999), pp. 494-653.

Alternatively ALD compounds of Formula (I) may be generated by the selective reduction of a carboxylic acid or a carboxylic acid derivative. One carboxylic acid derivative used for such purposes which is well known to the art is a Weinreb amide. Weinreb amides can be converted to aldehydes using reducing agents such as but not limited to, lithium aluminium hydride and diisobutylaluminium hydride.

Scheme 3



(V) (I)

Weinreb amides of Formula (V) may be prepared from the corresponding carboxylic acid using methods well known in the art.

Alternatively an Fmoc-protected amino acid can be coupled to a N-methylhydroxylamine modified resin such as Weinreb AM resin purchasable from Novabiochem. This can then be used to synthesise a resin bound Weinreb amide of formula (V) using standard resin-based Fmoc coupling methods. ALD compounds of formula (I) can subsequently be generated following treatment of the resin with a suitable reducing agent such as lithium aluminium hydride in an appropriate solvent such as tetrahydrofuran (see, for example, Fehrentz et al., 1995).

Alternatively ALD compounds of formula (I) may be prepared from a derivative which contains a masked aldehyde unit, one such example would be a dimethyl acetal. A review of aldehyde protecting groups can be found, for example, Protective Groups in Organic Synthesis, 3rd Ed., (T. Green and P. Wuts; 4th Edition; Wiley-Interscience, 1999), pp. 293-368.

Compositions

One aspect of the present invention pertains to a composition (e.g., a pharmaceutical composition) comprising an ALD compound, as described herein, and a pharmaceutically acceptable carrier, diluent, or excipient.

In one embodiment, the composition is in the form of a dry powder, for example, suitable for delivery (e.g., administration) using a dry powder inhaler (DPI). Examples of sutable DPIs are well-known in the art. DPI administration may be used to deliver the drug to the lung or the nose.

In one embodiment, the composition is in the form of a suspension, for example, suitable for delivery (e.g., administration) using a nebuliser. This may be used to deliver the drug to the lung or the nose.

In one embodiment, the composition is in the form of a solution or suspension in a liquid propellant, for example, suitable for delivery (e.g., administration) as an aerosol, for example, using a pressurised metered dose inhaler (pMDI). Examples of sutable pMDIs are well-known in the art. Suitable propellants are well-known in the art, and include, for example, dichlorodifluoromethane (CFC-12), trichlorofluoromethane, dichoro-tetrafluoroethane, HFA-134a, HFA-227, HCFC-22, HFA-152, isobutene, and carbon dioxide. This may be used to deliver the drug to the lung or the nose, and may additionally be used to delivery the drug to the skin.

In one embodiment, the composition is in the form of an aqueous solution, for example, suitable for delivery (e.g., administration) using a dropper, syringe, metered dose spray

pump or atomiser. This may be used to deliver the drug to the nose, to the skin, to the eye, and additionally may be used for injection.

In one embodiment, the composition further comprises one or more (e.g., 1, 2, 3, 4) additional therapeutic agents, as described herein.

Another aspect of the present invention pertains to a method of preparing a composition (e.g., a pharmaceutical composition) comprising admixing an ALD compound, as described herein, and a pharmaceutically acceptable carrier, diluent, or excipient.

Another aspect of the present invention pertains to a method of preparing a composition (e.g., a pharmaceutical composition) comprising admixing an ALD compound, as described herein; one or more (e.g., 1, 2, 3, 4) additional therapeutic agents, as described herein; and a pharmaceutically acceptable carrier, diluent, or excipient.

Uses

The compounds described herein are useful, for example, in the treatment of diseases and disorders that are ameliorated by the inhibition of a dust mite Group 1 peptidase allergen (e.g., Der p 1, Der f 1, Eur m 1), such as, for example, asthma; rhinitis; allergic conjunctivitis; atopic dermatitis; an allergic condition which is triggered by dust mites; an allergic condition that is triggered by a dust mite Group 1 peptidase allergen; and canine atopy.

Use in Methods of Inhibiting a Dust Mite Group 1 Peptidase Allergen

One aspect of the present invention pertains to a method of inhibiting a dust mite Group 1 peptidase allergen (e.g., Der p 1, Der f 1, Eur m 1), *in vitro* or *in vivo,* comprising contacting a dust mite Group 1 peptidase allergen with an effective amount of an ALD compound, as described herein.

One aspect of the present invention pertains to a method of inhibiting a dust mite Group 1 peptidase allergen (e.g., Der p 1, Der f 1, Eur m 1) in a cell, *in vitro* or *in vivo,* comprising contacting the cell with an effective amount of an ALD compound, as described herein.

Suitable assays for determining inhibition of a dust mite Group 1 peptidase allergen are described herein and/or are known in the art.

Use in Methods of Therapy

Another aspect of the present invention pertains to an ALD compound, as described herein, for use in a method of treatment of the human or animal body by therapy.

Another aspect of the present invention pertains to an ALD compound, as described herein, in combination with one or more (e.g., 1, 2, 3, 4) additional therapeutic agents, as described herein, for use in a method of treatment of the human or animal body by therapy.

Use in the Manufacture of Medicaments

Another aspect of the present invention pertains to use of an ALD compound, as described herein, in the manufacture of a medicament for use in treatment.

In one embodiment, the medicament comprises the ALD compound.

Another aspect of the present invention pertains to use of an ALD compound, as described herein, and one or more (e.g., 1, 2, 3, 4) additional therapeutic agents, as described herein, in the manufacture of a medicament for use in treatment.

In one embodiment, the medicament comprises the ALD compound and the one or more (e.g., 1, 2, 3, 4) additional therapeutic agents.

Methods of Treatment

Another aspect of the present invention pertains to a method of treatment comprising administering to a patient in need of treatment a therapeutically effective amount of an ALD compound, as described herein, preferably in the form of a pharmaceutical composition.

Another aspect of the present invention pertains to a method of treatment comprising administering to a patient in need of treatment a therapeutically effective amount of an ALD compound, as described herein, preferably in the form of a pharmaceutical composition, and one or more (e.g., 1, 2, 3, 4) additional therapeutic agents, as described herein, preferably in the form of a pharmaceutical composition.

Conditions Treated: Diseases and Disorders Mediated by a Dust Mite Group 1 Peptidase Allergen

In one embodiment (e.g., of use in methods of therapy, of use in the manufacture of medicaments, of methods of treatment), the treatment is treatment of a disease or disorder that is mediated by a dust mite Group 1 peptidase allergen (e.g., Der p 1, Der f 1, Eur m 1).

Conditions Treated: Diseases and Disorders Ameliorated by the Inhibition of a Dust Mite Group 1 Peptidase Allergen

In one embodiment (e.g., of use in methods of therapy, of use in the manufacture of medicaments, of methods of treatment), the treatment is treatment of: a disease or condition that is ameliorated by the inhibition of a dust mite Group 1 peptidase allergen (e.g., Der p 1, Der f 1, Eur m 1).

Conditions Treated: Particular Diseases and Disorders

In one embodiment (e.g., of use in methods of therapy, of use in the manufacture of medicaments, of methods of treatment), the treatment is treatment of: asthma, for example, atopic asthma; allergic asthma; atopic bronchial IgE-mediated asthma; bronchial asthma; extrinsic asthma; allergen-induced asthma; allergic asthma exacerbated by respiratory virus infection; infective asthma; infective asthma caused by bacterial infection; infective asthma caused by fungal infection; infective asthma caused by protozoal infection; or infective asthma caused by viral infection.

In one embodiment (e.g., of use in methods of therapy, of use in the manufacture of medicaments, of methods of treatment), the treatment is treatment of: bronchial hyper-reactivity associated with asthma; or bronchial hyper-responsiveness associated with asthma.

In one embodiment (e.g., of use in methods of therapy, of use in the manufacture of medicaments, of methods of treatment), the treatment is treatment of: airway remodelling associated with an allergic lung disease, for example, airway remodelling associated with asthma.

In one embodiment (e.g., of use in methods of therapy, of use in the manufacture of medicaments, of methods of treatment), the treatment is treatment of: asthma co-presented with a chronic obstructive lung disease, for example, asthma co-presented with emphysema; or asthma co-presented with chronic bronchitis.

In one embodiment (e.g., of use in methods of therapy, of use in the manufacture of medicaments, of methods of treatment), the treatment is treatment of: rhinitis, for example, allergic rhinitis; perennial rhinitis; persistent rhinitis; or IgE-mediated rhinitis.

In one embodiment (e.g., of use in methods of therapy, of use in the manufacture of medicaments, of methods of treatment), the treatment is treatment of: allergic conjunctivitis, for example, IgE-mediated conjunctivitis.

In one embodiment (e.g., of use in methods of therapy, of use in the manufacture of medicaments, of methods of treatment), the treatment is treatment of: atopic dermatitis.

In one embodiment (e.g., of use in methods of therapy, of use in the manufacture of medicaments, of methods of treatment), the treatment is treatment of: an allergic condition which is triggered by dust mites.

In one embodiment (e.g., of use in methods of therapy, of use in the manufacture of medicaments, of methods of treatment), the treatment is treatment of: an allergic condition which is triggered by dust mite Group 1 peptidase allergen (e.g., Der p 1, Der f 1, Eur m 1).

In one embodiment (e.g., of use in methods of therapy, of use in the manufacture of medicaments, of methods of treatment), the treatment is treatment of: canine atopy.

Treatment

The term "treatment," as used herein in the context of treating a condition, pertains generally to treatment and therapy, whether of a human or an animal (e.g., in veterinary applications), in which some desired therapeutic effect is achieved, for example, the inhibition of the progress of the condition, and includes a reduction in the rate of progress, a halt in the rate of progress, alleviatiation of symptoms of the condition, amelioration of the condition, and cure of the condition. Treatment as a prophylactic measure (i.e., prophylaxis) is also included. For example, use with patients who have not yet developed the condition, but who are at risk of developing the condition, is encompassed by the term "treatment."

For example, treatment includes the prophylaxis of asthma, reducing the incidence of asthma, reducing the severity of asthma, alleviating the symptoms of asthma, etc.

The term "therapeutically-effective amount," as used herein, pertains to that amount of a compound, or a material, composition or dosage form comprising a compound, which is

effective for producing some desired therapeutic effect, commensurate with a reasonable benefit/risk ratio, when administered in accordance with a desired treatment regimen.

Combination Therapies

The term "treatment" includes combination treatments and therapies, in which two or more treatments or therapies are combined, for example, sequentially or simultaneously. For example, the compounds described herein may also be used in combination therapies, e.g., in conjunction with other agents.

Typical examples of combinations for inhaled use in treatment of respiratory disease are fixed combinations of glucocorticoid receptor agonists and beta 2 adrenoceptor agonists. Such a combination product is "Advair" (also known as "Seretide"), which is a fixed combination of fluticasone propionate and salmeterol. Such combinations may be used in dry powder devices, pressurised metered dose inhalers and nebulisers. Many other respiratory agents may be used in fixed combinations in such devices. They may also be adminstered separately from different devices in different relative doses.

An inhaled combination product will be a fixed combination of a compound described herein with one or more additional agents (in which the ratios are decided on the merits of the individual components and selected from a suitable range by experiment) together with appropriate excipients.

For example, one aspect of the present invention pertains to a compound as described herein, in combination with one or more (e.g., 1, 2, 3, 4) additional therapeutic agents.

Thus, the agents (i.e., the compound described herein, plus one or more other agents) may be administered simultaneously in fixed combination or at different times by individually varying dose schedules from a similar or different inhalation device. The precise dosage regimen of either combination or sequential treatment will be commensurate with the properties of the therapeutic agent(s).

Additional Therapeutic Agents

The ALD compounds described herein may be used in combination with one or more (e.g., 1, 2, 3, 4) additional therapeutic agents, for example, in combination therapy as described herein.

In one embodiment, the one or more additional therapeutic agents are selected from agents used, or likely to be used, in the treatment of a respiratory disease.

In one embodiment, the one or more additional therapeutic agents are selected from: an anti-asthma agent and an anti-allergy agent.

In one embodiment, the one or more additional therapeutic agents are selected from:
a $beta_2$-adrenergic agonist;
an antagonist of the M3 muscarinic receptor;
a dual $beta_2$ adrenoceptor agonist - M3 muscarinic antagonist;
a glucocorticoid receptor agonist;
a leukotriene antagonist;
a 5-lipoxygenase inhibitor;
a cromone;
an immunosuppressant;
an immune response modifier, e.g., an agonist of one or more Toll-Like Receptors (e.g., TLR2, TLR4, TLR7, TLR8, TLR9) or a vaccine;
a xanthine derivative;
a selective phoshodiesterase (PDE) isoenzyme inhibitor, e.g., an inhibitor of PDE4 and/or PDE5;
an inhibitor of certain kinase enzymes, e.g., p38 mitogen-activated protein (MAP) kinase, IkappaB kinase 2 (IKK2), tyrosine-protein kinase (Syk), and phosphoinositide-3 kinase gamma (PI3Kgamma);
a histamine type 1 receptor antagonist;
a alpha adrenoceptor agonist vasoconstrictor sympathomimetic;
an inhibitor of a matrix metalloprotease;
a modulator of chemokine receptor function;
a cytokine;
a modulator of cytokine function;
an agent which act on a cytokine signalling pathway;
an immunoglobulin;
an immunoglobulin preparation;
an antagonist that modulates immunoglobulin function;
an antibody that modulates immunoglobulin function;
a lung surfactant protein, especially SP-A, SP-D;
an inhibitor of Der p 3, an inhibitor of Der p 6, and an inhibitor of Der p 9.

Use as an Acaricide

The ALD compounds described herein may also be used as an acaricide, e.g., to control the population of, or to kill, mites, e.g., dust mites.

Another aspect of the present invention pertains to an ALD compound, as described herein, for use as an acaricide.

Another aspect of the present invention pertains to a composition comprising an ALD compound, as described herein, for use as an acaricide.

Another aspect of the present invention pertains to an acaricide composition comprising an ALD compound, as described herein.

Another aspect of the present invention pertains to the use of an ALD compound, as described herein, as an acaricide.

Another aspect of the present invention pertains a method of killing mites (e.g., dust mites), comprising exposing said mites to an effective amount of an ALD compound, as described herein.

Another aspect of the present invention pertains a method of controlling (e.g., limiting) a mite (e.g., dust mite) population comprising exposing mites to an effective amount of an ALD compound, as described herein.

Other Uses

The ALD compounds described herein may also be used as cell culture additives to inhibit a dust mite Group 1 peptidase allergen (e.g., Der p 1, Der f 1, Eur m 1).

The ALD compounds described herein may also be used as part of an *in vitro* assay, for example, in order to determine whether a candidate host is likely to benefit from treatment with the compound in question.

The ALD compounds described herein may also be used as a standard, for example, in an assay, in order to identify other compounds, other dust mite Group 1 peptidase allergen inhibitors, other anti-asthma agents, etc.

Kits

One aspect of the invention pertains to a kit comprising (a) an ALD compound as described herein, or a composition comprising an ALD compound as described herein, e.g., preferably provided in a suitable container and/or with suitable packaging; and (b) instructions for use, e.g., written instructions on how to administer the compound or composition.

In one embodiment, the kit further comprises one or more (e.g., 1, 2, 3, 4) additional therapeutic agents, as described herein.

The written instructions may also include a list of indications for which the active ingredient is a suitable treatment.

Routes of Administration

The ALD compound or pharmaceutical composition comprising the ALD compound may be administered to a subject by any convenient route of administration, whether systemically/peripherally or topically (i.e., at the site of desired action).

Routes of administration include, but are not limited to, oral (e.g., by ingestion); buccal; sublingual; transdermal (including, e.g., by a patch, plaster, etc.); transmucosal (including, e.g., by a patch, plaster, etc.); intranasal (e.g., by nasal spray, drops or from an atomiser or dry powder delivery device); ocular (e.g., by eyedrops); pulmonary (e.g., by inhalation or insufflation therapy using, e.g., an aerosol, e.g., through the mouth or nose); rectal (e.g., by suppository or enema); vaginal (e.g., by pessary); parenteral, for example, by injection, including subcutaneous, intradermal, intramuscular, intravenous, intraarterial, intracardiac, intrathecal, intraspinal, intracapsular, subcapsular, intraorbital, intraperitoneal, intratracheal, subcuticular, intraarticular, subarachnoid, and intrasternal; by implant of a depot or reservoir, for example, subcutaneously or intramuscularly.

The Subject/Patient

The subject/patient may be a mammal, a rodent (e.g., a guinea pig, a hamster, a rat, a mouse), murine (e.g., a mouse), a lagomorph (e.g., a rabbit), avian (e.g., a bird), canine (e.g., a dog), feline (e.g., a cat), equine (e.g., a horse), porcine (e.g., a pig), ovine (e.g., a sheep), bovine (e.g., a cow), a primate, simian (e.g., a monkey or ape), a monkey (e.g., marmoset, baboon), an ape (e.g., gorilla, chimpanzee, orangutang, gibbon), or a human.

Furthermore, the subject/patient may be any of its forms of development, for example, a foetus.

In one preferred embodiment, the subject/patient is a human.
In one preferred embodiment, the subject/patient is a dog.

Formulations

While it is possible for the ALD compound to be administered alone, it is preferable to present it as a pharmaceutical formulation (e.g., composition, preparation, medicament) comprising at least one ALD compound, as described herein, together with one or more

other pharmaceutically acceptable ingredients well known to those skilled in the art, including, but not limited to, pharmaceutically acceptable carriers, diluents, excipients, adjuvants, fillers, buffers, preservatives, anti-oxidants, lubricants, stabilisers, solubilisers, surfactants (e.g., wetting agents), masking agents, colouring agents, flavouring agents, and sweetening agents. The formulation may further comprise other active agents, for example, other therapeutic or prophylactic agents.

Thus, the present invention further provides pharmaceutical compositions, as defined above, and methods of making a pharmaceutical composition comprising admixing at least one ALD compound, as described herein, together with one or more other pharmaceutically acceptable ingredients well known to those skilled in the art, e.g., carriers, diluents, excipients, etc. If formulated as discrete units (e.g., tablets, etc.), each unit contains a predetermined amount (dosage) of the compound.

The term "pharmaceutically acceptable," as used herein, pertains to compounds, ingredients, materials, compositions, dosage forms, etc., which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of the subject in question (e.g., human) without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio. Each carrier, diluent, excipient, etc. must also be "acceptable" in the sense of being compatible with the other ingredients of the formulation.

Suitable carriers, diluents, excipients, etc. can be found in standard pharmaceutical texts, for example, Remington's Pharmaceutical Sciences, 18th edition, Mack Publishing Company, Easton, Pa., 1990; and Handbook of Pharmaceutical Excipients, 5th edition, 2005.

The formulations may be prepared by any methods well known in the art of pharmacy. Such methods include the step of bringing into association the compound with a carrier which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association the compound with carriers (e.g., liquid carriers, finely divided solid carrier, etc.), and then shaping the product, if necessary.

The formulation may be prepared to provide for rapid or slow release; immediate, delayed, timed, or sustained release; or a combination thereof.

Formulations may suitably be in the form of liquids, solutions (e.g., aqueous, non-aqueous), suspensions (e.g., aqueous, non-aqueous), emulsions (e.g., oil-in-water, water-in-oil), elixirs, syrups, electuaries, mouthwashes, drops, tablets (including, e.g., coated tablets), granules, powders, losenges, pastilles, capsules (including,

e.g., hard and soft gelatin capsules), cachets, pills, ampoules, boluses, suppositories, pessaries, tinctures, gels, pastes, ointments, creams, lotions, oils, foams, sprays, mists, or aerosols.

Formulations may suitably be provided as a patch, adhesive plaster, bandage, dressing, or the like which is impregnated with one or more compounds and optionally one or more other pharmaceutically acceptable ingredients, including, for example, penetration, permeation, and absorption enhancers. Formulations may also suitably be provided in the form of a depot or reservoir.

The compound may be dissolved in, suspended in, or admixed with one or more other pharmaceutically acceptable ingredients. The compound may be presented in a liposome or other microparticulate which is designed to target the compound, for example, to blood components or one or more organs.

Formulations suitable for administration to the lung (e.g., by inhalation or insufflation therapy using, e.g., an aerosol, e.g., through the mouth) include those presented as a solution or suspension for delivery from a nebuliser; a dry powder for use in an appropriate inhaler device; and an aerosol spray for delivery from a pressurised pack with the use of a suitable propellant, such as dichlorodifluoromethane (CFC-12), trichlorofluoromethane, dichoro-tetrafluoroethane, HFA-134a, HFA-227, HCFC-22, HFA-152, isobutene, carbon dioxide, or other suitable gases. Devices for these methods of delivery are available. Formulations intended for nasal delivery can be adminsitered as aqueous solutions or suspensions, as solutions or suspensions in suitable propellants or as dry powders. Nasal droppers, nebulisers, atomisers, pressurised metered dose inhalers and dry powder inhalers for nasal delivery are available.

For administration by inhalation, the active compound is preferably in the form of microparticles. Suitable microparticles may be prepared by a variety of techniques, including spray-drying, freeze-drying and micronisation.

The microparticles may be formulated with excipients that aid delivery and release. For example, in a dry powder formulation, microparticles may be formulated with large carrier particles that aid the flow, for example, from a dry powder inhaler (DPI) into the lung. Suitable carrier particles are well-known in the art, and include lactose particles; they may have a mass median aerodynamic diameter of > 90 μm.

For administration using an aerosol, the active compound may be administered in a manner compatible with the inhaler system used. Suitable aerosol formulation may include, in addition to the active compound, excipients such as, for example, propellant (e.g., Frigen in the case of metered aerosols), surface-active substances, emulsifiers,

stabilizers, preservatives, flavourings, fillers (e.g., lactose in the case of powder inhalers) and, if appropriate, one or more additional active compounds.

For the purposes of inhalation of microparticulate formulations, a large number of systems are known with which aerosols of optimum particle size can be generated and administered, using an inhalation technique appropriate for the patient. In addition to the use of adaptors (spacers, expanders) and pear-shaped containers (e.g., Nebulator™, Volumatic™), and automatic devices emitting a puffer spray (e.g., Autohaler™), for metered aerosols, in particular in the case of powdered inhalers, a number of technical solutions are available (e.g., Diskhaler™, Rotadisk™, Turbohaler™). Additionally, the active compound may be delivered in a multi-chamber device, thus allowing for delivery of combination agents.

For administration to the nose or lung, the active compound may also be used when formulated as an aqueous dispersion of nanoparticulates, or as a dry powder nanoparticulate aerosol formulation, or as a propellant-based aerosol formulation. Suitable nanoparticles may be prepared by spray-drying or freeze-drying aqueous nanoparticulate dispersions of drugs. Methods for the preparation of nanoparticulate dispersions of drugs, the preparation of aqueous, dry powder and propellant-based formulations of nanoparticulate drugs and their use in aerosol delivery systems are known (see, e.g., Bosch et al., 2009).

