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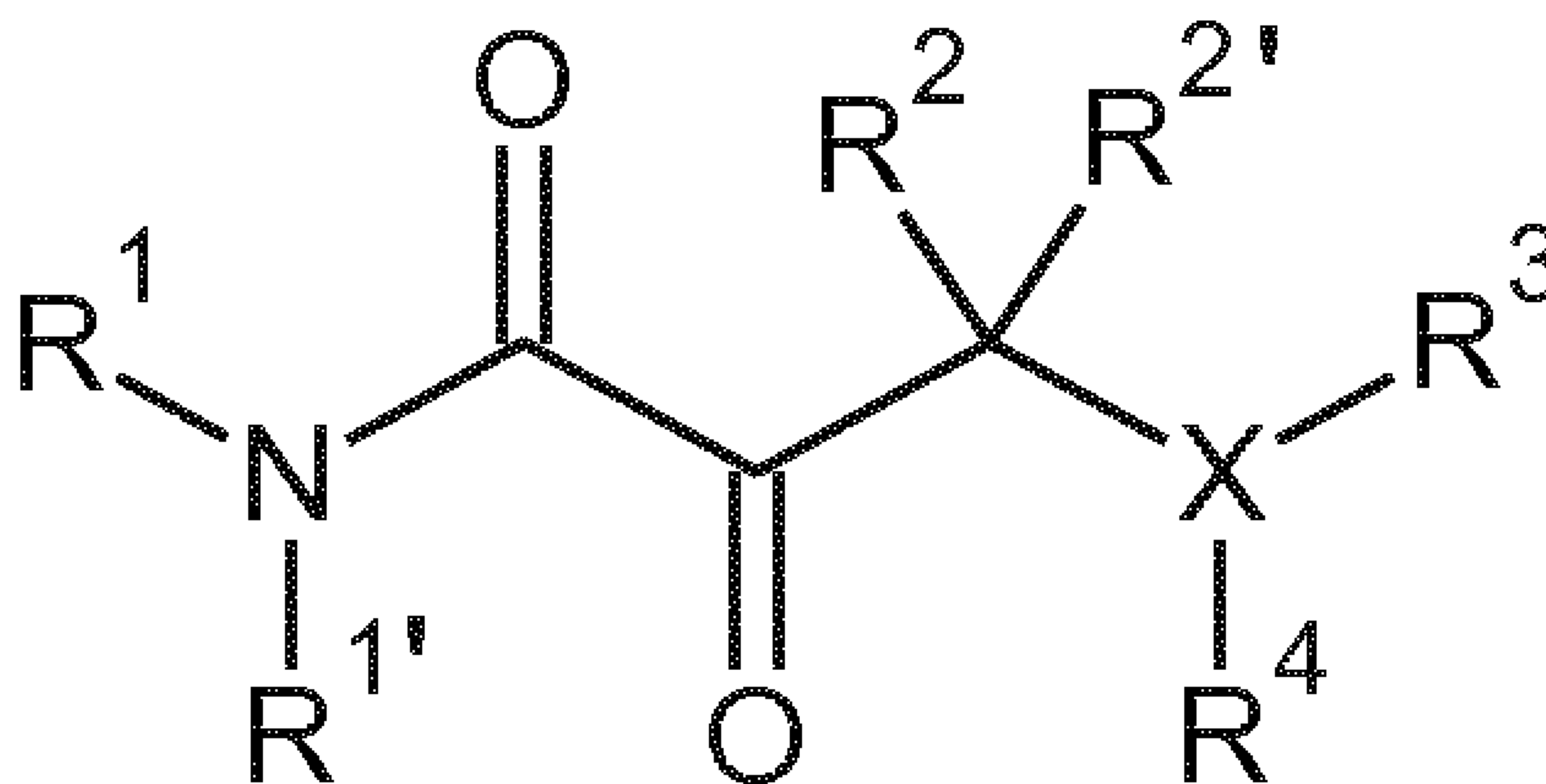
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(54) Titre : COMPOSES ANTIVIRAUX
(54) Title: ANTIVIRAL COMPOUNDS



(57) **Abrégé/Abstract:**

The present invention relates to novel compounds of general formula (I) wherein the groups X, and R¹ to R⁴ have the meanings given in the description and claims, process for preparing these compounds and their use as for treating, preventing or ameliorating viral infections and their use for treating, preventing or ameliorating diseases which are associated with PLA2G16.