Formulations suitable for oral administration (e.g., by ingestion) include liquids, solutions (e.g., aqueous, non-aqueous), suspensions (e.g., aqueous, non-aqueous), emulsions (e.g., oil-in-water, water-in-oil), elixirs, syrups, electuaries, tablets, granules, powders, capsules, cachets, pills, ampoules, boluses.

Formulations suitable for buccal administration include mouthwashes, losenges, pastilles, as well as patches, adhesive plasters, depots, and reservoirs. Losenges typically comprise the compound in a flavored basis, usually sucrose and acacia or tragacanth. Pastilles typically comprise the compound in an inert matrix, such as gelatin and glycerin, or sucrose and acacia. Mouthwashes typically comprise the compound in a suitable liquid carrier.

Formulations suitable for sublingual administration include tablets, losenges, pastilles, capsules, and pills.

Formulations suitable for oral transmucosal administration include liquids, solutions (e.g., aqueous, non-aqueous), suspensions (e.g., aqueous, non-aqueous), emulsions (e.g., oil-in-water, water-in-oil), mouthwashes, losenges, pastilles, as well as patches, adhesive plasters, depots, and reservoirs.

Formulations suitable for non-oral transmucosal administration include liquids, solutions (e.g., aqueous, non-aqueous), suspensions (e.g., aqueous, non-aqueous), emulsions (e.g., oil-in-water, water-in-oil), suppositories, pessaries, gels, pastes, ointments, creams, lotions, oils, as well as patches, adhesive plasters, depots, and reservoirs.

Formulations suitable for transdermal administration include gels, pastes, ointments, creams, lotions, and oils, as well as patches, adhesive plasters, bandages, dressings, depots, and reservoirs.

Tablets may be made by conventional means, e.g., compression or moulding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the compound in a free-flowing form such as a powder or granules, optionally mixed with one or more binders (e.g., povidone, gelatin, acacia, sorbitol, tragacanth, hydroxypropylmethyl cellulose); fillers or diluents (e.g., lactose, microcrystalline cellulose, calcium hydrogen phosphate); lubricants (e.g., magnesium stearate, talc, silica); disintegrants (e.g., sodium starch glycolate, cross-linked povidone, cross-linked sodium carboxymethyl cellulose); surface-active or dispersing or wetting agents (e.g., sodium lauryl sulfate); preservatives (e.g., methyl p-hydroxybenzoate, propyl p-hydroxybenzoate, sorbic acid); flavours, flavour enhancing agents, and sweeteners. Moulded tablets may be made by moulding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the compound therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile. Tablets may optionally be provided with a coating, for example, to affect release, for example an enteric coating, to provide release in parts of the gut other than the stomach.

Ointments are typically prepared from the compound and a paraffinic or a water-miscible ointment base.

Creams are typically prepared from the compound and an oil-in-water cream base. If desired, the aqueous phase of the cream base may include, for example, at least about 30% w/w of a polyhydric alcohol, i.e., an alcohol having two or more hydroxyl groups such as propylene glycol, butane-1,3-diol, mannitol, sorbitol, glycerol and polyethylene glycol and mixtures thereof. The topical formulations may desirably include a compound which enhances absorption or penetration of the compound through the skin or other affected areas. Examples of such dermal penetration enhancers include dimethylsulfoxide and related analogues.

Emulsions are typically prepared from the compound and an oily phase, which may optionally comprise merely an emulsifier (otherwise known as an emulgent), or it may comprises a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil. Preferably, a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stabiliser. It is also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabiliser(s) make up the so-called emulsifying wax, and the wax together with the oil and/or fat make up the so-called emulsifying ointment base which forms the oily dispersed phase of the cream formulations.

Suitable emulgents and emulsion stabilisers include Tween 60, Span 80, cetostearyl alcohol, myristyl alcohol, glyceryl monostearate and sodium lauryl sulfate. The choice of suitable oils or fats for the formulation is based on achieving the desired cosmetic properties, since the solubility of the compound in most oils likely to be used in pharmaceutical emulsion formulations may be very low. Thus the cream should preferably be a non-greasy, non-staining and washable product with suitable consistency to avoid leakage from tubes or other containers. Straight or branched chain, mono- or dibasic alkyl esters such as di-isoadipate, isocetyl stearate, propylene glycol diester of coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-ethylhexyl palmitate or a blend of branched chain esters known as Crodamol CAP may be used, the last three being preferred esters. These may be used alone or in combination depending on the properties required. Alternatively, high melting point lipids such as white soft paraffin and/or liquid paraffin or other mineral oils can be used.

Formulations suitable for intranasal administration, where the carrier is a liquid and the drug can be administered as an aqueous solution or suspension in a suitable vehicle or propellant, include, for example, nasal spray, nasal drops, or by aerosol administration by nebuliser, by pressurised metered dose inhaler or atomiser, include aqueous or oily preparations of the compound.

Formulations suitable for intranasal administration, where the carrier is a solid, include, for example, those presented as a coarse powder having a particle size, for example, in the range of about 20 to about 500 micrometres which is administered in the manner in which snuff is taken, i.e., by rapid inhalation through the nasal passage from a container of the powder held close up to the nose.

Formulations suitable for ocular administration include eye drops wherein the compound is dissolved or suspended in a suitable carrier, especially an aqueous solvent for the compound.

Formulations suitable for rectal administration may be presented as a suppository with a suitable base comprising, for example, natural or hardened oils, waxes, fats, semi-liquid

or liquid polyols, for example, cocoa butter or a salicylate; or as a solution or suspension for treatment by enema.

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the compound, such carriers as are known in the art to be appropriate.

Formulations suitable for parenteral administration (e.g., by injection), include aqueous or non-aqueous, isotonic, pyrogen-free, sterile liquids (e.g., solutions, suspensions), in which the compound is dissolved, suspended, or otherwise provided (e.g., in a liposome or other microparticulate). Such liquids may additional contain other pharmaceutically acceptable ingredients, such as anti-oxidants, buffers, preservatives, stabilisers, bacteriostats, suspending agents, thickening agents, and solutes which render the formulation isotonic with the blood (or other relevant bodily fluid) of the intended recipient. Examples of excipients include, for example, water, alcohols, polyols, glycerol, vegetable oils, and the like. Examples of suitable isotonic carriers for use in such formulations include Sodium Chloride Injection, Ringer's Solution, or Lactated Ringer's Injection. Typically, the concentration of the compound in the liquid is from about 1 ng/mL to about 10 µg/mL. The formulations may be presented in unit-dose or multi-dose sealed containers, for example, ampoules and vials, and may be stored in a freeze-dried (lyophilised) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules, and tablets.

Dosage

It will be appreciated by one of skill in the art that appropriate dosages of the ALD compounds, and compositions comprising the ALD compounds, can vary from patient to patient. Determining the optimal dosage will generally involve the balancing of the level of therapeutic benefit against any risk or deleterious side effects. The selected dosage level will depend on a variety of factors including, but not limited to, the activity of the particular ALD compound, the route of administration, the time of administration, the rate of excretion of the ALD compound, the duration of the treatment, other drugs, compounds, and/or materials used in combination, the severity of the condition, and the species, sex, age, weight, condition, general health, and prior medical history of the patient. The amount of ALD compound and route of administration will ultimately be at the discretion of the physician, veterinarian, or clinician, although generally the dosage will be selected to achieve local concentrations at the site of action which achieve the desired effect without causing substantial harmful or deleterious side-effects.

Administration can be effected in one dose, continuously or intermittently (e.g., in divided doses at appropriate intervals) throughout the course of treatment. Methods of determining the most effective means and dosage of administration are well known to those of skill in the art and will vary with the formulation used for therapy, the purpose of the therapy, the target cell(s) being treated, and the subject being treated. Single or multiple administrations can be carried out with the dose level and pattern being selected by the treating physician, veterinarian, or clinician.

In general, a suitable dose of the ALD compound is in the range of about 0.5 μg to about 20 mg per kilogram body weight of the subject per day. In practice, for an inhaled agent, the upper limit will be set by the chosen device for delivery. Where the compound is a salt, an ester, an amide, a prodrug, or the like, the amount administered is calculated on the basis of the parent compound and so the actual weight to be used is increased proportionately.

EXAMPLES

The following examples are provided solely to illustrate the present invention and are not intended to limit the scope of the invention, as described herein.

Chemical Synthesis

Abbreviations

Aq., aqueous;
Boc, *tert*-butoxycarbonyl;
Conc., concentrated;
DCM, dichloromethane;
DIC, diisopropylcarbodiimide;
DIPEA, N,N-diisopropylethylamine;
DMAP, 4-dimethylaminopyridine;
DMF, dimethylformamide;
DMSO, dimethylsulfoxide;
EDC, 1-Ethyl-3-[3-dimethylaminopropyl]carbodiimide;
ELSD, evaporative light scattering detection;
equiv., equivalents;
Et_2O, diethyl ether;
EtOAc, ethyl acetate;
Fmoc, fluorenylmethyloxycarbonyl;
h, hours;
HATU, 2-(7-Aza-1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate;
HOAT, 1-Hydroxy-7-Azabenzotriazole;
HOBt, N-Hydroxybenzotriazole;
HPLC, high performance liquid chromatography;
LC-MS, liquid chromatography mass spectrometry;
LDA, lithium diisopropylamide;
min, minutes;
MeOH, methanol;
MTBE, methyl-*tert*-butylether;
NMM, N-methylmorpholine;
NMR, nuclear magnetic resonance;
pet. ether, petroleum ether;
PS-Tosyl chloride, polystyrene supported tosyl chloride;
Rt, retention time;
Sat., saturated;
TFA, trifluoroacetic acid;

THF, tetrahydrofuran;
TIPS, triisopropylsilane;
TMS, tri-methylsilane;
TBTU, O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate;
UPLC, ultra high performance liquid chromatography;
% v/v, percentage volume to volume;
% w/v percentage weight to volume.

Analytical Methods

Reverse-Phase Preparative LC-MS: Mass-directed purification preparative LC-MS using a preparative C-18 column (Phenomenex Luna C18 (2), 100 x 21.2 mm, 5 µm).

Analysis of products and intermediates has been carried using reverse-phase analytical HPLC-MS or UPLC-MS, using the parameters set out below. Purity was typically assessed by diode array at 210-400 nm.

HPLC Analytical Methods:

AnalpH2_45C: Phenomenex Luna C18(2) 5 µm, 100 x 4.6mm; A = water + 0.1% TFA; B= MeCN + 0.1% TFA; 45°C; %B: 0min 5%, 4.4min 95%, 5.3min 95%, 5.31min 5%, 6.5min 5%; 2.5ml/min.

AnalpH2: Phenomenex Luna C18 (2) 5 µm, 100 x 4.6 mm; A = water + 0.1% formic acid; B = MeCN + 0.1% formic acid; 35°C; % B: 0 min 5%, 4.4 min 95%, 5.3 min 95%, 5.31 min 5%, 6.5 min 5%; 2.5 mL/min.

AnalpH2_MeOH: Phenomenex Luna C18 (2) 3 µm, 50 x 3.0 mm; A = water + 0.1% formic acid; B = MeOH; 45°C; % B: 0 min 5%, 4.4 min 95%, 5.2 min 95%, 5.21 min 5%, 6.5 min 5%; 1.1 mL/min.

AnalpH2_MeOH_4min: Phenomenex Luna C18 (2) 3 µm, 50 x 4.6 mm; A = water + 0.1% formic acid; B = MeOH; 45°C; % B: 0 min 5%, 1 min 37.5%, 3 min 95%, 3.5 min 95%, 3.51 min 5%, 4.5 min 5%; 2.25 mL/min.

Aldehyde_QC_1: Phenomenex Luna C18 (2) 5 µm, 150 x 4.6 mm; A = water + 0.1% TFA; B = MeCN + 0.1% TFA; 55°C; % B: 0 min 5%, 0.5 min 5%, 7.5 min 95%, 10min 95%, 10.1 min 5%, 13min 5%; 1.5 mL/min.

Aldehyde_QC_2: Phenomenex Luna C18 (2) 5 µm, 150 x 4.6 mm; A = water + 0.1% TFA; B = MeCN + 0.1% TFA; 50°C; % B: 0 min 5%, 0.1 min 5%, 8 min 95%, 10.5 min 95%, 10.55 min 5%, 13.5 min 5%; 1.5 mL/min.

Aldehyde_QC_3: Phenomenex Luna C18 (2) 5 µm, 150 x 4.6 mm; A = water + 0.1% TFA; B = MeCN + 0.1% TFA; 55°C; % B: 0 min 5%, 1 min 5%, 7 min 95%, 10min 95%, 10.15 min 5%, 13 min 5%; 1.5 mL/min.

Aldehyde_QC (Gemini)_1: Phenomenex Gemini C18 (2) 5 µm, 150 x 4.6 mm; A = water + 0.1% TFA; B = MeCN + 0.1% TFA; 55°C; % B: 0 min 5%, 0.5 min 5%, 7.5 min 95%, 10 min 95%, 10.1 min 5%, 13 min 5%; 1.5 mL/min.

Aldehyde_QC (Gemini)_2: Phenomenex Gemini C18 (2) 5 µm, 150 x 4.6 mm; A = water + 0.1% TFA; B = MeCN + 0.1% TFA; 55°C; % B: 0 min 5%, 0.5 min 5%, 7.5 min 95%, 10 min 95%, 10.1 min 5%, 13 min 5%; 2 mL/min.

UPLC Analytical Methods:

Method_2_Bic: Acquity UPLC BEH C-8, 1.7 µm, 100 x 2.1 mm; 40°C; A = 0.005 M ammonium bicarbonate (aq.); B = acetonitrile; % B: 0 min 30%, 4 min 80%, 6 min 80%, 6.1 min 30%; 0.3 mL/min.

Method_2_TFA_UPLC_2: Acquity UPLC BEH C18 1.7 µm, 100 x 2.1 mm; 25°C; A = water + 0.025% TFA; B = acetonitrile + 0.025% TFA; % B: 0 min 30%, 4 min 80%, 6 min 80%, 6.1 min 30%; 0.4 mL/min.

Method_4_TFA_UPLC_2: Acquity UPLC BEH C18 1.7 µm, 100 x 2.1 mm; 25°C A = water + 0.025% TFA; B = acetonitrile + 0.025% TFA; % B: 0 min 10%, 4 min 80%, 6 min 80%, 6.1 min 10%; 0.3 mL/min.

UPLC Analytical Methods:

Method_2_Bic: Acquity UPLC BEH C-8, 1.7 µm, 100 x 2.1 mm; 40°C; A = 0.005 M ammonium bicarbonate (aq.); B = acetonitrile; % B: 0 min 30%, 4 min 80%, 6 min 80%, 6.1 min 30%; 0.3 mL/min.

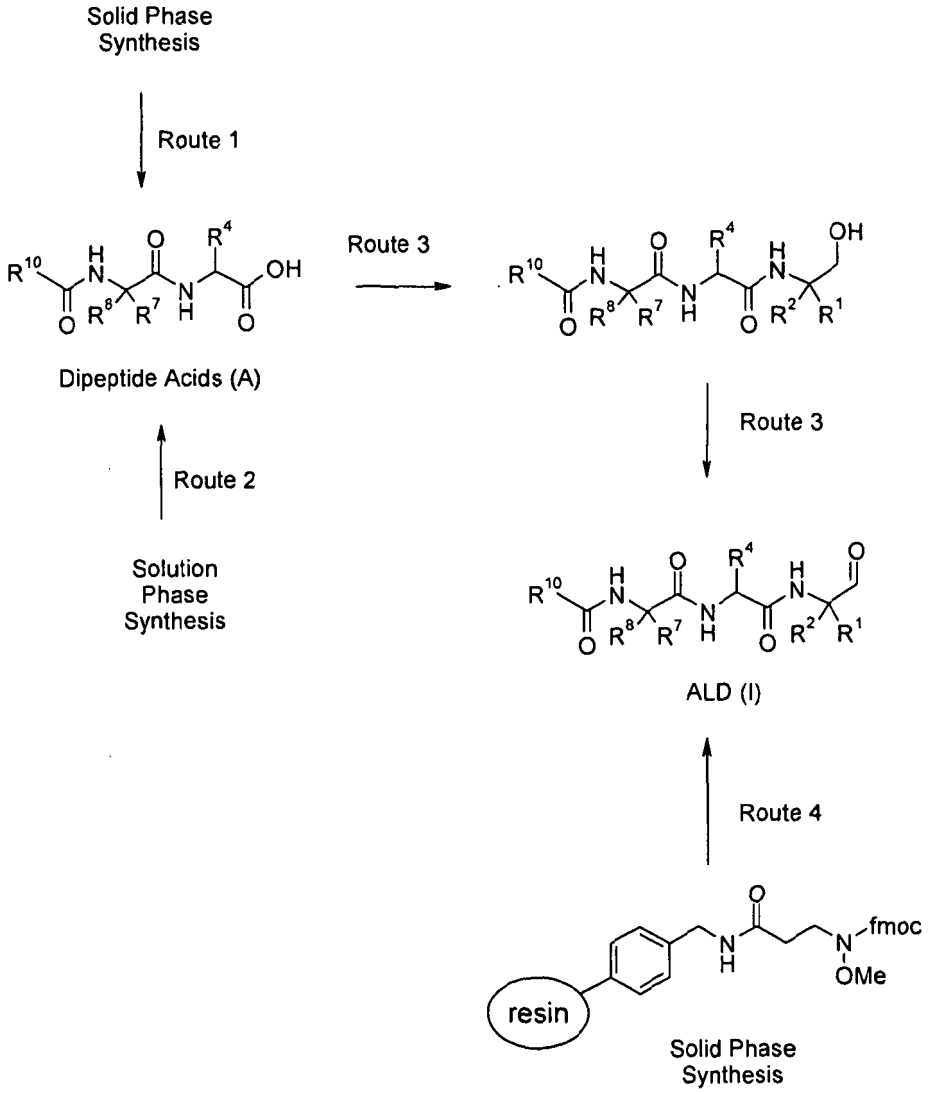
Method_2_TFA_UPLC_2: Acquity UPLC BEH C18 1.7 µm, 100 x 2.1 mm; 25°C; A = water + 0.025% TFA; B = acetonitrile + 0.025% TFA; % B: 0 min 30%, 4 min 80%, 6 min 80%, 6.1 min 30%; 0.4 mL/min.

Method_4_TFA_UPLC_2: Acquity UPLC BEH C18 1.7 µm, 100 x 2.1 mm; 25°C A = water + 0.025% TFA; B = acetonitrile + 0.025% TFA; % B: 0 min 10%, 4 min 80%, 6 min 80%, 6.1 min 10%; 0.3 mL/min.

A General Approach for the Synthesis of ALD Compounds (I)

Some general methods used for the synthesis of ALD compounds of the present invention are illustrated in the following scheme.

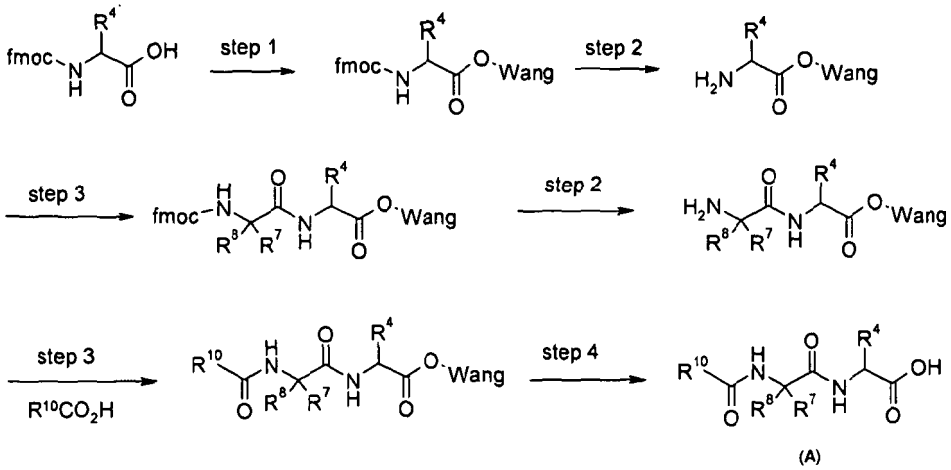
Scheme 5



Synthesis of Dipeptide Intermediates (A)

Route 1: Dipeptide Intermediates (A) *via* Solid Phase Peptide Synthesis

Scheme 6



Peptides were synthesised on Wang resin using standard amide coupling procedures (see., e.g., Chan, W. C. and White, P. D., *Fmoc Solid Phase Peptide Synthesis A Practical Approach*, Oxford University Press, 2000). Fmoc-amino acids were purchased from commercial suppliers (e.g., Advanced Chemtech, Bachem, NovaBiochem or Polypeptide). Peptide grade DMF, which is free of dimethylamine, was used for peptide couplings to prevent any unwanted removal of Fmoc groups. Kaiser tests were used to indicate successful coupling of Fmoc-amino acids.

Typical Procedure

Step 1 - Coupling of First Amino Acid to Wang Resin:

Wang resin was swollen with an appropriate volume of DMF then drained under vacuum. The Fmoc-amino acid (6 equiv.) was added followed by an appropriate volume of DMF (5 mL/g of resin), sufficient to cover the resin and peptide, and this mixture was shaken for 30 min. After that time, DIC (3 equiv.) and DMAP (catalytic) were added and the mixture was shaken for 4-5 h. The resin was drained under vacuum, washed with DCM and MeOH then re-swollen with DCM. Successful coupling could be indicated by carrying out step 2 on a small portion of the resin and performing a Kaiser test to indicate the presence of a free NH_2 group. In general, the exact amount of amino acid attached to the resin was not quantified and subsequent reactions were performed on the basis of the maximum loading as indicated from the supplier. For amino acids that were purchased pre-attached to Wang resin, approximate loadings are supplied by the supplier and these were used for calculating amounts of reagent for subsequent steps.

Step 2 - Fmoc-Deprotection:

The resin was shaken with an appropriate volume of 20% v/v piperidine in DMF (5 mL/g resin) for 1 h then washed with DMF, DCM, MeOH and re-swollen with DCM. A positive Kaiser Test (blue colour) indicates the presence of a free NH_2 group.

Step 3 - Amide Coupling:

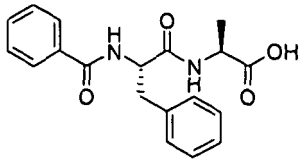
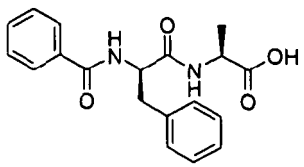
The resin was shaken in an appropriate volume of DMF (~5 mL/g resin) with the appropriate Fmoc-amino acid (2 equiv.) or capping group $R_{10}CO_2H$ (2 equiv.), TBTU (2 equiv.) and DIPEA (4 equiv. or 6 equiv. if, e.g., HCl salt is used) for 4-5 h. After that time, the resin was drained under vacuum, washed with DMF, DCM, MeOH and re-swollen with DCM. A negative Kaiser test (no colour change) indicates that all of the free amino sites have coupled. If the solution remained blue, step 3 was repeated.

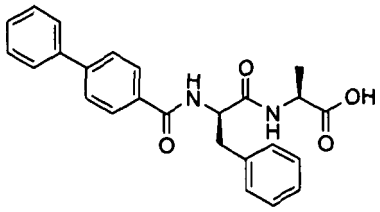
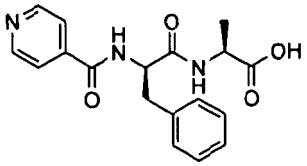
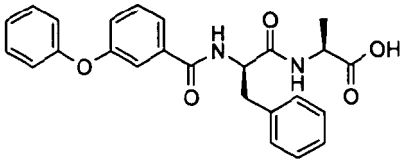
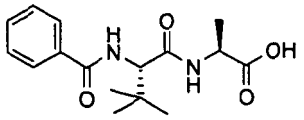
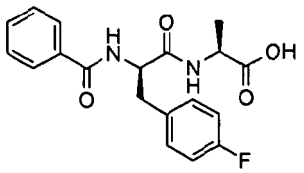
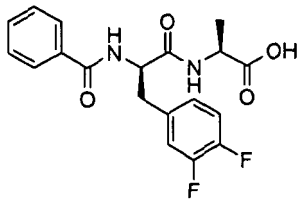
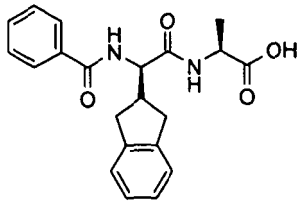
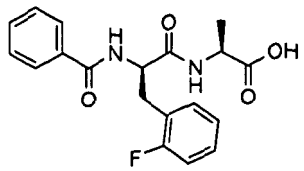
Steps 2 and 3 were repeated for the coupling of additional amino acids and capping groups as necessary.

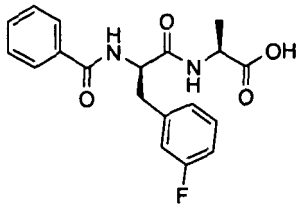
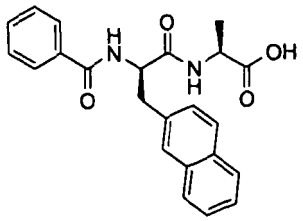
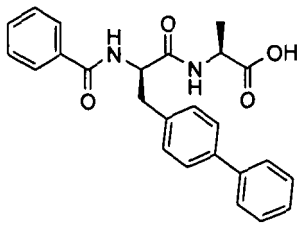
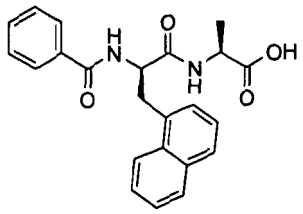
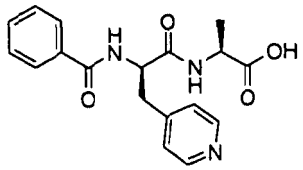
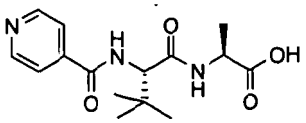
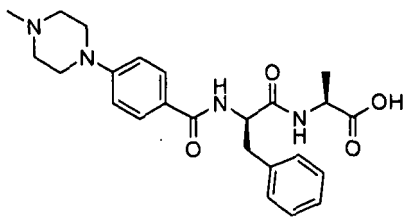
Step 4 - Resin Cleavage:

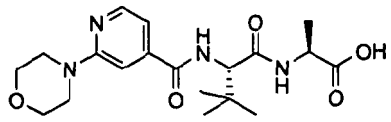
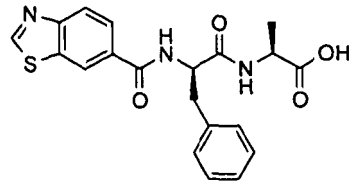
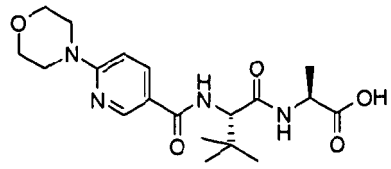
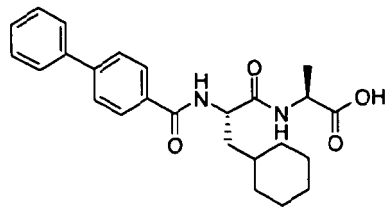
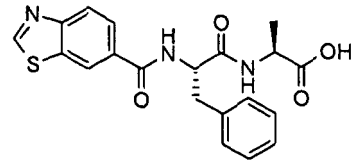
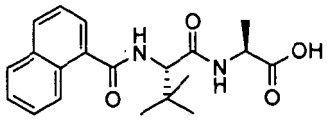
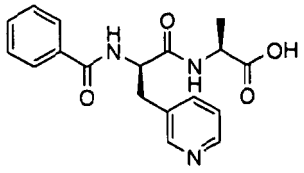
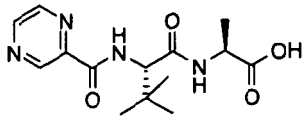
The resin was shaken with the cleavage solution consisting of 95% TFA, 2.5% TIPS and 2.5% water (10 mL/g of resin) for 90 min, and then drained into an appropriate vessel. The resin was washed with DCM under vacuum filtration. The solvent was subsequently evaporated under vacuum, then azeotroped with toluene to remove any residual water or triturated with *iso*-hexane and diethyl ether or MTBE to leave the crude product residue. The resulting peptide (**A**) was either used crude or further purified by trituration with ether, flash column chromatography or reverse-phase preparative HPLC.

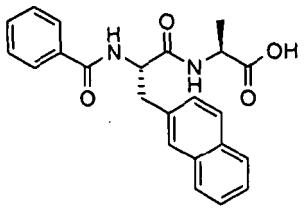
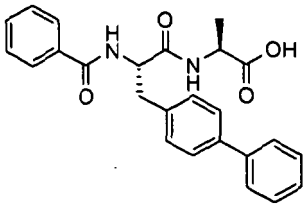
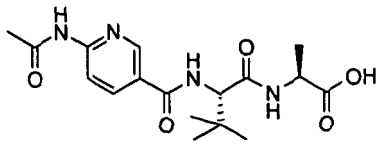
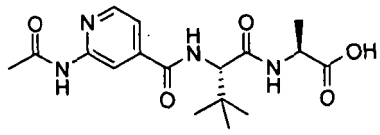
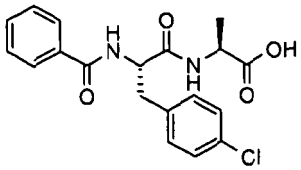
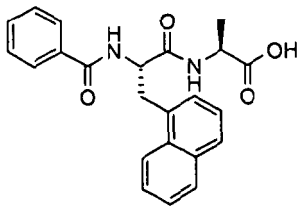
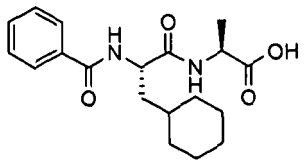
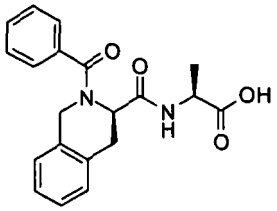
Dipeptide Intermediates (**A**) Prepared by Route 1

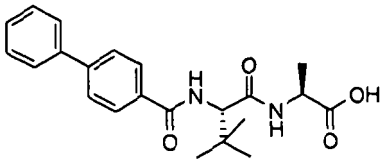
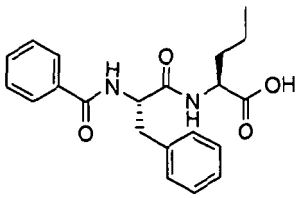
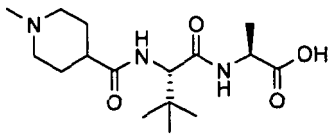
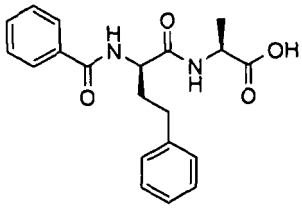
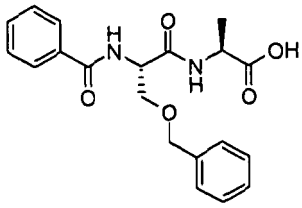
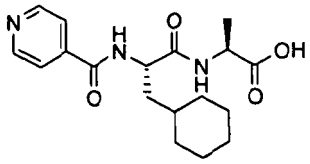
Compound	Code	Analytical Data	Yield
	**A1**	AnalpH2; Rt = 2.76mins; m/z 341 (MH^+); white solid	2.6 g, 60%
	**A2**	AnalpH2_MeOH; Rt = 3.78mins; m/z 341 (MH^+); white solid	1.09 g, 17%

Compound	Code	Analytical Data	Yield
	**A3**	AnalpH2_MeOH; Rt = 4.54mins; m/z 417 (MH^+); pale pink solid	318 mg, 40%
	**A4**	AnalpH2_MeOH; Rt = 3.04mins; m/z 342 (MH^+); pale orange solid	368 mg, 57%
	**A5**	AnalpH2_MeOH; Rt = 4.54mins; m/z 433 (MH^+); white solid	378 mg, 46%
	**A6**	AnalpH2_MeOH; Rt = 3.59mins; m/z 307 (MH^+); white solid	105 mg, 80%
	**A7**	AnalpH2_MeOH; Rt = 3.85mins; m/z 359 (MH^+); white solid	171 mg, 49%
	**A8**	AnalpH2_MeOH; Rt = 3.98mins; m/z 377 (MH^+); white solid	269 mg, 73%
	**A9**	AnalpH2_MeOH; Rt = 4.12mins; m/z 367 (MH^+); white solid	213 mg, 60%
	**A10**	AnalpH2_MeOH; Rt = 3.78mins; m/z 359 (MH^+); white solid	183 mg, 52%

Compound	Code	Analytical Data	Yield
	**A11**	AnalpH2_MeOH; Rt = 3.85mins; m/z 359 (MH^+); white solid	190 mg, 54%
	**A12**	AnalpH2_MeOH; Rt = 4.23mins; m/z 391 (MH^+); white solid	160 mg, 42%
	**A13**	AnalpH2_MeOH; Rt = 4.49mins; m/z 417 (MH^+); white solid	307 mg, 75%
	**A14**	AnalpH2_MeOH; Rt = 4.26mins; m/z 391 (MH^+); white solid	317 mg, 83%
	**A15**	AnalpH2_MeOH_4 min; Rt = 1.12mins; m/z 342 (MH^+); white solid	105 mg, 31%
	**A16**	AnalpH2_MeOH_4 min; Rt = 1.77mins; m/z 308 (MH^+); white foam	427 mg, 72%
	**A17**	AnalpH2_MeOH_4 min; Rt = 1.51mins; m/z 440 (MH^+); white powder	154 mg, 13%

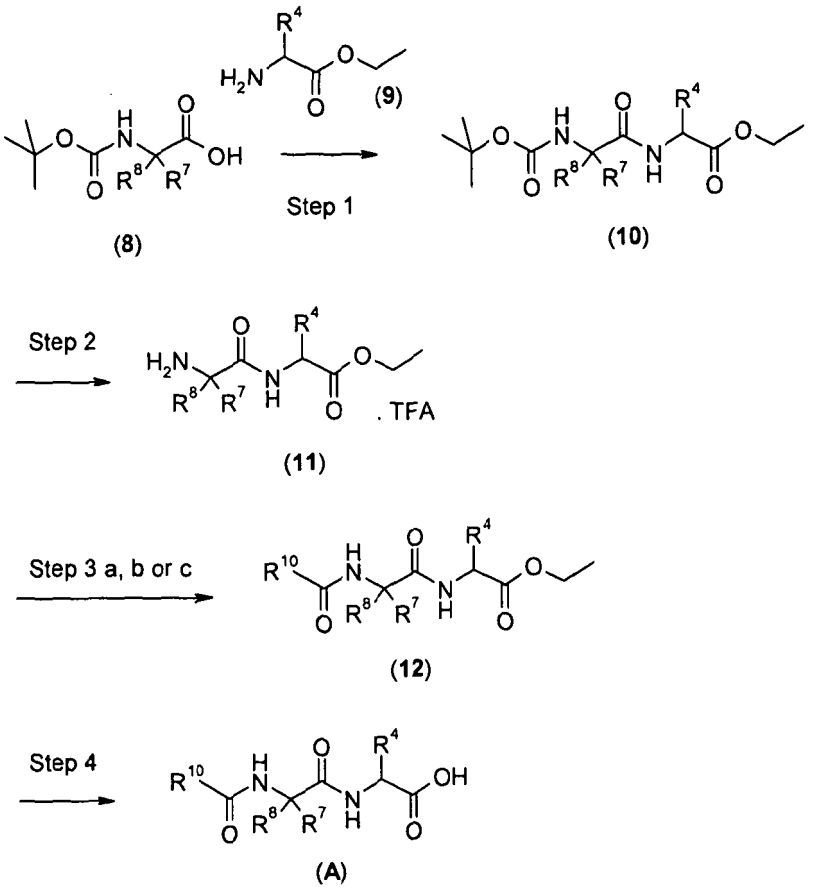
Compound	Code	Analytical Data	Yield
	**A18**	AnalpH2_MeOH_4 min; Rt = 2.16mins; m/z 393 (MH^+); white solid	408 mg, 73%
	**A19**	AnalpH2_MeOH_4 min; Rt = 2.52mins; m/z 398 (MH^+)	133mg, 13%
	**A20**	AnalpH2_MeOH_4 min; Rt = 2.24mins; m/z 393 (MH^+); white solid	328 mg, 60%
	**A21**	AnalpH2_MeOH_4 min; Rt = 4.84 mins; m/z 423 (MH^+); white solid	22 mg, 4%
	**A22**	AnalpH2_MeOH_4 min; Rt = 2.53mins; m/z 398 (MH^+); white solid	88 mg, 15%
	**A23**	AnalpH2_MeOH_4 min; Rt = 2.74mins; m/z 357 (MH^+); white solid	187 mg, 37%
	**A24**	AnalpH2_MeOH; Rt = 1.19mins; m/z 342 (MH^+); white solid	138 mg, 32%
	**A25**	AnalpH2_MeOH_4 min; Rt = 2.13mins; m/z 309 (MH^+); white solid	233 mg, 53%

Compound	Code	Analytical Data	Yield
	**A26**	AnalpH2; Rt = 3.14mins; m/z 391 (MH^+); white solid	181 mg, 41%
	**A27**	AnalpH2; Rt = 3.39mins; m/z 417 (MH^+); white solid	168 mg, 37%
	**A28**	AnalpH2_MeOH_4 min; Rt = 2.08mins; m/z 365 (MH^+); white solid	405 mg, 78%
	**A29**	AnalpH2_MeOH_4 min; Rt = 2.02mins; m/z 365 (MH^+); white solid	323 mg, 63%
	**A30**	AnalpH2; Rt = 3.04mins; m/z 375/377 (MH^+); white solid	193 mg, 43%
	**A31**	AnalpH2; Rt = 3.14mins; m/z 391 (MH^+); white solid	142 mg, 32%
	**A32**	AnalpH2_MeOH; Rt = 4.25mins; m/z 347 (MH^+); white solid	22 mg, 15%
	**A33**	AnalpH2_MeOH; Rt = 3.66mins; m/z 353 (MH^+); white solid	189 mg, 54%

Compound	Code	Analytical Data	Yield
	**A34**	AnalpH2_MeOH; Rt = 4.47 mins; m/z 383 (MH^+); white solid	146 mg, 27%
	**A35**	AnalpH2_MeOH_4 min; Rt = 2.76mins; m/z 369 (MH^+); white solid	165 mg, 35%
	**A36**	AnalpH2_MeOH_4 min; Rt = 0.71/0.84mins; m/z 328 (MH^+); Transleucent solid	383 mg, 17%
	**A37**	AnalpH2_MeOH; Rt = 4.01mins; m/z 355 (MH^+); white solid	163 mg, 43%
	**A38**	AnalpH2_MeOH; Rt = 3.83mins; m/z 371 (MH^+); white solid	57 mg, 24%
	**A45**	AnalpH2_MeOH; Rt = 3.68 mins; m/z 348 (MH^+); white solid	61 mg, 12%

Route 2: Dipeptide Intermediates (**A**) *via* Solution Phase Peptide Synthesis

Scheme 7



Typical Procedure

*Step 1 - Synthesis of BOC-Amino Dipeptide Ethyl Esters (**10**):*

A solution of compound (**8**) (10 g, 1 equiv.) in THF (100 mL) was treated with *iso*-butyl chloroformate (1.05 equiv.) at -40°C, and NMM (1 equiv.), and stirred at -40°C for 30 min. A solution of compound (**9**) (1.1 equiv.) in a DMF and THF (40 mL, 1:1) mixture was added to the above reaction mixture at -40°C followed by addition of NMM (1 equiv.). The resulting mixture was stirred at -40°C for 2 h. The precipitated salts were filtered and washed with EtOAc (200 mL). The combined filtrate was washed with 10% w/v citric acid solution (2 x 50 mL), 5% w/v $NaHCO_3$ solution (2 x 50 mL), brine solution (50 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a crude residue. This was stirred with pet. ether (100 mL) for 30 min. The desired product (**10**) was isolated by filtration. (If necessary, the product was further washed with a 1:1 mixture of pentane-Et_2O to remove additional impurities.)

*Step 2 - Synthesis of Amino Dipeptide Ethyl Esters (**11**):*

A solution of compound (**10**) (5g, 1 equiv.) in DCM (50 mL) was treated with TFA (5 equiv.) at 0°C and stirred at room temperature for 16 h. The volatiles were concentrated and the residue was stirred with Et_2O (150 mL) for 10 min and then filtered to collect the precipitated solid which was washed with *n*-pentane (50 mL) to obtain compound (**11**).

*Step 3a - Synthesis of Amido Dipeptide Ethyl Esters (**12**):*

To a solution of compound (**11**) (10 g, 1 equiv.) and DIPEA (3 equiv.) in DCM (100 mL) at -20°C was added the appropriate acid chloride ($R^{10}COCl$, 0.9 equiv.) and the reaction mixture was stirred at -20°C for 1 h. The reaction mixture was filtered to remove salts and the filtrate washed with 10% w/v citric acid solution (2 x 50 mL), 5% $NaHCO_3$ solution (2 x 50 mL) and brine solution (50 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a crude residue. This was further purified by trituration to give compound (**12**).

*Step 3b - Synthesis of Amido Dipeptide Ethyl Esters (**12**):*

To a stirred mixture of carboxylic acid ($R^{10}CO_2H$, 1.8 g, 1 equiv.) in THF (100 mL) at -40°C was added *iso*-butyl chloroformate (1.05 equiv.) followed by NMM (2.5 equiv.). After 30 min, a solution of compound (**11**) (1 equiv.) in THF (20 mL) was added to the above reaction mixture at -40°C and stirred for 1 h. After that time, the THF was evaporated from the reaction mixture and the residue dissolved in EtOAc (200 mL), washed with (aq.) 10% w/v $NaHCO_3$ solution (2 x 100 mL), brine solution (100 mL), dried (Na_2SO_4) and concentrated to obtain a crude residue. This was dissolved in $CHCl_3$ (20 mL) and *n*-pentane was added to precipitate crude (**12**) which was collected by filtration. The solid was washed with *n*-pentane to give the desired compound (**12**).

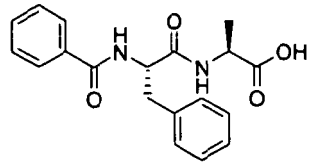
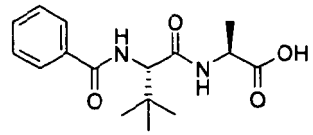
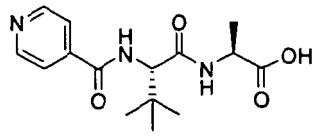
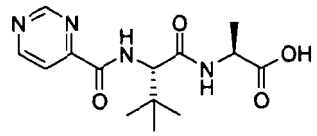
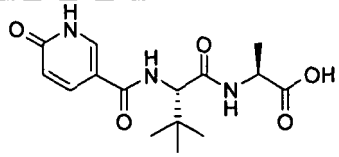
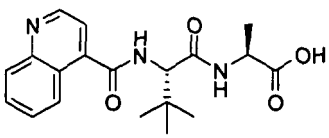
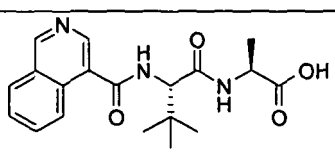
*Step 3c - Synthesis of Amido Dipeptide Ethyl Esters (**12**):*

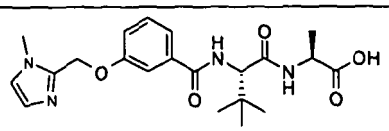
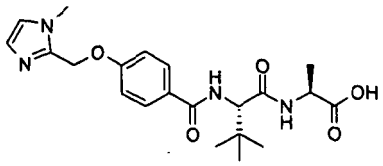
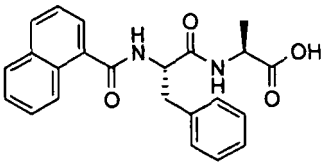
To a solution of carboxylic acid ($R^{10}CO_2H$, 360 mg, 2.87 mmol, 1 equiv.) in DMF (10 mL) at 0°C was added EDC.HCl (1.2 equiv.), $HOBt.H_2O$ (1.2 equiv.) and DIPEA (2.5 equiv.) followed compound (**11**) (1 equiv.). The reaction mixture was stirred at ambient temperature for 16 h. The reaction mixture was concentrated and the resulting residue was dissolved in EtOAc (50 mL), washed with brine (2 x 10 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (typically neutral alumina, 1% MeOH/$CHCl_3$) afforded the desired compound (**12**).

*Step 4 - Synthesis of Capped Dipeptides (**A**):*

To a solution of compound (**12**) (1 equiv.) in THF (6 volumes) and H_2O (6 volumes) was added $LiOH.H_2O$ (4 equiv.) at 0°C. The reaction mixture was stirred for 2 h. The volatiles (THF) were removed from the reaction mixture, the aqueous was adjusted to pH ~7 with (aq.) 10% w/v citric acid solution. The precipitated solid was collected by filtration, washed with H_2O (50mL), *n*-pentane (50mL) and dried to obtain the corresponding capped dipeptide intermediate (**A**).