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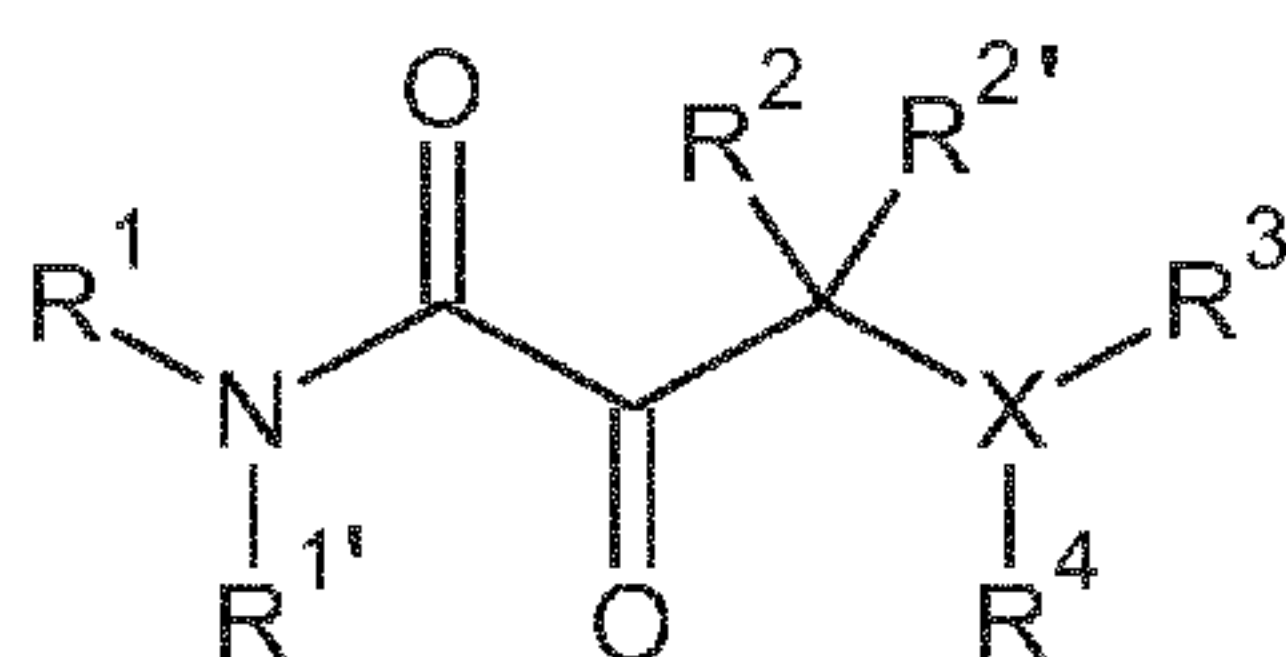
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(54) Title: ANTIVIRAL COMPOUNDS

(57) Abstract: The present invention relates to novel compounds of general formula (I) wherein the groups X, and R¹ to R⁴ have the meanings given in the description and claims, process for preparing these compounds and their use as for treating, preventing or ameliorating viral infections and their use for treating, preventing or ameliorating diseases which are associated with PLA2G16.

DEMANDE OU BREVET VOLUMINEUX

LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVET COMPREND PLUS D'UN TOME.

CECI EST LE TOME 1 DE 4
CONTENANT LES PAGES 1 À 118

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JUMBO APPLICATIONS/PATENTS

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THIS IS VOLUME 1 OF 4
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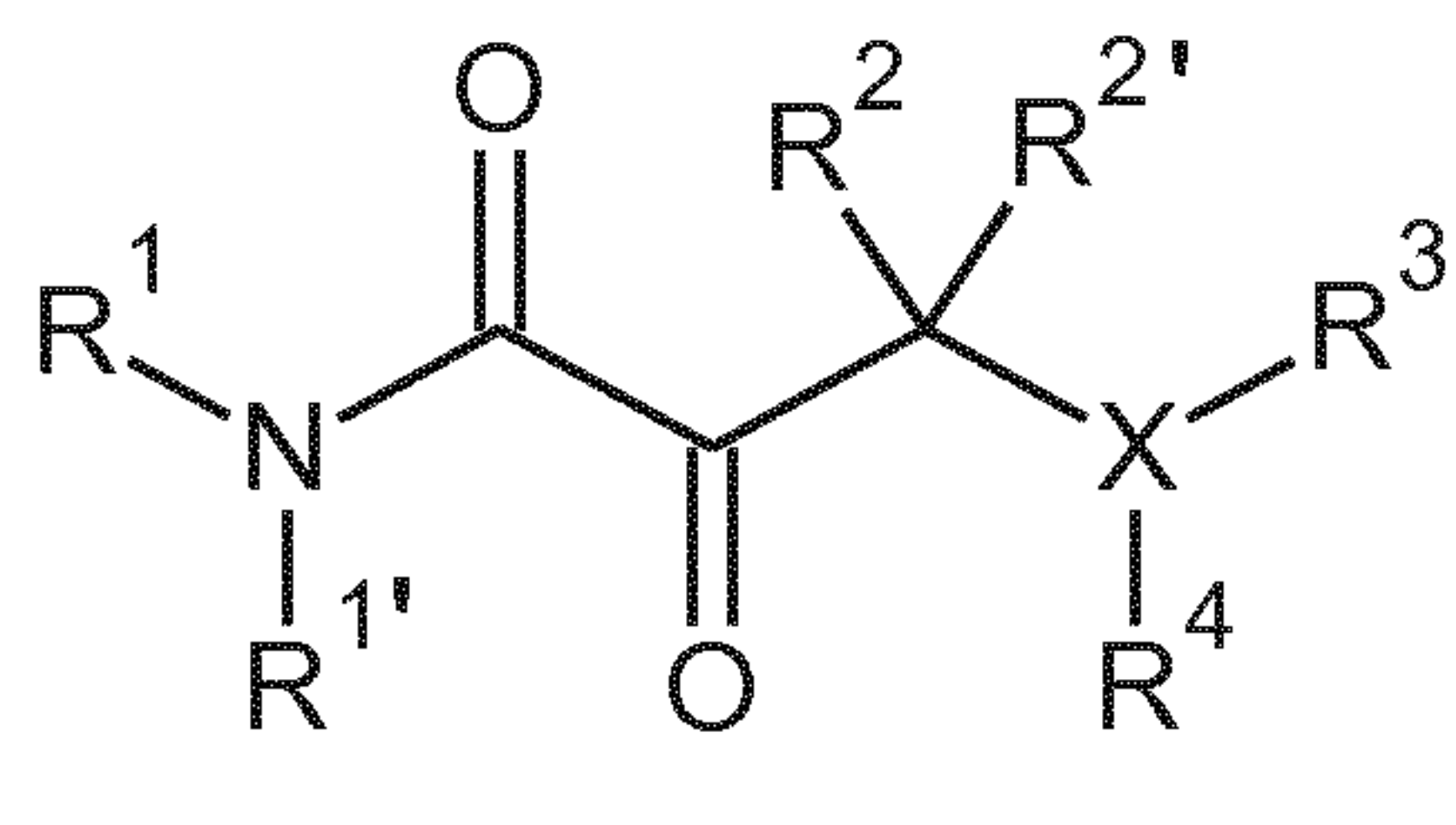
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ANTIVIRAL COMPOUNDS

Description

Field of the Invention

[001] The present invention relates to novel compounds of general formula I



wherein the groups X, and R¹ to R⁴ have the meanings given in the description and claims, process for preparing these compounds and their use as medicaments.