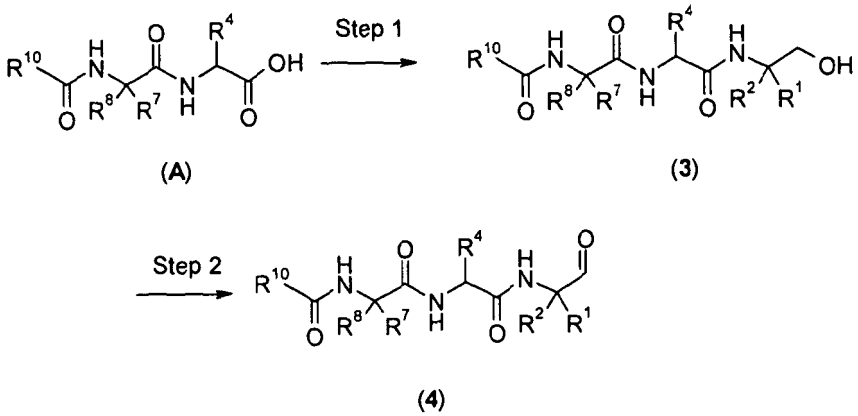
Dipeptide Intermediates (**A**) Prepared by Route 2

Compound	Code	Analytical Data	Yield
	**A1**	Method_2_Bic; Rt = 1.01mins; m/z 339 $(M-H)^{-1}$; white solid	4.5 g, 22%
	**A6**	Method_2_TFA_UPLC_2; Rt = 1.54mins; m/z 307 (MH^+); white solid	2g, 16%
	**A16**	Method_2_TFA_UPLC_2; Rt = 1.78mins; m/z 336 (MH^+); off white solid	2.8g, 19%
	**A39**	Method_4_TFA_UPLC_2; Rt = 2.40mins; m/z 307 $(M-H)^-$; white solid	220 mg, 8%
	**A40**	Method_4_TFA_UPLC_2; Rt = 1.90mins; m/z 324 (MH^+); white solid	300 mg, 13%
	**A41**	AnalpH2_MeOH_4min; Rt = 2.25mins; m/z 357 (MH^+); white solid	257 mg, 13%
	**A42**	AnalpH2_MeOH_4min; Rt = 2.20mins; m/z 358 (MH^+); white solid	150 mg, 16%

Compound	Code	Analytical Data	Yield
	**A43**	AnalpH2_MeOH_4min; Rt = 1.49mins; m/z 417 (MH^+); white solid	Used crude
	**A44**	AnalpH2_MeOH_4min; Rt = 1.42mins; m/z 417 (MH^+); transleucent solid	Used crude
	**A47**	R_f: 0.4 (50% MeOH/$CHCl_3$); white solid	1.6g, 42%

Route 3: Synthesis of ALD Compounds *via* Tri-Petide Alcohol

Scheme 8



(A) (3) (4)

Typical Procedure

*Step 1 - Synthesis of Peptidyl Alcohols (**3**):*

To a solution of acid (**A**) (1 equiv.) in THF (25-50 mg/mL) and optionally DMF (0.05-0.25 volumes) at -40°C was added NMM (3.1 equiv.) and *iso*-butyl chloroformate (1.1 equiv.). The reaction mixture was stirred at -40°C for approximately 30 min (extent of formation of the mixed anhydride can be monitored by quenching an aliquot of the reaction mixture in, e.g., excess pyrrolidine and analysing extent of amide formation by LC-MS). A solution of the amino alcohol (1.1 equiv.) in THF or DMF (0.1 volumes) was added dropwise. The reaction was stirred at -40°C for approximately 1 h until complete as measured by LC-MS. Additional amino alcohol could be added if required. The reaction mixture was allowed to warm to ambient temperature. The resulting mixture was diluted with EtOAc

(10 volumes) and sat. aq. $NaHCO_3$ (10 volumes). The layers were separated and the aqueous layer extracted with EtOAc (2 x 10 volumes). The combined organic phases were washed with water (3 x 10 volumes) and brine (10 volumes) and concentrated under vacuum. The resulting alcohol (**3**) was either used directly or purified by flash column chromatography.

*Step 2 - Synthesis of Peptidyl Aldehydes (**4**):*

To a stirred solution of the corresponding alcohol (**3**) (1 equiv.) in dry DCM (1 mL/15-200 mg of alcohol) and optionally dry DMF (10-100% v/v depending upon solubility) at ambient temperature was added Dess-Martin periodinane (2 equiv.) in portions. The reaction mixture was stirred at ambient temperature and monitored by LC-MS until full conversion to product aldehyde had occurred (typically 1 h to 1 day). Where necessary, more Dess-Martin periodinane was added to complete the oxidation. The reaction mixture was quenched by addition of sat. (aq.) $NaHCO_3$ (1 volume) and (aq.) $Na_2S_2O_3$ (10% w/v). The mixture was stirred for approximately 30 min, diluted with EtOAc (10 volumes) and washed with sat. (aq.) $NaHCO_3$ (2 x 5 volumes), deionised water (5 volumes) and brine (5 volumes). The organic layer was subsequently dried over $MgSO_4$ and evaporated to give the desired compound which was either triturated with ether or purified by reverse-phase preparative HPLC (a H_2O + 0.1% TFA:MeCN + 0.1% TFA gradient at 50°C was used for preparative HPLC) followed by lyophilisation to give the desired compound (**4**).

Route 4: Synthesis of ALD compounds using Weinreb Resin

Typical Procedure

Step 1 – Deprotecting the Fmoc-Weinreb-AM Resin:

Fmoc-Weinreb-AM resin was swollen with an appropriate volume of DMF then drained under vacuum, washed twice with DCM then drained under vacuum. The resin was shaken with an appropriate volume of 20% v/v piperidine in DMF (8 mL/g resin) for 1 h then washed with DMF, DCM, MeOH and re-swollen with DCM. A positive chloranil test (orange/red colour) indicates the presence of a free NH group.

Step 2 - Coupling of First Amino Acid to H-Weinreb-AM Resin:

To the resin was added the appropriate Fmoc-amino acid (2 equiv.), HATU (2 equiv.) and DIPEA (4 equiv.) in an appropriate volume of DMF (3 mL/ g of resin), sufficient to cover the resin dissolve the reagents, and this mixture was shaken for 5 h. After that time the resin was drained under vacuum, washed with DMF, DCM and MeOH then re-swollen

with DCM. Successful coupling could be indicated by performing a chloranil test to demonstrate the absence of a free NH group (lack of orange/red colour). In general, the exact amount of amino acid attached to the resin was not quantified and subsequent reactions were performed on the basis of the maximum loading as indicated from the supplier. For amino acids that were purchased pre-attached to Wang resin, approximate loadings are supplied by the supplier and these were used for calculating amounts of reagent for subsequent steps.

Step 3 - Fmoc-Deprotection:

The resin was swollen with an appropriate volume of DCM then drained under vacuum, washed twice with DMF then drained under vacuum. The resin was shaken with an appropriate volume of 20% v/v piperidine in DMF (15 mL/g resin) for 0.5 – 1 h, then washed with DMF, DCM, MeOH and re-swollen with DCM. A positive Kaiser test (blue colour) indicates the presence of a free NH_2 group.

Step 4 - Coupling of Subsequent Amino Acids / Capping Groups to H-AA-Weinreb-AM Resin:

The resin was shaken with the appropriate Fmoc-amino acid (2 equiv.) or capping group $R_{10}CO_2H$ (3 equiv.), TBTU (2 equiv.) and DIPEA (4 equiv. or 6 equiv. if, e.g., HCl salt is used) in an appropriate volume of DMF (~3 - 5 mL/g resin) for 4 - 5 h. After that time, the resin was drained under vacuum, washed with DMF, DCM, MeOH and re-swollen with DCM. A negative Kaiser test (no colour change) indicates that all of the free amino sites have coupled. If the solution remained blue, step 4 was repeated.

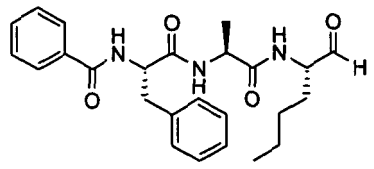
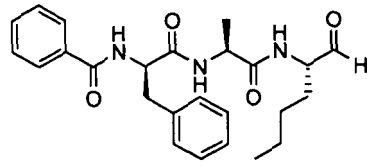
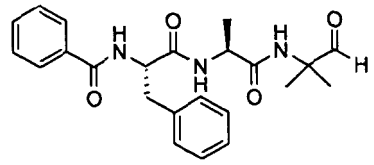
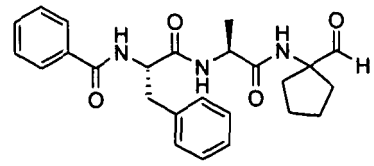
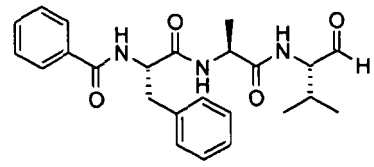
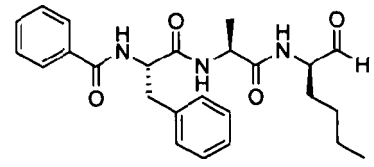
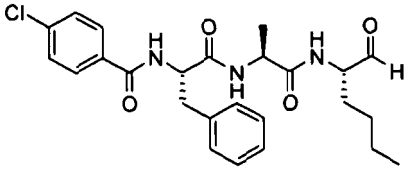
Steps 3 and 4 were repeated for the coupling of additional amino acids or capping groups as necessary.

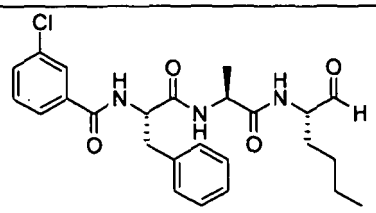
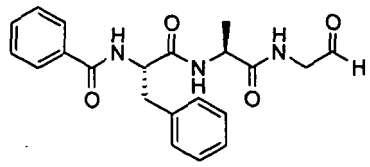
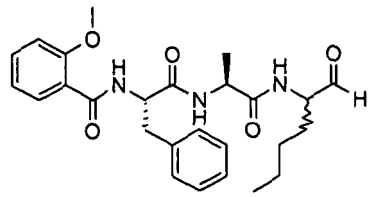
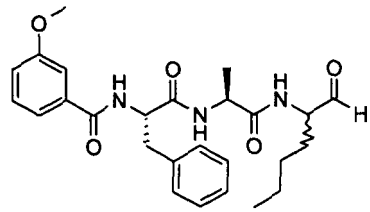
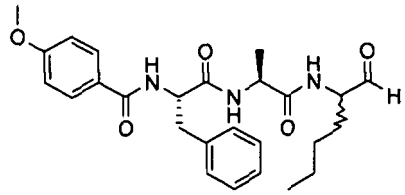
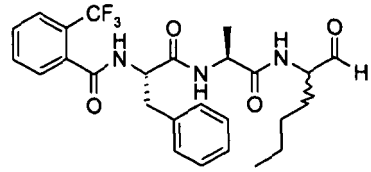
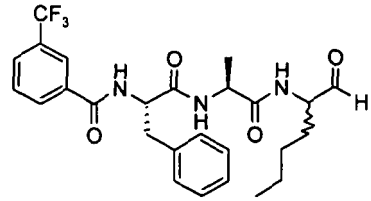
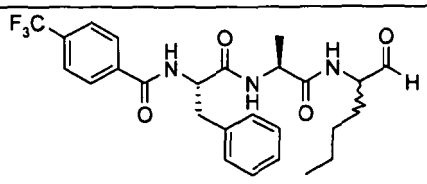
Step 5 - Resin Cleavage:

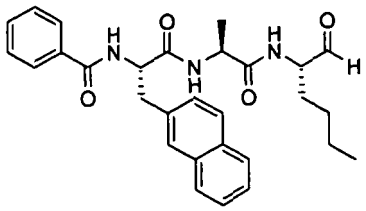
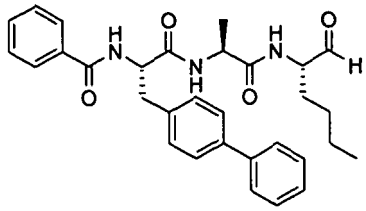
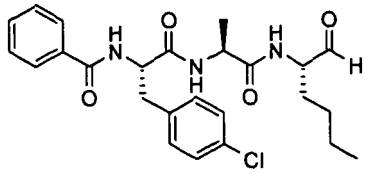
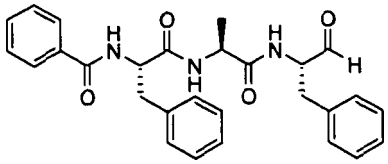
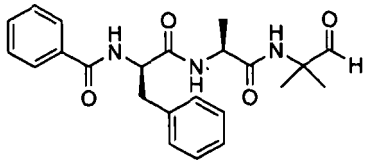
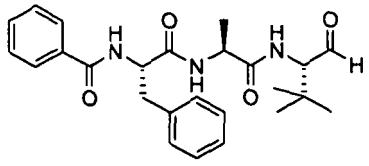
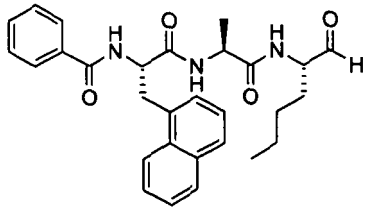
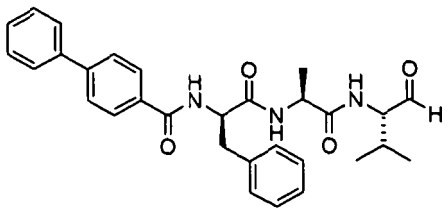
The resin was swollen in anhydrous THF (4 mL/g resin) and was gently stirred at 0°C under an inert atmosphere (e.g. nitrogen). A solution of $LiAlH_4$ (4 equiv.) in THF (~2.5M) was added to the resin and the mixture was gently stirred for 1 h. After this time the mixture was quenched at 0°C by dropwise addition of a sat. aq. solution of $KHSO_4$ (~1.5 mL/g resin) followed by a solution of aq. Rochelle salt (sodium potassium tartrate; 1.2M, 4 equiv.). The quenched mixture was allowed to warm to ambient temperature and was diluted with water (4 mL/g resin). The mixture was extracted with DCM (3 x 5 mL/g resin) using a hydrophobic frit to retain the aqueous phase, residual resin and insoluble salts. The combined DCM phase was dried over Na_2SO_4.

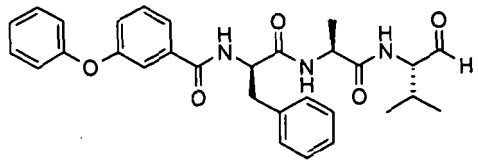
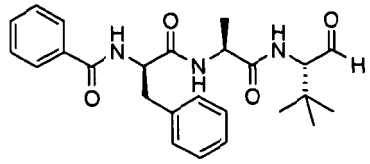
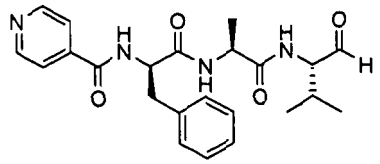
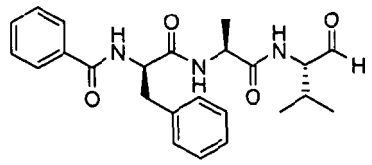
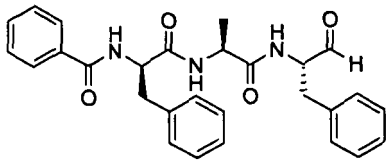
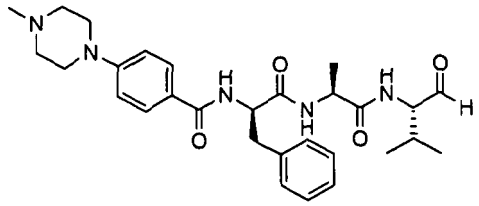
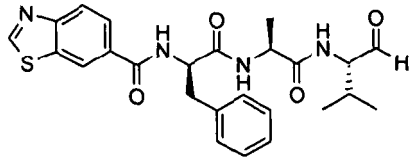
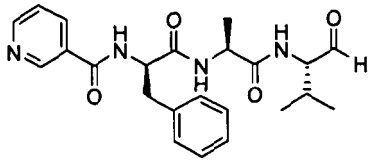
Synthesized ALD Compounds

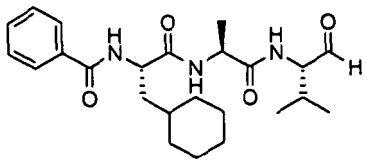
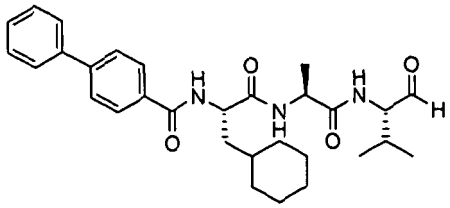
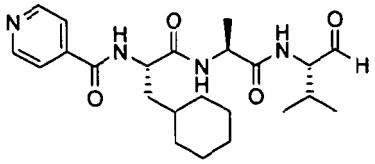
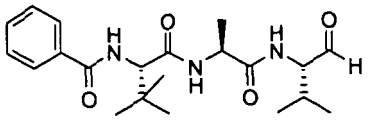
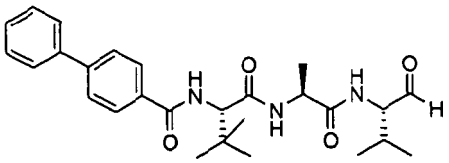
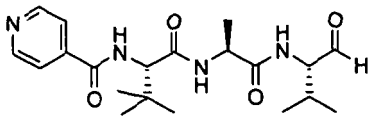
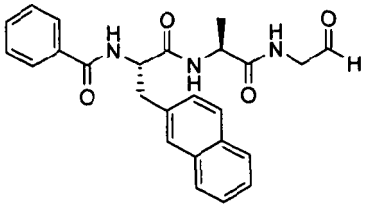
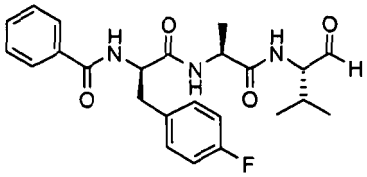
For aldehydes synthesised by route 3 the corresponding dipeptide acids are shown in brackets. Yields are quoted from these dipeptide acids for route 3 and based upon theoretical resin loadings for route 4.

Code	Compound	Route	Analytical Data	Yield
ALD-001		3 (A1)	AnalpH2_45C; Rt 3.22 min, m/z 438 (MH^+); white solid.	157 mg, 37%
ALD-002		3 (A2)	white powder.	38 mg, 7%
ALD-003		3 (A1)	Aldehyde_QC (Gemini)_1; Rt 5.70 min; m/z 410 (MH^+); white solid.	2 mg, 2%
ALD-004		3 (A1)	Aldehyde_QC (Gemini)_1; Rt 6.04 min; m/z 436 (MH^+); white solid.	55 mg, 41%
ALD-005		3 (A1)	Aldehyde_QC (Gemini)_1; Rt 5.82 min; m/z 424 (MH^+); white solid.	76 mg, 56%
ALD-006		3 (A1)	Aldehyde_QC (Gemini)_1; Rt 6.08 min; m/z 438 (MH^+); white solid.	80 mg, 53%
ALD-007		4	Aldehyde_QC (Gemini)_1; Rt 6.52 min; m/z 472 (MH^+); white solid.	7.6 mg, 6%

Code	Compound	Route	Analytical Data	Yield
ALD-008		4	Aldehyde_QC (Gemini)_1; Rt 6.49 min; m/z 472 (MH^+); cream solid.	12.8 mg, 10%
ALD-009		3 (A1)	Aldehyde_QC (Gemini)_1; Rt 4.99 min; m/z 382 (MH^+); white solid.	5.7 mg, 5%
ALD-010		4	Aldehyde_QC_3; Rt 6.43 min; m/z 468 (MH^+); *off* white solid.	7.9 mg, 5%
ALD-011		4	Aldehyde_QC_3; Rt 6.34 min; m/z 468 (MH^+); white solid.	4.2 mg, 3%
ALD-012		4	Aldehyde_QC_3; Rt 6.29 min; m/z 468 (MH^+); white solid.	7.5 mg, 5%
ALD-013		4	Aldehyde_QC_3; Rt 6.53 min; m/z 506 (MH^+); white solid.	19 mg, 12%
ALD-014		4	Aldehyde_QC_3; Rt 6.83 min; m/z 506 (MH^+); white solid.	11 mg, 7%
ALD-015		4	Aldehyde_QC_3; Rt 6.85 min; m/z 506 (MH^+); white solid.	4 mg, 2%

Code	Compound	Route	Analytical Data	Yield
ALD-016		3 (A31)	Aldehyde_QC_3; Rt 6.71 min; m/z 488 (MH^+); white solid.	6 mg, 6%
ALD-017		3 (A27)	Aldehyde_QC_3; Rt 6.98 min; m/z 514 (MH^+); white solid.	10 mg, 11%
ALD-018		3 (A30)	Aldehyde_QC_3; Rt 6.59 min; m/z 472 (MH^+); white solid.	10 mg, 39%
ALD-019		3 (A1)	Aldehyde_QC_3; Rt 6.15 min; m/z 472 (MH^+); white solid.	29 mg, 36%
ALD-020		3 (A2)	Aldehyde_QC_3; Rt 5.95 min; m/z 410 (MH^+); white solid.	83 mg, 85%
ALD-021		3 (A1)	Aldehyde_QC_3; Rt 6.36 min; m/z 438 (MH^+); white solid.	72 mg, 55%
ALD-022		3 (A31)	white solid.	2 mg, 3%
ALD-023		3 (A3)	Aldehyde_QC (Gemini)_1; Rt 6.79 min; m/z 500 (MH^+); white solid.	14 mg, 10%

Code	Compound	Route	Analytical Data	Yield
ALD-024		3 (A5)	Aldehyde_QC (Gemini)_1; Rt 6.80 min; m/z 516 (MH^+); white solid.	92 mg, 69%
ALD-025		3 (A2)	Aldehyde_QC (Gemini)_1; Rt 6.27 min; m/z 438 (MH^+); white solid.	22 mg, 15%
ALD-026		3 (A4)	Aldehyde_QC (Gemini)_1; Rt 4.11 min; m/z 425 (MH^+); white solid.	59 mg, 52%
ALD-027		3 (A2)	Aldehyde_QC (Gemini)_1; Rt 5.86 min; m/z 424 (MH^+); white solid.	40 mg, 27%
ALD-028		3 (A2)	Aldehyde_QC (Gemini)_1; Rt 5.97 min; m/z 472 (MH^+); white solid.	15 mg, 9%
ALD-029		4	Aldehyde_QC (Gemini)_1; Rt 4.38 min; m/z 522 (MH^+); white solid.	2 mg, 1%
ALD-030		4	Aldehyde_QC (Gemini)_1; Rt 5.68 min; m/z 481 (MH^+); white solid.	3 mg, 3%
ALD-031		4	Aldehyde_QC (Gemini)_1; Rt 4.28 min; m/z 425 (MH^+); white solid.	4 mg, 3%

Code	Compound	Route	Analytical Data	Yield
ALD-032		3 (A32)	Aldehyde_QC (Gemini)_1; Rt 6.51 min; m/z 430 (MH^+); white solid.	15 mg, 60%
ALD-033		3 (A21)	Aldehyde_QC (Gemini)_1; Rt 7.38 min; m/z 506 (MH^+); white solid.	9 mg, 46%
ALD-034		3 (A45)	Aldehyde_QC (Gemini)_1; Rt 4.73 min; m/z 431 (MH^+); white solid.	21 mg, 32%
ALD-035		3 (A6)	Aldehyde_QC (Gemini)_1; Rt 5.79 min; m/z 390 (MH^+); white solid.	30 mg, 28%
ALD-036		3 (A34)	Aldehyde_QC (Gemini)_1; Rt 6.84 min; m/z 466 (MH^+); white solid.	50.4 mg, 35%
ALD-037		3 (A16)	Aldehyde_QC (Gemini)_1; Rt 3.97 min; m/z 391 (MH^+); colourless amorphous solid.	11 mg, 17%
ALD-038		3 (A31)	Aldehyde_QC (Gemini)_1; Rt 5.56 min; m/z 432 (MH^+); white solid.	4mg, 7%
ALD-039		3 (A7)	Aldehyde_QC_1; Rt 6.22 min; m/z 442 (MH^+); white solid.	88 mg, 50%

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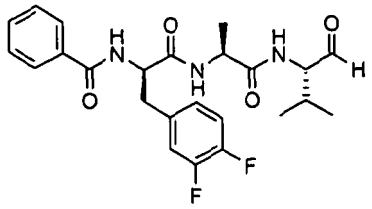
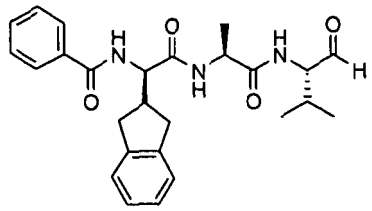
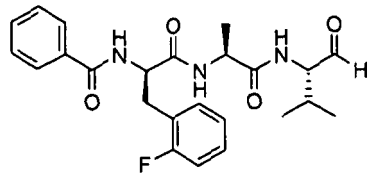
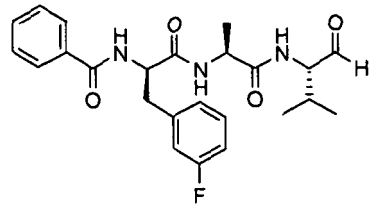
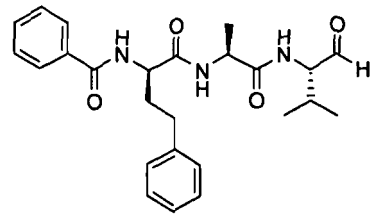
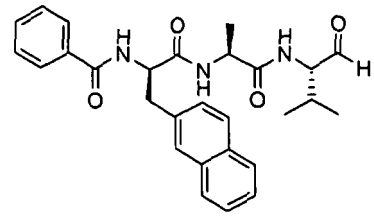
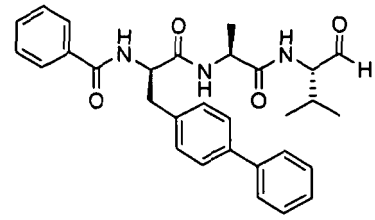
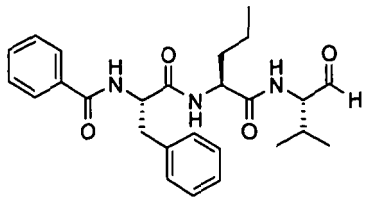
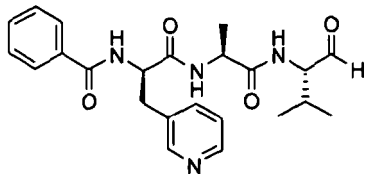
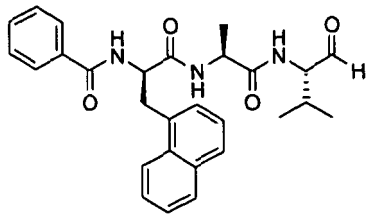
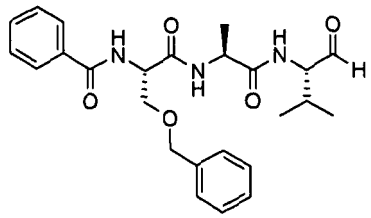
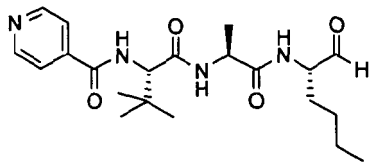
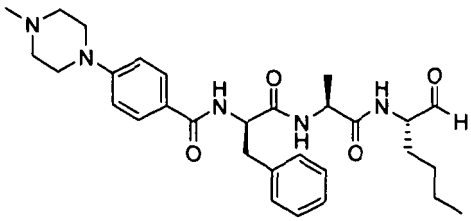
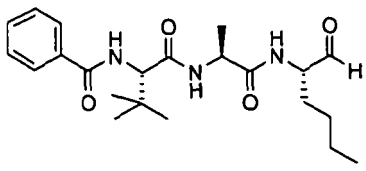
ALD-040		3 (A8)	Aldehyde_QC_1; Rt 6.38 min; m/z 460 (MH^+); white solid.	33 mg, 20%
ALD-041		3 (A9)	Aldehyde_QC_1; Rt 8.12 min; m/z 450 (MH^+); white solid.	59 mg, 24%
ALD-042		3 (A10)	Aldehyde_QC_1; Rt 6.19 min; m/z 442 (MH^+); colourless solid.	32.8 mg, 22%
ALD-043		3 (A11)	Aldehyde_QC_1; Rt 6.24 min; m/z 442 (MH^+); colourless solid.	43 mg, 42%
ALD-044		3 (A37)	Aldehyde_QC_1; Rt 6.04 min; m/z 438 (MH^+); white solid.	49 mg, 47%
ALD-045		3 (A12)	Aldehyde_QC (Gemini)_2; Rt 6.79 min; m/z 474 (MH^+); white solid.	37 mg, 37%
ALD-046		3 (A13)	Aldehyde_QC (Gemini)_2; Rt 6.78 min; m/z 500 (MH^+); white solid.	25 mg, 24%

Code	Compound	Route	Analytical Data	Yield
ALD-047		3 (A35)	Aldehyde_QC_2; Rt 6.65 min; m/z 452 (MH^+); white amorphous solid.	135 mg, 72%
ALD-048		3 (A24)	Aldehyde_QC (Gemini)_2; Rt 3.41 min; m/z 425 (MH^+); white solid.	1 mg, 1%
ALD-049		3 (A14)	Aldehyde_QC (Gemini)_2; Rt 5.93 min; m/z 474 (MH^+); white solid.	32 mg, 42%
ALD-050		3 (A38)	Aldehyde_QC (Gemini)_2; Rt 5.57 min; m/z 454 (MH^+); white solid.	3 mg, 4%
ALD-051		3 (A16)	Aldehyde_QC_2; Rt 4.30 min; m/z 405 (MH^+); white solid.	84 mg, 42%
ALD-052		3 (A17)	Aldehyde_QC_2; Rt 4.74 min; m/z 536 (MH^+); colourless solid.	23 mg, 13%
ALD-053		3 (A6)	Aldehyde_QC_2; Rt 6.30 min; m/z 404 (MH^+); white solid.	139 mg, 43%

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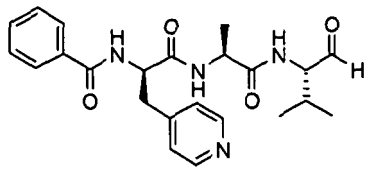
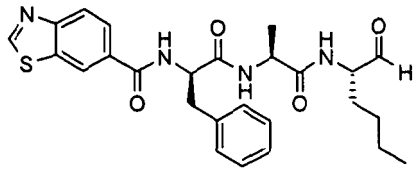
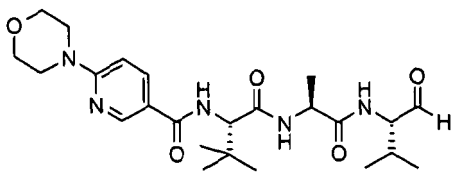
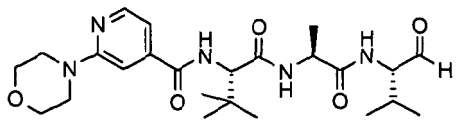
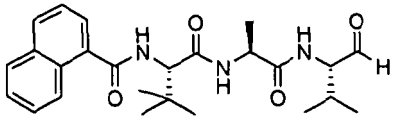
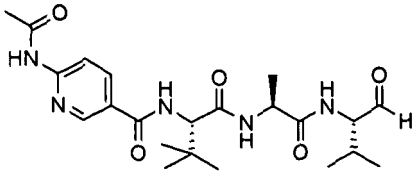
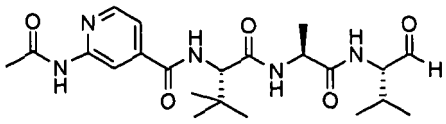
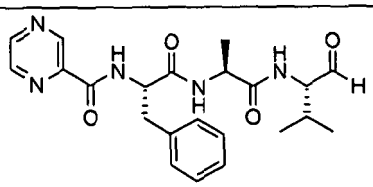
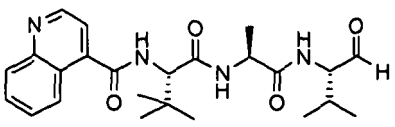
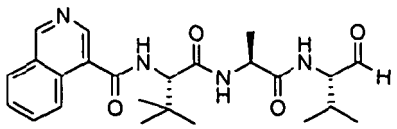
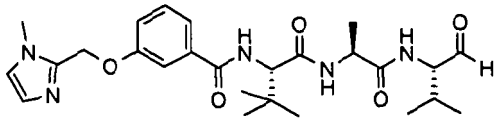
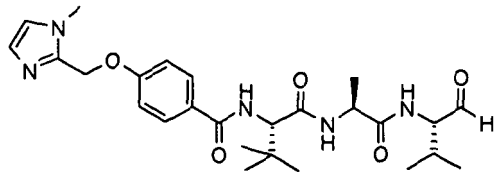
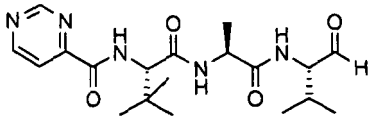
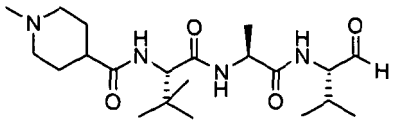
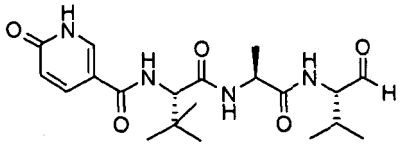
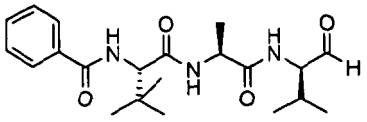
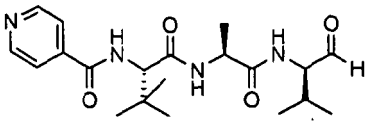
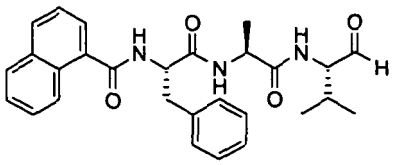
ALD-054		3 (A15)	Aldehyde_QC_2; Rt 3.96 min; m/z 425 (MH^+); white solid.	44 mg, 70%
ALD-055		3 (A19)	Aldehyde_QC_2; Rt 6.05 min; m/z 495 (MH^+); white solid.	11mg, 26%
ALD-056		3 (A20)	Aldehyde_QC_2; Rt 4.32 min; m/z 476 (MH^+); white solid.	40 mg, 24%
ALD-057		3 (A18)	Aldehyde_QC_2; Rt 4.26 min; m/z 476 (MH^+); pale yellow solid.	106 mg , 64%
ALD-058		3 (A23)	Aldehyde_QC_2; Rt 6.57 min; m/z 440 (MH^+); white solid.	101 mg, 63%
ALD-059		3 (A26)	Aldehyde_QC_2; Rt 4.67 min; m/z 448 (MH^+); white solid.	86 mg, 51%
ALD-060		3 (A29)	Aldehyde_QC_2; Rt 4.56 min; m/z 448 (MH^+); white solid.	67 mg, 43%
ALD-061		3 (A25)	Aldehyde_QC_2; Rt 5.39 min; m/z 426 (MH^+); white solid.	8.2 mg, 11%
ALD-062		3 (A41)	Aldehyde_QC_2; Rt 4.52 min; m/z 441 (MH^+); white solid.	130 mg, 71%

Code	Compound	Route	Analytical Data	Yield
ALD-063		3 (A42)	Aldehyde_QC_2; Rt 4.40 min; m/z 441 (MH^+); white amorphous solid.	184 mg, 64%
ALD-064		3 (A43)	Aldehyde_QC_2; Rt 4.49 min; m/z 500 (MH^+); beige solid.	104 mg, 39%
ALD-065		3 (A44)	Aldehyde_QC_2; Rt 4.50 min; m/z 500 (MH^+); white amorphous solid.	30 mg, 34%
ALD-066		3 (A39)	Aldehyde_QC_2; Rt 5.24 min; m/z 392 (MH^+); white solid.	55 mg, 31%
ALD-067		3 (A36)	Aldehyde_QC_2; Rt 3.84 min; m/z 411 (MH^+); white solid.	7 mg, 29%
ALD-068		3 (A40)	Aldehyde_QC_2; Rt 4.28 min; m/z 407 (MH^+); white solid.	9 mg, 56%
ALD-069		3 (A6)	Aldehyde_QC_2; Rt 4.28 min; m/z 390 (MH^+); white solid.	129 mg, 63%
ALD-070		3 (A16)	Aldehyde_QC_2; Rt 4.00 min; m/z 391 (MH^+); white solid.	23 mg, 27%
ALD-071		3 (A47)	.Aldehyde_QC_2; Rt 6.56 min; m/z 474 (MH^+); white solid.	205 mg, 50%

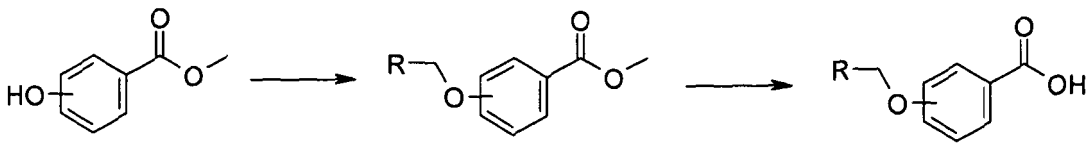
^{1}H NMR data for some of the above compounds is shown below.

Code	^{1}H NMR data
ALD-002	^{1}H NMR (400 MHz, D_6-DMSO): δ 9.36 (1H, d, J = 0.8 Hz), 8.71 (1H, d, J = 7.3 Hz), 8.45 (1H, d, J = 7.6 Hz), 8.22 (1H, d, J = 7.1 Hz), 7.81-7.78 (2H, m), 7.55-7.50 (1H, m), 7.48-7.42 (2H, m), 7.38-7.34 (2H, m), 7.30-7.25 (2H, m), 7.21-7.15 (1H, m), 4.68-4.61 (1H, m), 4.37-4.30 (1H, m), 4.06-4.00 (1H, m), 3.06-3.01 (2H, m), 1.78-1.69 (1H, m), 1.60-1.46 (1H, m), 1.35-1.14 (7H, m), 0.83-0.77 (3H, m).
ALD-022	^{1}H NMR (400 MHz, CD_3CN): δ 9.44 (1H, d, *J* = 0.8 Hz), 8.22 (1H, br.d, *J* = 7.6 Hz), 7.93 (1H, br.d, *J* = 8.3 Hz), 7.82 (1H, br.d, *J* = 7.8 Hz), 7.73-7.69 (2H, m), 7.65-7.59 (1H, m), 7.58-7.52 (2H, m), 7.50-7.40 (4H, m), 7.34 (1H, d, *J* = 7.1 Hz), 7.11 (1H, d, *J* = 7.1 Hz), 7.06 (1H, d, *J* = 6.8 Hz), 4.87-4.80 (1H, m), 4.40-4.31 (1H, m), 4.19-4.10 (1H, m), 3.81 (1H, dd, *J* = 14.4, 5.5), 3.53 (1H, dd, *J* = 14.4, 9.1), 1.87-1.77 (1H, m), 1.62-1.52 (1H, m), 1.38-1.25 (7H, m), 0.90-0.85 (3H, m).

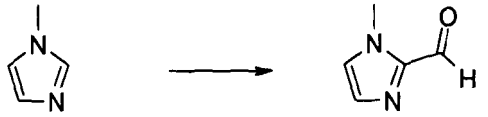
Additional Synthesis Details

Described below are the syntheses of materials and reagents that may not be readily or commercially available, and synthetic sequences outside the scope of those outlined above.

Synthesis of Ether Linked Benzoic Acid Intermediates - General Procedure:



*Synthesis of 1-Methyl-1H-imidazole-2-carbaldehyde (**BB5**):*



(BB5)

To a solution of 1-methyl imidazole (57 g, 0.7 mmol) in THF (250 mL) was added LDA (2 M solution in THF, 348 mL) at -60°C and the stirred for 3 h. The reaction mixture was cooled -78°C, DMF (75 mL) was added rapidly, and the reaction mixture was slowly allowed to warm to room temperature and stirred at ambient temperature overnight. The reaction mixture was cooled to 0°C, a solution of NaH_2PO_4 (100 g in 350 mL H_2O) was added and the resulting mixture was stirred for 30 min. The mixture was filtered to remove insoluble material and the filtrate was extracted with DCM (4 x 400 mL). The combined organic extracts were concentrated *in vacuo* and the crude residue was

purified by column chromatography (silica gel, 100-200 mesh, 30% EtOAc/pet. ether) to provide (**BB5**) (41g, 53%) as a yellow solid. R_f: 0.3 (15% MeOH/$CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 9.82 (1H, s), 7.28 (1H, app d), 7.13 (1H, app d), 4.04 (3H, s); *m/z* 111 $(MH)^+$.

*Synthesis of (1-Methyl-1H-imidazol-2-yl)methanol (**BB6**):*

(**BB5**) (**BB6**)

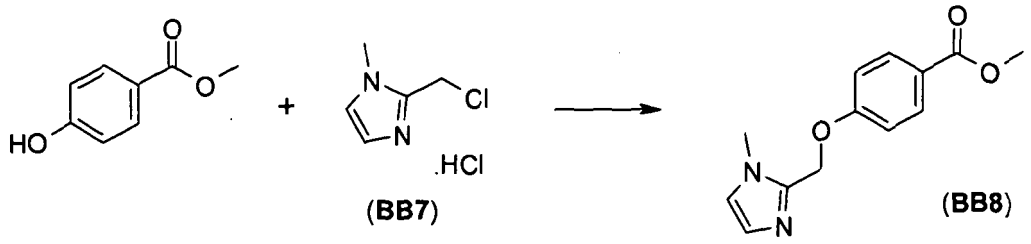
To a solution of compound (**BB5**) (40.5 g, 368 mmol) in MeOH (300 mL) at 0°C was added $NaBH_4$ (20.89 g, 551 mmol) portion wise. The reaction mixture was slowly warmed to room temperature and stirred for 5 h. The reaction mixture was cooled to 0°C, H_2O (150 mL) was added and the mixture was stirred for 30 min at room temperature then concentrated *in vacuo*. The crude residue was dissolved in H_2O (150 mL) and extracted with $CHCl_3$ (4 x 200mL). The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was stirred with Et_2O (150 mL) and filtered to afford (**BB6**) (36 g, 87%) as a white solid. R_f: 0.4 (15% MeOH/$CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 6.89 (1H, app d), 6.83 (1H, app d), 4.66 (2H, s), 3.72 (3H, s); *m/z* 113 $(MH)^+$.

*Synthesis of 2-(Chloromethyl)-1-methyl-1H-imidazole Hydrochloride (**BB7**):*

(**BB6**) (**BB7**)

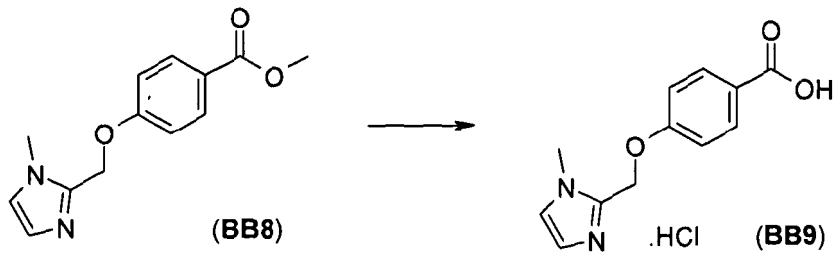
To a solution of (**BB6**) (35.5 g, 316.96 mmol) in DCM (1500 mL) was added $SOCl_2$ (330 mL, 4436 mmol) at 0°C, warmed to room temperature and stirred for 5 h. The reaction mixture was concentrated, the residue was washed with DCM (2 x 500 mL), followed by Et_2O (2 x 200 mL) to obtain (**BB7**) (50 g, 95%) as an off-white solid. R_f: 0.4 (EtOAc). ^1H NMR (400 MHz, DMSO-d_6): δ 7.76 (1H, app d), 7.70 (1H, app d), 5.17 (2H, s), 3.87 (3H, s); *m/z* 131 $(MH)^+$.

*Synthesis of Methyl-4-((1-methyl-1H-imidazol-2-yl)methoxy)benzoate (**BB8**):*



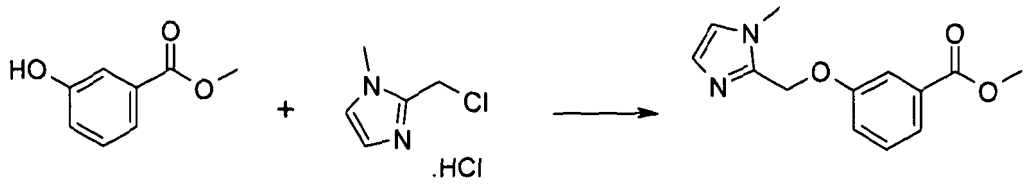
A suspension of 4-hydroxy benzoic acid methyl ester (18 g, 118.42 mmol) and powdered anhydrous K_2CO_3 (40.85 g, 296 mmol) in dry DMF (150 mL) was heated to 100°C. To the stirred reaction mixture was added (**BB7**) (25.5 g, 153.6 mmol) in six portions. The reaction mixture was stirred for 6 h and then cooled to room temperature and filtered. The filtrate was dissolved in H_2O (200 mL), extracted with EtOAc (2 x 250mL), the combined organics were washed with brine solution (3 x 100mL), dried over Na_2SO_4, concentrated *in vacuo*. The resulting crude compound was purified by column chromatography (100-200 mesh silica gel, eluted with 2% MeOH-$CHCl_3$) to provide (**BB8**) (17.1g, 52%) as an off-white solid. R_f: 0.2 (50% EtOAc/pet. ether). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.0 (2H, d, *J* = 8.8 Hz), 7.33 (2H, d, *J* = 8.8 Hz), 7.02 (1H, app d), 6.91 (1H, app d), 5.22 (2H, s), 3.88 (3H, s), 3.73 (3H, s); *m/z* 247 $(MH)^+$.

*Synthesis of 4-(1-Methyl-1H-imidazol-2-yl)methoxybenzoic Acid Hydrochloride (**BB9**):*



To a solution of (**BB8**) (24.1 g, 97.96 mmol) in MeOH (180 mL) was added aq. 5 N NaOH (70 mL) solution at room temperature. The reaction mixture was stirred at room temperature for 8 h and concentrated *in vacuo*. The residue was dissolved in H_2O (100 mL) and washed with Et_2O (2 x 100 mL), the aqueous layer was cooled in an ice bath and acidified with 6 N aq. HCl (pH ~6). The precipitated solid was collected by filtration and washed with pet ether (200 mL) and dried to provide (**BB9**) (20.7 g, 76%) as a white solid. R_f: 0.6 (5% MeOH/$CHCl_3$). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.92 (2H, d, *J* = 8.8 Hz), 7.42 (1H, s), 7.21-7.19 (3H, m), 5.36 (2H, s), 3.76 (3H, s); *m/z* 233 $(MH)^+$.

*Synthesis of Methyl-3-(1-methyl-1H-imidazol-2-yl)methoxy Benzoate (**BB10**):*



(**BB7**) (**BB10**)

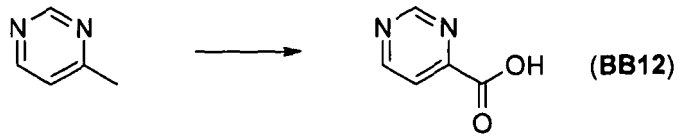
A suspension of 3-hydroxy benzoic acid methyl ester (18 g, 118.42 mmol) and powdered anhydrous K_2CO_3 (40.85 g, 296 mmol) in dry DMF (150 mL) was heated to 100°C. To the reaction mixture was added (**BB7**) (25.5 g, 153.6 mmol) in six portions. The reaction mixture was stirred for 6 h and then was cooled to room temperature and filtered. The filtrate was dissolved in H_2O (200 mL), extracted with EtOAc (2 x 250 mL), and the combined organics were washed with brine solution (3x100mL), dried (Na_2SO_4) and concentrated *in vacuo*. The resulting crude compound was purified by column chromatography (100-200 mesh silica gel, 2% MeOH-$CHCl_3$) to provide (**BB10**) (15.3 g, 52%) as an off-white solid. R_f: 0.2 (50% EtOAc/pet. ether). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67-7.55 (2H, m), 7.36 (1H, t, *J* = 7.6 Hz), 7.25 (1H, app d), 7.02 (1H, app d), 6.91 (1H, app d), 5.19 (2H, s), 3.92 (3H, s), 3.74 (3H, s); *m/z* 247 (MH^+).

*Synthesis of Methyl-3-(1-methyl-1H-imidazol-2-yl)methoxy Benzoic Acid Hydrochloride (**BB11**):*

(**BB10**) (**BB11**)

To a solution of (**BB10**) (15.1 g, 61.38 mmol) in MeOH (150 mL) was added 5 N aq. NaOH (40 mL) solution at room temperature. The reaction mixture was stirred at room temperature for 5 h and concentrated *in vacuo*. The residue was dissolved in H_2O (150 mL) and washed with Et_2O (2 x 100mL), the aqueous layer was cooled in an ice bath and acidified with 6 N aq. HCl (pH ~6). The precipitated solid was collected by filtration, washed with chilled H_2O (50 mL) and pet. ether (200 mL) and dried to provide (**BB11**) (7.8g, 46%) as an off-white solid. R_f: 0.6 (15% MeOH/$CHCl_3$). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.65-7.56 (2H, m), 7.43 (1H, t, *J* = 8 Hz), 7.35-7.30 (1H, m), 7.26-7.20 (m, 1H), 6.92-6.90 (m, 1H), 5.21 (2H, s), 3.7 (3H, s); *m/z* 233 (MH^+).

*Synthesis of Pyrimidine-4-carboxylic Acid (**BB12**):*



(**BB12**)

To a solution of 4-methylpyrimidine (4g, 46.5 mmol) in pyridine (20 mL) was added SeO_2 (8.7 g, 79.06 mmol) at room temperature. The reaction mixture was then heated to 60°C for 2 h, and then stirred at room temperature for 16 h. The reaction mixture was diluted with DCM (50 mL) and filtered to remove selenium waste. The filtrate was concentrated to give a residue that was stirred with H_2O (20 mL), the precipitated solid was filtered and washed with acetone (2 x 20 mL) and dried to provide (**BB12**) (3.1g, 58%) as a brown solid. R_f: 0.2 (40%MeOH/$CHCl_3$). ^1H NMR (400MHz, DMSO-d_6): δ 13.8 (1H, br s), 9.37 (1H, s), 9.07 (1H, d, J = 5.2 Hz), 8.01 (1H, d, J = 4 Hz); *m/z* 123 $(M-H)^-$.

Biological Methods- Enzyme Assays

Many of the compounds contain a centre which is sufficiently basic, and were purified in such a way, that it is likely that they were obtained as the corresponding trifluoroacetic acid (TFA) salt. Consequently, in the biological studies described herein, it is believed that the following compounds were studied in the form of the corresponding TFA salt: ALD-026, ALD-029, ALD-031, ALD-034, ALD-037, ALD-051, ALD-052, ALD-054, ALD-056, ALD-057, ALD-059, ALD-060, ALD-062, ALD-063, ALD-064, ALD-065, ALD-067, ALD-070.

Assay for Der p 1

Der p 1 purification:

House dust mites of the species Dermatophagoides pteronyssinus were cultured as described (see Zhang et al., 2007). Der p 1 was purified chromatographically and its identity confirmed by SDS-PAGE and MALDI-TOF mass spectrometry (see Zhang et al., 2007). Its concentration in solution was determined in a quartz cuvette by absorbance at 280 nm using an extinction coefficient of 47,705 M^{-1} cm^{-1}.

Der p 1 enzyme activity assay:

The fluorogenic substrate used for measuring Der p 1 proteolytic activity was 2-aminobenzoylvalylalanylnorleucylseryl-(3-nitro)tyrosinyl aspartamide. This compound is internally quenched by fluorescence resonance energy transfer (FRET), but upon

cleavage its emission at 420 nm increases when the substrate is excited at 330 nm (see Zhang et al., 2007).

Test compounds were dissolved in dry DMSO and maintained at 4°C as stock solutions until being diluted for use in screening assays. Final concentration of DMSO in all enzymatic assays was 0.5% v/v.

Reaction mixtures were assembled in a 96-well plate format (Perkin Elmer Optiplate 96F, Perkin Elmer LAS, Seer Green, Buckinghamshire, UK) using a Perkin Elmer MultiPROBE II Plus HTS EX robot with Gripper attachment. Plates were pre-formatted with serial dilutions (10 µL/well) of test compound or appropriate control in reaction buffer (composition: potassium phosphate buffer pH 8.25 containing 1 mM EDTA), to which a further 60 µL of reaction buffer was added. Dithiothreitol (DTT, 10 µL/well, 1 mM final concentration) was then added together with 10 µL of Der p 1 dissolved at 2.5 µg/mL in reaction buffer supplemented with 1 mM DTT. Reaction mixtures were then incubated at room temperature for 20 minutes before initiating the reaction by the addition of 10 µL of substrate (12.5 µM final concentration). The plate was immediately transferred to a fluorescence plate reader (Perkin Elmer Fusion Alpha-FP or Perkin Elmer Envision) equipped with a temperature-controlled carrier set at 30°C and the reaction followed by excitation/emission at 330/420 nm.

Enzyme assay data analysis

Inhibitory activity was analysed from progress curves of reactions in the presence of a range of inhibitor concentrations. Initial reaction velocities were calculated by computational non-linear regression and the degree of inhibition produced by compounds determined, from which the concentration required to inhibit the reaction by 50% (IC_{50}) was calculated according to the scheme below:

Initial velocity in each well was converted to fractional activity by Equation 1:

Equation 1:

Fractional activity = (Initial rate at inhibitor concentration [X] / Initial rate at inhibitor concentration zero) * 100

Then, IC_{50} was determined by fitting the data of fractional activity and inhibitor concentration to a 4-parameter logistic curve, using Equation 2:

Equation 2:

$$V = V_{min} + [V_{max} - V_{min}] / [1 + (X / IC_{50}) \text{ Hillslope }]$$

where:
V is the fractional activity of the enzyme in the presence of inhibitor at concentration [X];
[X] is the inhibitor concentration;
V_{min} is the minimum of Y observed at high inhibitor concentration;
V_{max} is the maximum of Y observed at zero inhibitor concentration; and
Hillslope is the slope of the dose-response (inhibition) curve.

Biological Data - Der p 1 Enzyme Assay

The following compounds were studied using the Der p 1 assay described above:
ALD-001 to ALD-073.

All of the compounds were found to have a Der p 1 IC_{50} of less than 20 μM.

The following compounds were found to have a Der p 1 IC_{50} of less than 2 μM:

ALD-001, ALD-002, ALD-003, ALD-005, ALD-006, ALD-007, ALD-008, ALD-009, ALD-010, ALD-011, ALD-012, ALD-013, ALD-014, ALD-015, ALD-016, ALD-017, ALD-018, ALD-019, ALD-021, ALD-022, ALD-023, ALD-024, ALD-026, ALD-027, ALD-028, ALD-029, ALD-030, ALD-031, ALD-032, ALD-033, ALD-034, ALD-035, ALD-036, ALD-037, ALD-038, ALD-039, ALD-040, ALD-041, ALD-042, ALD-043, ALD-044, ALD-045, ALD-046, ALD-047, ALD-048, ALD-049, ALD-050, ALD-051, ALD-052, ALD-053, ALD-054, ALD-055, ALD-056, ALD-057, ALD-058, ALD-059, ALD-060, ALD-061, ALD-062, ALD-063, ALD-064, ALD-065, ALD-066, ALD-067, ALD-068, ALD-069, ALD-070, ALD-071.

The following compounds were found to have a Der p 1 IC_{50} of less than 200 nM:

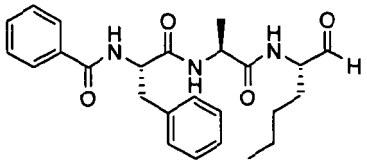
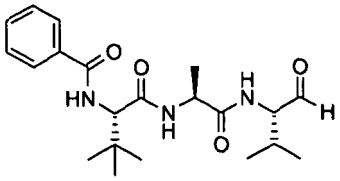
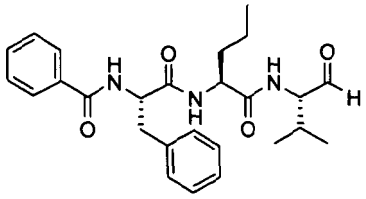
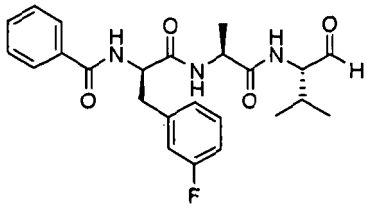
ALD-001, ALD-002, ALD-005, ALD-006, ALD-007, ALD-008, ALD-010, ALD-011, ALD-012, ALD-013, ALD-014, ALD-015, ALD-016, ALD-017, ALD-018, ALD-019, ALD-022, ALD-023, ALD-024, ALD-026, ALD-027, ALD-029, ALD-030, ALD-031, ALD-032, ALD-033, ALD-034, ALD-035, ALD-036, ALD-037, ALD-039, ALD-040, ALD-041, ALD-042, ALD-043, ALD-044, ALD-045, ALD-046, ALD-047, ALD-048, ALD-049, ALD-050, ALD-051, ALD-052, ALD-053, ALD-054, ALD-055, ALD-056, ALD-057, ALD-058, ALD-059, ALD-060, ALD-061, ALD-062, ALD-063, ALD-064, ALD-065, ALD-066, ALD-067, ALD-068, ALD-069, ALD-070, ALD-071.

The following compounds were found to have a Der p 1 IC_{50} of less than 20 nM:

ALD-001, ALD-002, ALD-005, ALD-007, ALD-008, ALD-010, ALD-011, ALD-012, ALD-013, ALD-015, ALD-016, ALD-018, ALD-022, ALD-026, ALD-029, ALD-030, ALD-032, ALD-034, ALD-035, ALD-037, ALD-039, ALD-040, ALD-042, ALD-043, ALD-045, ALD-051, ALD-052, ALD-053, ALD-055, ALD-058, ALD-060, ALD-062, ALD-063, ALD-064, ALD-065, ALD-071.

Data for several ALD compounds are shown in the following table.

Table 1
Der p 1 IC_{50} Data for ALD Compounds

Code	Compound	Der p 1 IC_{50} (nM)
ALD-001		4
ALD-035		8
ALD-047		21
ALD-043		18

Biological Methods - Allergen challenge studies in vivo

Animal identification and randomisation:

The studies were performed in male Brown Norway rats (approximate weight 350 g at time of allergen challenge) obtained from Harlan UK Ltd. Each animal was allocated a

unique identification number after sensitisation, identified by a waterproof tail mark, and randomly assigned to a treatment group. All studies were conducted in accordance with the Animals (Scientific Procedures) Act 1986, with UK Home Office Guidance on the implementation of the Act and with all applicable Codes of Practice for the care and housing of laboratory animals.

Housing and environment:

Animals were initially housed within an air-conditioned colony room within the animal house until being transferred to a procedure room. Animals were caged in groups of up to 5. During the study, the rooms and cages were cleaned at regular intervals to maintain hygiene. The rooms were illuminated by fluorescent lights set to give a 12 hour light-dark cycle (on 07.00, off 19.00), as recommended in the Home Office Animals (Scientific Procedures) Act 1986. Air temperature (target temperature 21°C ± 2°C) and relative humidity (which was not controlled) was measured during acclimatisation and the in-life phase. A diet of RM-1 (Special Diets Services, Witham, UK) and mains tap water was offered ad libitum.

Sensitization procedure to House Dust Mite (HDM) allergen:

A mixture of HDM allergens was harvested from a laboratory culture of Dermatophagoides pteronyssinus. Allergen dose was standardized according to the Der p 1 content of the mixture as determined by an ELISA measurement referenced against the IUIS standard for Der p 1. The allergen sensitization dose for each animal on each day contained 10 µg Der p 1. Freeze-dried stocks of HDM allergen mixture stored at -20°C were reconstituted in their original volumes of 0.22 µm filter-sterilised de-ionised water containing 5 mM L-cysteine and 0.05% v/v Tween 20 and diluted to working concentration using sterile Dulbecco's phosphate buffered saline containing 5 mM L-cysteine and 0.05% v/v Tween 20. Animals were sensitized to a mixture of all HDM allergens on Days 0, 7, and 14 by intraperitoneal injection (0.5 mL) of the mixture formulated as described above.

Physiological recordings:

On Day 21 of the sensitization and challenge protocol, rats were anaesthetised with pentobarbitone (100 mg/kg, i.p.) and ventilated via a tracheal cannula (approximately 7 mL/kg, 1 Hz) with a mixture of air and oxygen (50:50). The anaesthetised, ventilated animals were paralysed with norcuron (4 mg/kg, i.m.). Ventilation was monitored by a flow transducer (Fleisch, type 0000) in-line with the respiratory pump. Coincident pressure changes within the thorax were monitored directly via an intrathoracic cannula, so that the pressure difference between the trachea and thorax could be measured and

displayed. From these measurements of flow and differential pressure, both airways resistance (RL) and dynamic compliance (Cdyn) were calculated for each respiratory cycle on a digital electronic respiratory analyser (PMS, Mumed Ltd, UK). Blood pressure and heart rate were recorded from the carotid artery by means of a transducer.

Drug delivery and allergen challenge:

Drugs were dissolved in DMSO as 10 mM stock solutions and then diluted in sterile saline (Baxter Healthcare, Berkshire, UK) for use in treatment. Drug solutions (100 µL of a 40 µM solution) were administered by the intra-tracheal (i.t.) route using a Penn Century IA-1C sapphire orifice aerosoliser fitted to an FMJ-250 high pressure syringe (Penn Century, Philadelphia, PA, USA). For these studies, the tip of the IA-1C aerosoliser was inserted inside the tracheal cannula and the volume of drug delivered regulated by means of volumetric stops on the syringe plunger. This combination of aerosoliser and syringe generates a plume of liquid with droplets 16-22 µm in mass median aerodynamic diameter.

Allergen challenge was with a mixture of HDM allergens containing a 10 µg dose of Der p 1. Freeze-dried stocks of HDM allergen mixture stored at -20°C were reconstituted in their original volumes of 0.22 µm filter-sterilised deionised water containing 5 mM L-cysteine and 0.05% v/v Tween 20 and diluted to working concentration using sterile Dulbecco's phosphate buffered saline containing 5 mM L-cysteine and 0.05% v/v Tween 20. Allergen challenge (100 µL) was performed by the intratracheal (i.t.) route using a Penn Century aerosoliser as described above.

Study Design:

The study design comprised groups of 12 animals which had been actively sensitized to HDM allergens as described above. On day 21 of the study, the groups received two separate challenges with HDM allergens by the intratracheal (i.t.) route. In all cases, the effect of challenge 1 had fully resolved before the second challenge was made. At an interval of 2 hours before the second allergen challenge, animals received a dose of test compounds.

Data analysis:

To evaluate the effect of allergen challenge and its modification by test compounds, lung function parameters were measured prior to allergen delivery (baseline) and at the peak response. The numerical difference in the lung function parameter (e.g., change in airway resistance) was recorded as the magnitude of the allergen challenge. This process was repeated after the animals had been dosed with test compound. Statistical

analysis of the responses before and after administration of the test compound was used to determine if the compound exerted a significant effect. It was found by experiment to be equally valid to conduct these statistical comparisons either by comparing the change in the lung function parameter per se before and after treatment with test compound, or by expressing the magnitude of the second allergen challenge as a percentage of the first challenge and performing the statistical evaluation using the transformed data.

Biological Data - Allergen challenge studies in vivo

Validation of study design

Figure 1 is a bar graph of the magnitude of response following Challenge 1 (left) and Challenge 2 (right), expressed as a percentage of the magnitude of the response following Challenge 1.

Figure 1 illustrates the results obtained when a group of rats sensitized to HDM allergens were subjected to two successive challenges with the same allergen mixture by the intratracheal (i.t.) route on Day 21 after sensitization was commenced. The average median response for challenge 1 was determined and defined as 100%. In each rat, the magnitude of the second response was then determined and expressed as the percentage of the response to challenge 1. For the purposes of illustration of the second challenge response, the data are shown as the median and interquartile range determined in 12 animals.

These data indicate that the magnitude of the second challenge is similar to that seen in the first challenge, enabling the modulating effect of a drug administered between the two treatments to be determined.

Effects of compounds on acute allergic bronchoconstriction:

Compound ALD-035 was studied using *in vivo* allergen challenge methods described above.

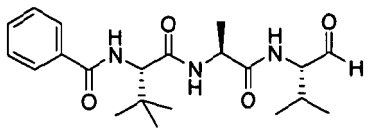
Code	Structure
ALD-035	

Figure 2 is a bar graph showing the percentage inhibition of the acute bronchoconstrictor response to allergen following administration of Compound ALD-035 at 15, 30 and 60 minutes prior to allergen challenge.

Groups of 8-9 rats were challenged by the i.t. route with a mixture of house dust mite allergens (Challenge 1) and the acute bronchoconstrictor response in each animal declared as 100%. Compound ALD-035 was dosed by the i.t. route 15, 30 or 60 min prior to a second allergen challenge. The resulting acute bronchoconstrictor response was measured and the percentage inhibition of Challenge 1 calculated for each animal. Data show the mean percentage inhibition of the control allergen response (open columns), with error bars indicating the standard error of the mean. Statistical significance was evaluated by one-way ANOVA and pairwise multiple comparisons made using the Student-Newman-Keuls procedure. Asterisks denote significant inhibition ($P<0.05$) compared to the control allergen challenge. For skilled persons, inhibition of acute bronchoconstriction following allergen provocation in experimental models such as this is known to be indicative of a clinically beneficial effect in asthma.

* * *

The foregoing has described the principles, preferred embodiments, and modes of operation of the present invention. However, the invention should not be construed as limited to the particular embodiments discussed. Instead, the above-described embodiments should be regarded as illustrative rather than restrictive, and it should be appreciated that variations may be made in those embodiments by workers skilled in the art without departing from the scope of the present invention.

REFERENCES

A number of patents and publications are cited herein in order to more fully describe and disclose the invention and the state of the art to which the invention pertains. Full citations for these references are provided below.

Each of these references is incorporated herein by reference in its entirety into the present disclosure, to the same extent as if each individual reference was specifically and individually indicated to be incorporated by reference.

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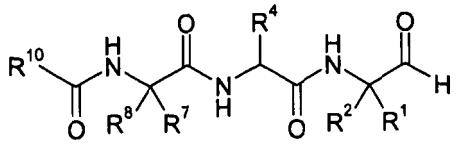
CLAIMS

1. A compound selected from compounds of the following formula, and pharmaceutically acceptable salts, hydrates, and solvates thereof:



wherein:

$-R^1$ is independently -H or $-R^{1A}$;
$-R^{1A}$ is independently saturated aliphatic C_{1-6}alkyl, phenyl, or benzyl;

$-R^2$ is independently -H;

$-R^4$ is independently -Me;

$-R^7$ is independently $-R^{7A}$ or $-R^{7B}$;

$-R^{7A}$ is independently saturated aliphatic C_{1-6}alkyl;

$-R^{7B}$ is independently $-L^{7B1}-R^{7BB}$, $-R^{7BB}$, $-L^{7B2}-O-R^{7BB}$, or $-L^{7B2}-O-L^{7B1}-R^{7BB}$;
$-L^{7B1}-$ is independently saturated aliphatic C_{1-3}alkylene;
$-L^{7B2}-$ is independently saturated aliphatic C_{1-3}alkylene;
$-R^{7BB}$ is independently $-R^{7BB1}$, $-R^{7BB2}$, $-R^{7BB3}$, or $-R^{7BB4}$;
$-R^{7BB1}$ is independently phenyl or naphthyl, and is optionally substituted;
$-R^{7BB2}$ is independently C_{5-10}heteroaryl, and is optionally substituted;
$-R^{7BB3}$ is independently C_{3-7}cycloalkyl, and is optionally substituted, or is optionally fused to a benzene ring;
$-R^{7BB4}$ is independently saturated bridged C_{5-10}cycloalkyl, and is optionally substituted;

$-R^8$ is independently -H or $-R^{8A}$;
$-R^{8A}$ is independently saturated aliphatic C_{1-6}alkyl;

or $-R^7$ and $-R^8$, taken together with the carbon atom to which they are attached, form a saturated C_{3-7}cycloalkyl ring, a saturated bridged C_{5-10}cycloalkyl ring, or a non-aromatic C_{3-7}heterocyclic ring, which is optionally substituted;

$-R^{10}$ is independently $-R^{10A}$, $-R^{10B}$, $-R^{10C}$, or $-R^{10D}$;
$-R^{10A}$ is independently phenyl or naphthyl, and is optionally substituted;
$-R^{10B}$ is independently C_{5-10}heteroaryl, and is optionally substituted;
$-R^{10C}$ is independently saturated C_{3-7}cycloalkyl, and is optionally substituted; and
$-R^{10D}$ is independently non-aromatic C_{3-10}heterocyclyl, and is optionally substituted.

2. A compound according to claim 1, wherein $-R^1$ is independently $-R^{1A}$.

3. A compound according to claim 1 or 2, wherein $-R^{1A}$, if present, is independently saturated aliphatic C_{1-6}alkyl.

4. A compound according to claim 1 or 2, wherein $-R^{1A}$, if present, is independently saturated aliphatic C_{3-4}alkyl.

5. A compound according to claim 1 or 2, wherein $-R^{1A}$, if present, is independently -iPr.

6. A compound according to claim 1 or 2, wherein $-R^{1A}$, if present, is independently -nBu.

7. A compound according to any one of claims 1 to 6, wherein $-R^7$ is independently $-R^{7A}$.

8. A compound according to any one of claims 1 to 6, wherein $-R^7$ is independently $-R^{7B}$.

9. A compound according to any one of claims 1 to 8, wherein $-R^{7A}$, if present, is independently saturated aliphatic C_{3-4}alkyl.

10. A compound according to any one of claims 1 to 8, wherein $-R^{7A}$, if present, is independently -tBu.

11. A compound according to any one of claims 1 to 10, wherein $-R^{7B}$, if present, is independently $-L^{7B1}-R^{7BB}$.

12. A compound according to any one of claims 1 to 11, wherein $-L^{7B1}-$, if present, is independently $-CH_2-$.

13. A compound according to any one of claims 1 to 12, wherein $-R^{7BB}$, if present, is independently $-R^{7BB1}$.

14. A compound according to any one of claims 1 to 12, wherein $-R^{7BB}$, if present, is independently $-R^{7BB2}$.

15. A compound according to any one of claims 1 to 12, wherein $-R^{7BB}$, if present, is independently $-R^{7BB3}$.

16. A compound according to any one of claims 1 to 12, wherein $-R^{7BB}$, if present, is independently $-R^{7BB4}$.

17. A compound according to any one of claims 1 to 16, wherein $-R^{7BB1}$, if present, is independently phenyl or naphthyl, and is optionally substituted with one or more substituents $-R^{X3}$.

18. A compound according to any one of claims 1 to 16, wherein $-R^{7BB1}$, if present, is independently phenyl or naphthyl, and is optionally substituted with one or more substituents independently selected from -F, -Cl, -Br, -I, -Me, and -Ph.

19. A compound according to any one of claims 1 to 16, wherein $-R^{7BB1}$, if present, is independently phenyl.

20. A compound according to any one of claims 1 to 16, wherein $-R^{7BB1}$, if present, is independently naphthyl.

21. A compound according to any one of claims 1 to 20, wherein $-R^{7BB2}$, if present, is independently C_{5-10}heteroaryl, and is optionally substituted with one or more substituents $-R^{X3}$.

22. A compound according to any one of claims 1 to 20, wherein $-R^{7BB2}$, if present, is independently C_{5-6}heteroaryl.

23. A compound according to any one of claims 1 to 20, wherein $-R^{7BB2}$, if present, is independently pyridyl, and is optionally substituted with one or more substituents $-R^{X3}$.

24. A compound according to any one of claims 1 to 20, wherein $-R^{7BB2}$, if present, is independently pyridyl.

25. A compound according to any one of claims 1 to 24, wherein $-R^{7BB3}$, if present, is independently C_{3-7}cycloalkyl, and is optionally substituted with one or more substituents $-R^{X2}$, or is optionally fused to a benzene ring.

26. A compound according to any one of claims 1 to 24, wherein $-R^{7BB3}$, if present, is independently cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or cycloheptyl.

27. A compound according to any one of claims 1 to 24, wherein $-R^{7BB3}$, if present, is independently cyclohexyl.

28. A compound according to any one of claims 1 to 27, wherein $-R^{7BB4}$, if present, is independently saturated bridged C_{5-10}cycloalkyl, and is optionally substituted with one or more substituents $-R^{X2}$.

29. A compound according to any one of claims 1 to 27, wherein $-R^{7BB4}$, if present, is independently adamantyl.

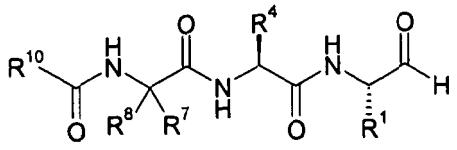
30. A compound according to any one of claims 1 to 29, wherein $-R^{8}$ is independently -H.

31. A compound according to any one of claims 1 to 29, wherein $-R^{8}$ is independently $-R^{8A}$.

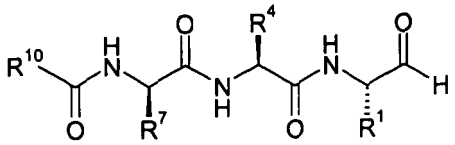
32. A compound according to any one of claims 1 to 31, wherein $-R^{8A}$, if present, is independently -Me.

33. A compound according to any one of claims 1 to 6, wherein $-R^{7}$ and $-R^{8}$, taken together with the carbon atom to which they are attached, form cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.

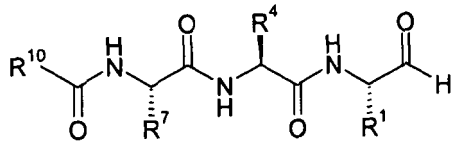
34. A compound according to any one of claims 1 to 33, wherein the carbon atom to which $-R^{4}$ is attached, and the carbon atom to which $-R^{1}$ and $-R^{2}$ is attached, have the configurations shown in the following formula:



35. A compound according to any one of claims 1 to 30, wherein $-R^8$ is -H, and wherein the carbon atom to which $-R^4$ is attached, the carbon atom to which $-R^1$ and $-R^2$ is attached, and the carbon atom to which $-R^7$ and $-R^8$ are attached, have the configurations shown in the following formula:



36. A compound according to any one of claims 1 to 30, wherein $-R^8$ is -H, and wherein the carbon atom to which $-R^4$ is attached, the carbon atom to which $-R^1$ and $-R^2$ is attached, and the carbon atom to which $-R^7$ and $-R^8$ are attached, have the configurations shown in the following formula:



37. A compound according to any one of claims 1 to 36, wherein $-R^{10}$ is independently $-R^{10A}$.

38. A compound according to any one of claims 1 to 36, wherein $-R^{10}$ is independently $-R^{10B}$.

39. A compound according to any one of claims 1 to 36, wherein $-R^{10}$ is independently $-R^{10D}$.

40. A compound according to any one of claims 1 to 39, wherein $-R^{10A}$, if present, is independently phenyl or naphthyl, and is optionally substituted with one or more substituents $-R^{X3}$.

41. A compound according to any one of claims 1 to 39, wherein $-R^{10A}$, if present, is independently phenyl, and is optionally substituted with one or more substituents $-R^{X3}$.

42. A compound according to any one of claims 1 to 39, wherein -R^{10A}, if present, is independently phenyl, and is optionally substituted with one or more substituents independently selected from:
-F, -Cl, -Br, -I,
C_{1-4}alkyl, -O-C_{1-4}alkyl,
-CF_3, -OCF_3,
phenyl, -O-phenyl,
-NH_2, -NH(C_{1-4}alkyl), -N(C_{1-4}alkyl)$_2$,
-NH(C=O)(C_{1-4}alkyl),
pyrrolidino, piperidino, morpholino, piperizino, N-(C_{1-4}alkyl)-piperizino,
-O-CH_2CH_2-NH_2, -O-CH_2CH_2-NH(C_{1-4}alkyl), -O-CH_2CH_2-N(C_{1-4}alkyl)$_2$,
-O-CH_2CH_2-pyrrolidino, -O-CH_2CH_2-piperidino, -O-CH_2CH_2-morpholino,
-O-CH_2CH_2-piperizino, -O-CH_2CH_2-{N-(C_{1-4}alkyl)-piperizino},
-O-CH_2-imidazol-2-yl, and -O-CH_2-{N-(C_{1-4}alkyl)-imidazol-2-yl}.

43. A compound according to any one of claims 1 to 39, wherein -R^{10A}, if present, is independently phenyl.

44. A compound according to any one of claims 1 to 43, wherein -R^{10B}, if present, is independently C_{5-10}heteroaryl, and is optionally substituted with one or more substituents -R^{X3}.

45. A compound according to any one of claims 1 to 43, wherein -R^{10B}, if present, is independently C_{5-6}heteroaryl, and is optionally substituted with one or more substituents -R^{X3}.

46. A compound according to any one of claims 1 to 43, wherein -R^{10B}, if present, is independently pyridyl, and is optionally substituted with one or more substituents -R^{X3}.

47. A compound according to any one of claims 1 to 43, wherein -R^{10B}, if present, is independently pyridyl, and is optionally substituted with one or more substituents independently selected from:
-NH_2, -NH(C_{1-4}alkyl), -N(C_{1-4}alkyl)$_2$,
pyrrolidino, piperidino, morpholino, piperizino, N-(C_{1-4}alkyl)-piperizino,
-NHC(=O)(C_{1-4}alkyl), and
=O.

48. A compound according to any one of claims 1 to 43, wherein -R^{10B}, if present, is independently benzothiazolyl, quinolinyl, or isoquinolinyl.

49. A compound according to any one of claims 1 to 48, wherein $-R^{10C}$, if present, is independently saturated C_{3-7}cycloalkyl, and is optionally substituted with one or more substituents $-R^{X2}$.

50. A compound according to any one of claims 1 to 48, wherein $-R^{10C}$, if present, is independently cyclopentyl or cyclohexyl.

51. A compound according to any one of claims 1 to 50, wherein $-R^{10D}$, if present, is independently non-aromatic C_{3-10}heterocyclyl, and is optionally substituted with one or more substituents $-R^{X2}$.

52. A compound according to any one of claims 1 to 50, wherein $-R^{10D}$ is independently piperidin-4-yl, and is optionally substituted with one or more substituents independently selected from C_{1-4}alkyl.

53. A compound according to any one of claims 1 to 52, wherein each $-R^{X2}$, if present, is independently selected from:

-F, -Cl, -Br, -I, $-R^T$, phenyl, -OH, $-OR^T$, $-C(=O)R^T$, $-NH_2$, $-NHR^T$, $-NR^T_2$, pyrrolidino, piperidino, morpholino, piperizino, N-(C_{1-4}alkyl)-piperizino, $-NHC(=O)R^T$, and $-NR^TC(=O)R^T$;

wherein each $-R^T$ is independently saturated aliphatic C_{1-6}alkyl, phenyl, or $-CH_2$-phenyl;

wherein each phenyl is optionally substituted with one or more groups selected from: -F, -Cl, -Br, -I, $-R^{TT}$, $-CF_3$, -OH, $-OR^{TT}$, or $-OCF_3$, wherein each $-R^{TT}$ is independently saturated aliphatic C_{1-4}alkyl.

54. A compound according to claim 53, wherein each $-R^T$ is independently saturated aliphatic C_{1-4}alkyl.

55. A compound according to any one of claims 1 to 54, wherein each $-R^{X3}$, if present, is independently selected from:

-F, -Cl, -Br, -I,

$-R^V$,

$-CH=CH_2$, $-C\equiv CH$, cyclopropyl,

$-CF_3$, $-CHF_2$, $-OCF_3$, $-OCHF_2$,

-CN,

$-NO_2$,

-OH, $-OR^V$,

$-L^V$-OH, $-L^V-OR^V$,

$-O-L^V$-OH, $-O-L^V-OR^V$,

$-NH_2$, $-NHR^V$, $-NR^V_2$,

pyrrolidino, piperidino, morpholino,
piperizino, N-(C_{1-4}alkyl)-piperizino,
-L^V-NH_2, -L^V-NHR^V, -L^V-NR^V_2,
-L^V-pyrrolidino, -L^V-piperidino, -L^V-morpholino,
-L^V-piperizino, -L^V-{N-(C_{1-4}alkyl)-piperizino},
-L^V-imidazol-2-yl, -L^V-{N-(C_{1-4}alkyl)-imidazol-2-yl},
-O-L^V-NH_2, -O-L^V-NHR^V, -O-L^V-NR^V_2,
-O-L^V-pyrrolidino, -O-L^V-piperidino, -O-L^V-morpholino,
-O-L^V-piperizino, -O-L^V-{N-(C_{1-4}alkyl)-piperizino},
-O-L^V-imidazol-2-yl, -O-L^V-{N-(C_{1-4}alkyl)-imidazol-2-yl},
-NHC(=O)R^V, -NR^VC(=O)R^V,
-C(=O)R^V,
-C(=O)OH, -C(=O)OR^V,
-C(=O)NH_2, -C(=O)NHR^V, -C(=O)NR^V_2,
-C(=O)-pyrrolidino, -C(=O)-piperidino, -C(=O)-morpholino,
-C(=O)-piperizino, -C(=O)-{N-(C_{1-4}alkyl)-piperizino}-,
-$NHC(=O)NH_2$, -NHC(=O)NHR^V, -NHC(=O)NR^V_2,
-NHC(=O)-pyrrolidino, -NHC(=O)-piperidino, -NHC(=O)-morpholino,
-NHC(=O)-piperizino, -NHC(=O)-{N-(C_{1-4}alkyl)-piperizino}-,
-$S(=O)_2R^V$,
-$S(=O)_2NH_2$, -$S(=O)_2NHR^V$, -$S(=O)_2NR^V_2$, and
=O;

wherein each -L^V- is independently saturated aliphatic C_{2-4}alkylene;

wherein each -R^V is independently saturated aliphatic C_{1-6}alkyl, phenyl, -CH_2-phenyl, C_{5-6}heteroaryl, or -CH_2-C_{5-6}heteroaryl;

wherein each phenyl is optionally substituted with one or more groups selected from: -F, -Cl, -Br, -I, -R^{VV}, -CF_3, -OH, -OR^{VV}, or -OCF_3;

wherein each C_{5-6}heteroaryl is optionally substituted with one or more groups selected from: -F, -Cl, -Br, -I, -R^{VV}, -CF_3, -OH, -OR^{VV}, or -OCF_3;

wherein each -R^{VV} is independently saturated aliphatic C_{1-4}alkyl;

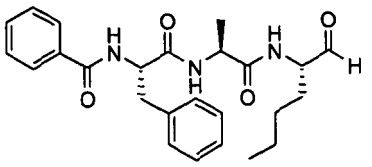
and additionally, two adjacent groups -R^{X3} may together form -OCH_2O-, -OCH_2CH_2O-, -CH_2OCH_2- or -OCH_2CH_2-;

and additionally, two adjacent groups -R^{X3} may, together with the ring atoms to which they are attached, form a C_{5-7}carbocyclic ring or a C_{5-7}heterocyclic ring.

56. A compound according to claim 55, wherein each $-R^{X3}$, if present, is independently selected from:
-F, -Cl, -Br, -I,
$-R^V$,
-OH, $-OR^V$,
$-NH_2$, $-NHR^V$, $-NR^V_2$,
pyrrolidino, piperidino, morpholino,
piperizino, and N-(C_{1-4}alkyl)-piperizino.

57. A compound according to claim 55 or 56, wherein each $-R^V$ is independently saturated aliphatic C_{1-4}alkyl.

58. A compound according to claim 1, selected from the following compounds and pharmaceutically acceptable salts, hydrates, and solvates thereof:



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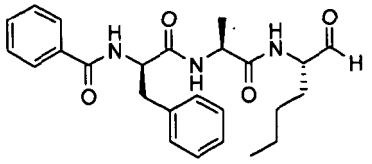

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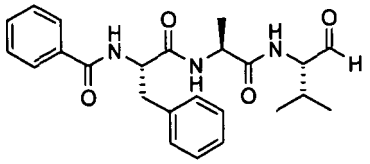

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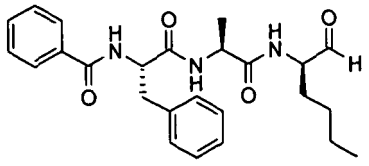

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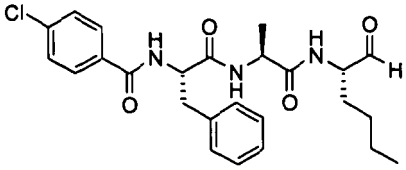

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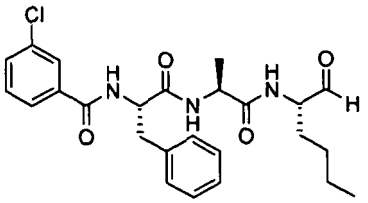

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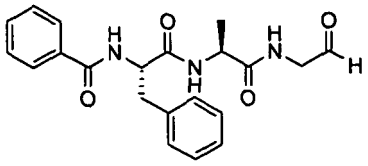

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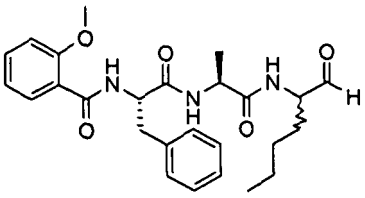

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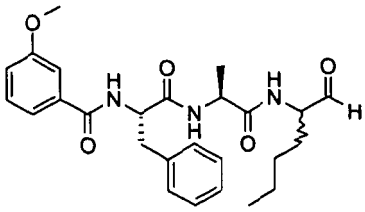

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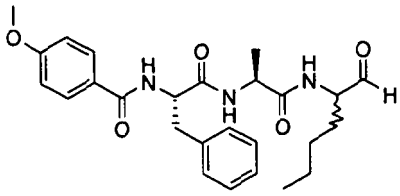

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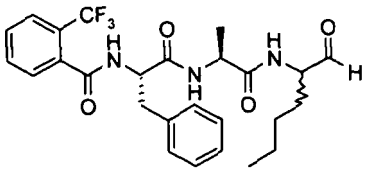

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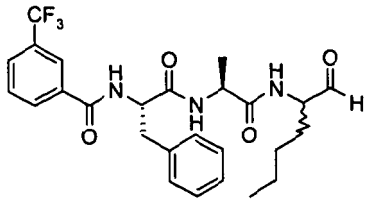

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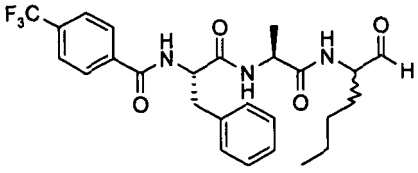

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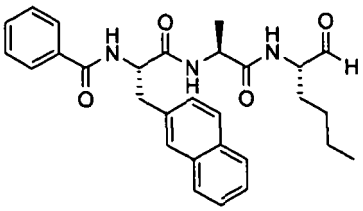

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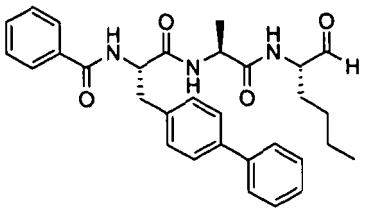

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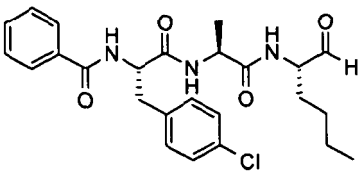

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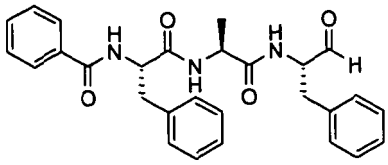

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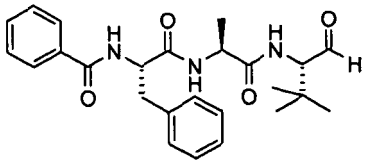

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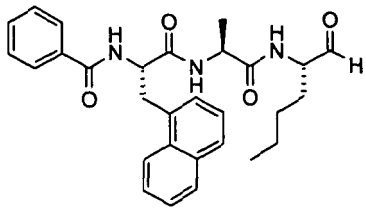

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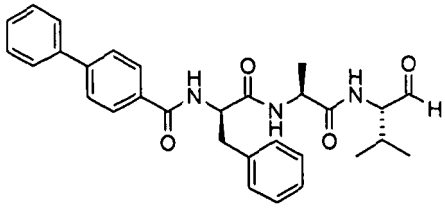

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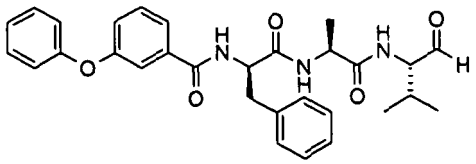

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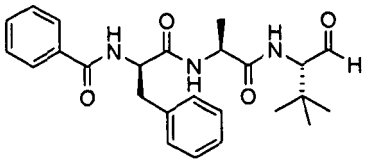

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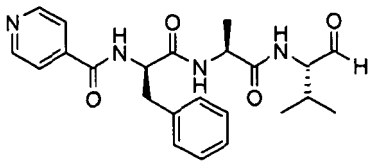

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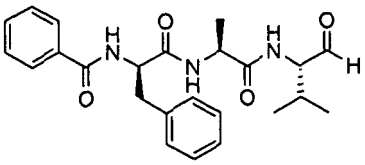

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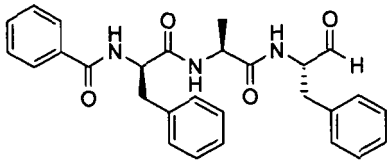

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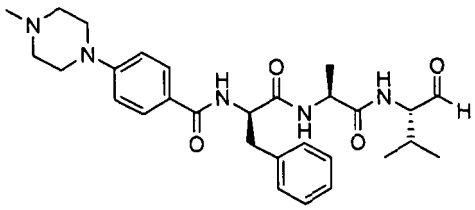

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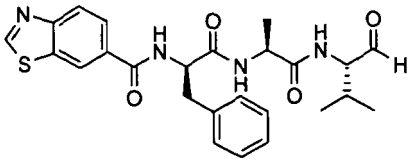

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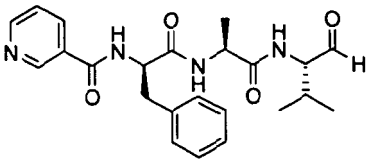

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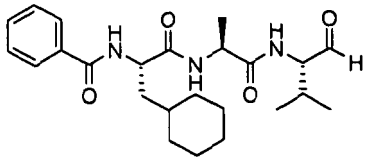

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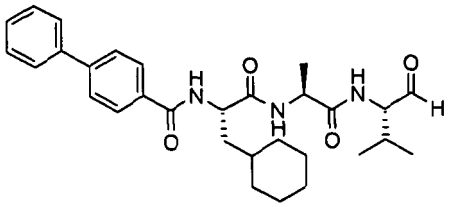

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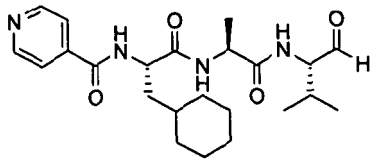

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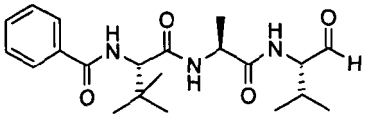

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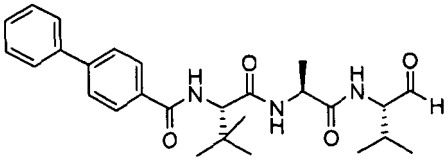

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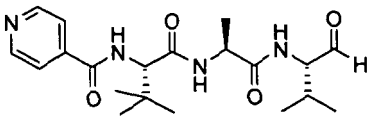

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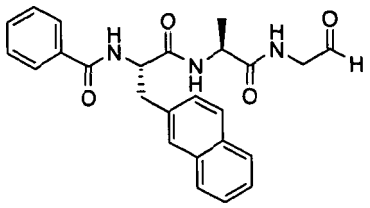

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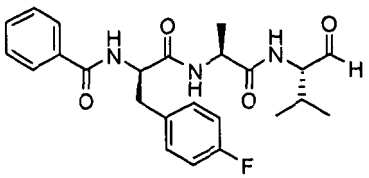

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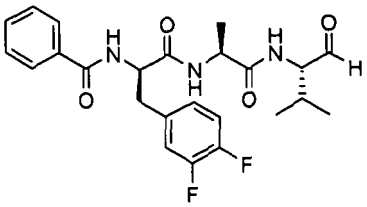

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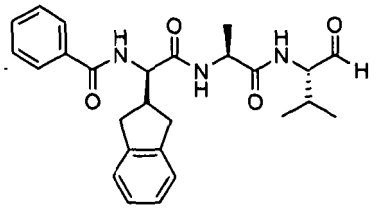

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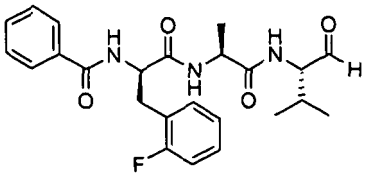

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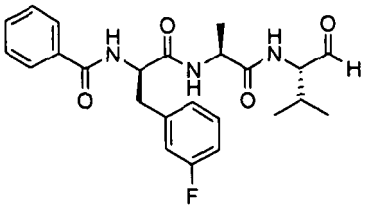

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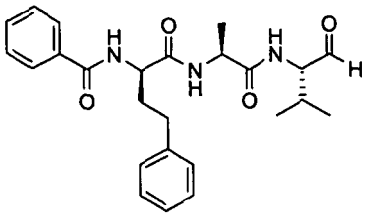

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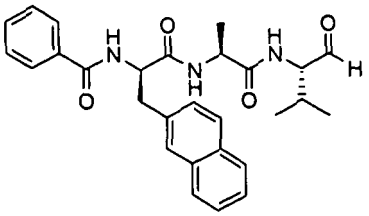

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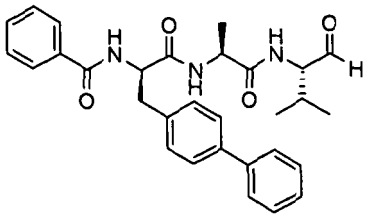

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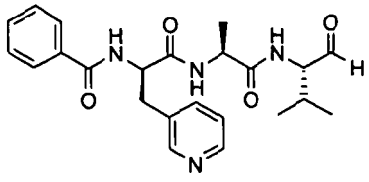

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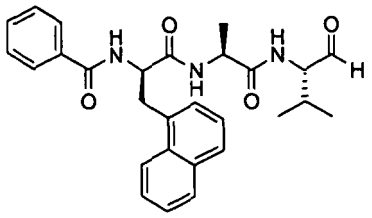

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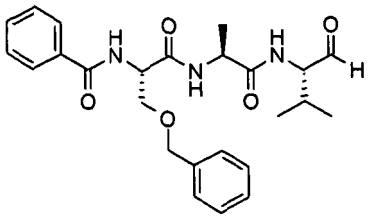

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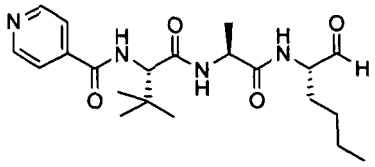

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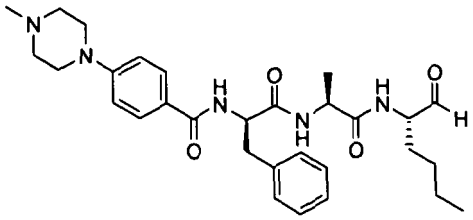

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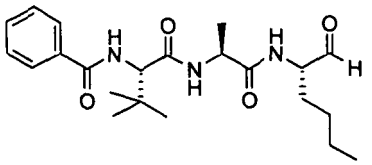

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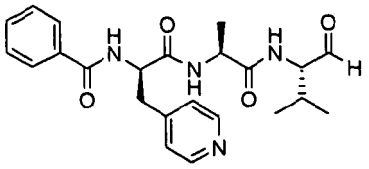

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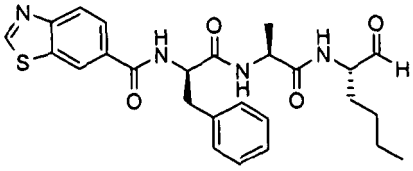

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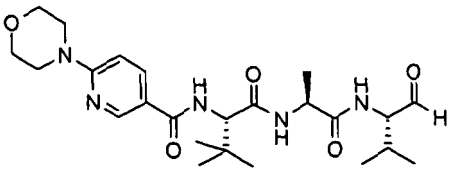

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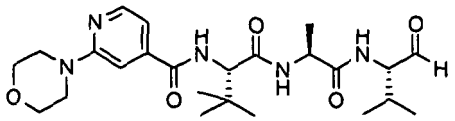

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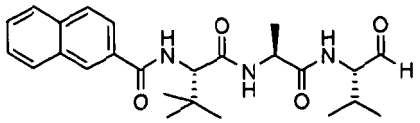

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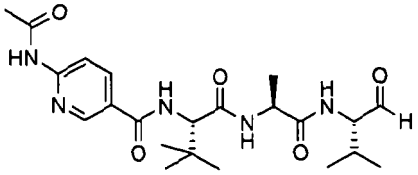

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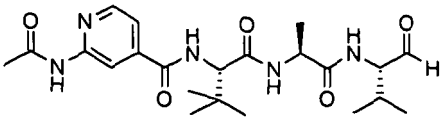

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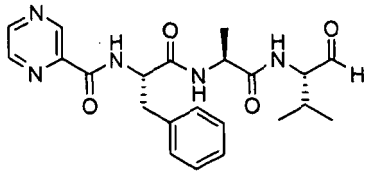

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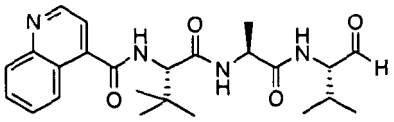

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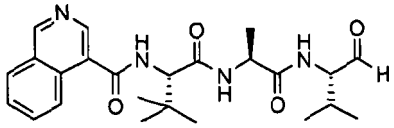

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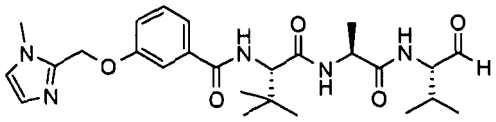

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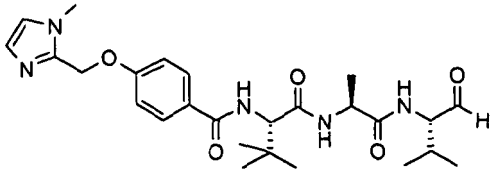

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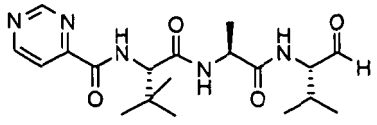

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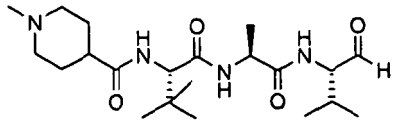

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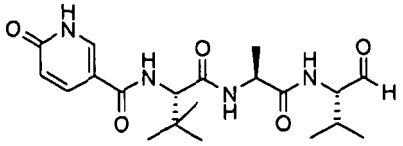

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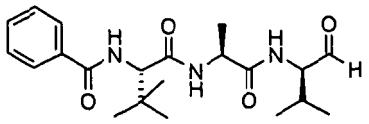

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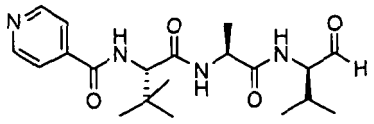

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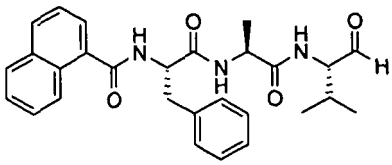


(ALD-071).

59. A composition comprising a compound according to any one of claims 1 to 58, and a pharmaceutically acceptable carrier, diluent, or excipient.

60. A method of preparing a composition comprising admixing a compound according to any one of claims 1 to 58 and a pharmaceutically acceptable carrier, diluent, or excipient.

61. A compound according to claim 1, for use in a method of treatment of the human or animal body by therapy.

62. A compound according to any one of claims 1 to 58, for use in a method of treatment of:

asthma, for example, atopic asthma; allergic asthma; atopic bronchial IgE-mediated asthma; bronchial asthma; extrinsic asthma; allergen-induced asthma; allergic asthma exacerbated by respiratory virus infection; infective asthma; infective asthma caused by bacterial infection; infective asthma caused by fungal infection; infective asthma caused by protozoal infection; or infective asthma caused by viral infection;

bronchial hyperreactivity associated with asthma; or bronchial hyperresponsiveness associated with asthma;

airway remodelling associated with an allergic lung disease, for example, airway remodelling associated with asthma;

asthma co-presented with a chronic obstructive lung disease, for example, asthma co-presented with emphysema; or asthma co-presented with chronic bronchitis;

rhinitis, for example, allergic rhinitis; perennial rhinitis; persistent rhinitis; or IgE-mediated rhinitis;

allergic conjunctivitis, for example, IgE-mediated conjunctivitis;

atopic dermatitis;

an allergic condition which is triggered by dust mites;

an allergic condition which is triggered by dust mite Group 1 peptidase allergen (e.g., Der p 1, Der f 1, Eur m 1); or

canine atopy.

63. Use of a compound according to any one of claims 1 to 58, in the manufacture of a medicament for the treatment of:

asthma, for example, atopic asthma; allergic asthma; atopic bronchial IgE-mediated asthma; bronchial asthma; extrinsic asthma; allergen-induced asthma; allergic asthma exacerbated by respiratory virus infection; infective asthma; infective asthma caused by bacterial infection; infective asthma caused by fungal infection; infective asthma caused by protozoal infection; or infective asthma caused by viral infection;

bronchial hyperreactivity associated with asthma; or bronchial hyperresponsiveness associated with asthma;

airway remodelling associated with an allergic lung disease, for example, airway remodelling associated with asthma;

asthma co-presented with a chronic obstructive lung disease, for example, asthma co-presented with emphysema; or asthma co-presented with chronic bronchitis;

rhinitis, for example, allergic rhinitis; perennial rhinitis; persistent rhinitis; or IgE-mediated rhinitis;

allergic conjunctivitis, for example, IgE-mediated conjunctivitis;

atopic dermatitis;

an allergic condition which is triggered by dust mites;

an allergic condition which is triggered by dust mite Group 1 peptidase allergen (e.g., Der p 1, Der f 1, Eur m 1); or

canine atopy.

64. A method of treatment, comprising administering to a subject in need of treatment a therapeutically-effective amount of a compound according to any one of claims 1 to 58, wherin the treatment of treatment of:

asthma, for example, atopic asthma; allergic asthma; atopic bronchial IgE-mediated asthma; bronchial asthma; extrinsic asthma; allergen-induced asthma; allergic asthma exacerbated by respiratory virus infection; infective asthma; infective asthma caused by bacterial infection; infective asthma caused by fungal infection; infective asthma caused by protozoal infection; or infective asthma caused by viral infection;

bronchial hyperreactivity associated with asthma; or bronchial hyperresponsiveness associated with asthma;

airway remodelling associated with an allergic lung disease, for example, airway remodelling associated with asthma;

asthma co-presented with a chronic obstructive lung disease, for example, asthma co-presented with emphysema; or asthma co-presented with chronic bronchitis;

rhinitis, for example, allergic rhinitis; perennial rhinitis; persistent rhinitis; or IgE-mediated rhinitis;

allergic conjunctivitis, for example, IgE-mediated conjunctivitis;

atopic dermatitis;

an allergic condition which is triggered by dust mites;

an allergic condition which is triggered by dust mite Group 1 peptidase allergen (e.g., Der p 1, Der f 1, Eur m 1); or

canine atopy.

65. A compound according to claim 62, use according to claim 63, or a method according to claim 64, wherein the treatment further comprises treatment with one or more additional therapeutic agents selected from agents used, or likely to be used, in the treatment of a respiratory disease.

66. A method of inhibiting a dust mite Group 1 peptidase allergen (e.g., Der p 1, Der f 1, Eur m 1), *in vitro* or *in vivo,* comprising contacting a dust mite Group 1 peptidase allergen (e.g., Der p 1, Der f 1, Eur m 1) with an effective amount of a compound according to any one of claims 1 to 58.

67. A method of inhibiting a dust mite Group 1 peptidase allergen (e.g., Der p 1, Der f 1, Eur m 1) in a cell, *in vitro* or *in vivo,* comprising contacting the cell with an effective amount of a compound according to any one of claims 1 to 58.

68. A compound according any one of claims 1 to 58, for use as an acaricide.

69. A composition comprising a compound according to any one of claims 1 to 58, for use as an acaricide.

70. An acaricide composition comprising a compound according to any one of claims 1 to 58.

71. Use of a compound according to any one of claims 1 to 58 as an acaricide.

72. A method of killing mites (e.g., dust mites), comprising exposing said mites to an effective amount of a compound according to any one of claims 1 to 58.

73. A method of controlling (e.g., limiting) a mite (e.g., dust mite) population comprising exposing mites to an effective amount of a compound according to any one of claims 1 to 58.

FIGURE 1

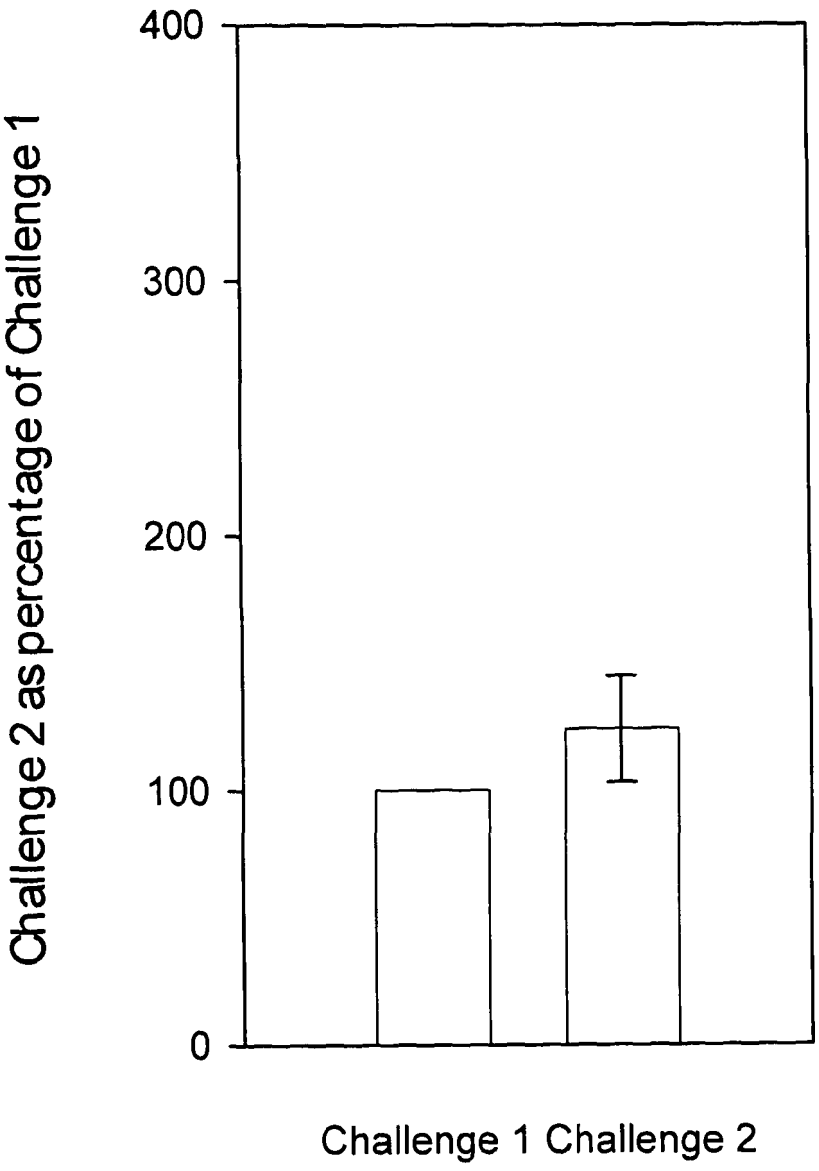
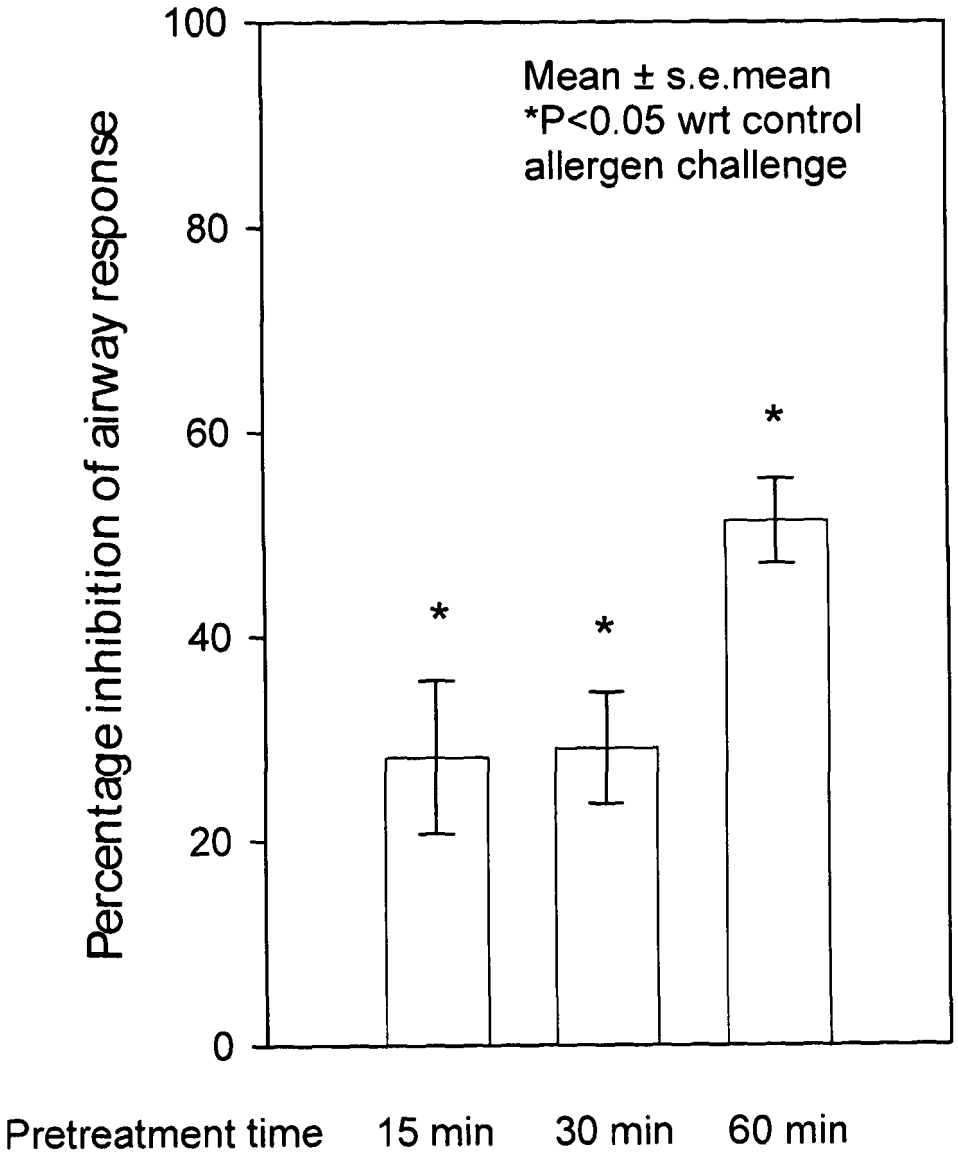

400
300
200
100
0
Challenge 2 as percentage of Challenge 1
Challenge 1 Challenge 2

FIGURE 2


100
80
60
40
20
0
Percentage inhibition of airway response
Mean ± s.e.mean
*P<0.05 wrt control
allergen challenge
*
*
*
Pretreatment time
15 min
30 min
60 min

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2011/001011

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07K5/06 A61K38/05 A61P33/14
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MARTIN J. O'DONNELL ET AL: "UPS on Weinreb Resin: A Facile Solid-Phase Route to Aldehyde and Ketone Derivatives of "Unnatural" Amino Acids and Peptides", JOURNAL OF COMBINATORIAL CHEMISTRY, vol. 2, no. 2, 1 March 2000 (2000-03-01), pages 172-181, XP55005944, ISSN: 1520-4766, DOI: 10.1021/cc990071y compounds 15e-h -----	1,2,7,8, 11-13, 17-19, 30, 34-37, 40-43, 68-70
A	WO 97/04004 A1 (PEPTIDE THERAPEUTICS LTD [GB]; JOHNSON TONY [GB]; HART TERRANCE [GB];) 6 February 1997 (1997-02-06) claim 20; compounds 1-40 -----	1-73

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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Date of the actual completion of the international search	Date of mailing of the international search report
5 September 2011	12/09/2011

Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/GB2011/001011

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