Background Art

[002] Viruses are major causes of disease and death throughout the world. Although vaccines and public health measures have greatly reduced the incidence of certain viral infections, such approaches have been less successful in tackling many viruses of significant medical and/or veterinary importance.

[003] For example, chronic infection with hepatitis C virus (HCV) is a major health problem that affects more than 170 million people worldwide and is a causative agent of liver cirrhosis, hepatocellular carcinoma, and liver failure. Flaviviruses such as West Nile virus (WNV), Japanese Encephalitis virus (JEV), and the Dengue viruses (DENV) are significant human pathogens that cause millions of infections each year.

Rhinoviruses are the most common viral infectious agents in humans and are the predominant cause of the common cold.

[004] Pathogenic viruses can be classified into two general types with respect to the viral structure: enveloped viruses and non-enveloped viruses. Some well-known enveloped viruses include herpes virus, influenza virus, paramyxovirus, respiratory syncytial virus, corona virus, HIV, hepatitis B virus, hepatitis C virus and SARS-CoV virus. Non-enveloped viruses, sometimes referred to as "naked" viruses, include the families Picornaviridae, Reoviridae, Caliciviridae, Adenoviridae and Parvoviridae. Members of these families include rhinovirus, poliovirus, adenovirus, hepatitis A virus, norovirus, papillomavirus, and rotavirus.

[005] The phospholipase A2, group XVI (PLA2G16) was identified as a new molecular target for antiviral drugs (WO2011160043).

[006] *PLA2G16* encodes an A2 group XVI phospholipase which is also reported to play roles in tumor metastasis (Xiong S. et al., Proc Natl Acad Sci U S A. 2014 Jul 29;111(30), 11145-11150; Li L. et al., Oncotarget. 7(14), 18021-18035, 2016).

[007] *PLA2G16* has also been reported to play a crucial role in the development of obesity in mouse models (Jaworski K. et al., Nat. Med. 15 (2): 159–68, 2009).

[008] Catalano John et al. disclose α -ketoamide-based small molecules as inhibitors of cathepsin K bearing a *tert*-butoxycarbonyl protecting group. The inhibitory compounds act as antiresorptive agent by attenuating type I collagen hydrolysis in bone (Bioorganic & Medicinal Chemistry Letters 2004, 14(3):719-722). Steffen Weik et al. describe phosphorane supported C-C coupling reaction for synthesis of α -ketocarbonyl products (Angewandte Chemie International Edition 2003, 42(22):2491-2494). Basso A et al. disclose solid-phase synthesis of modified oligopeptides via Passerini multicomponent reaction (Tetrahedron Letters 2003, 44(11):2367-2370). Li Z et al. describe novel peptidyl α -keto amide inhibitors of capains and other cysteine proteases (Journal of Medicinal Chemistry 1996, 39:4089-4098). Makoto Tsuda et al., disclose endopeptidase inhibitory activity of non-peptidyl poststatin analogues wherein the pyrrolidine moiety does not bear an oxo substituent. (The Journal of Antibiotics 1996). Chatterjee S et al., disclose α -ketoamide inhibitors of calpain I (Bioorganic & Medicinal Chemistry Letters 1999, 9(16):2371-2374). WO98/25883 A1 describe ketobenzamides as calpain inhibitors. Ota Eisuke et al., describe photo-induced formation of cyclopropanols from α -ketoamides via γ -C-H bond activation (Tetrahedron Letters 2015, 56(44):5991-5999). Antipicornaviral compounds are disclosed in WO01/10894. WO2013/049382 discloses antiviral agents bearing a pyrrolidin-2-one residue.

[009] However, there are still relatively few viral diseases for which effective drugs are available. Thus, there is still a need for new antiviral compounds and for new approaches to identifying such compounds. It is a further aim of the present invention to provide for new compounds which have an inhibitory effect on the enzyme *PLA2G16* *in vitro* and *in vivo* and have suitable pharmacological and/or pharmacokinetic properties to enable them to be used as medicaments.

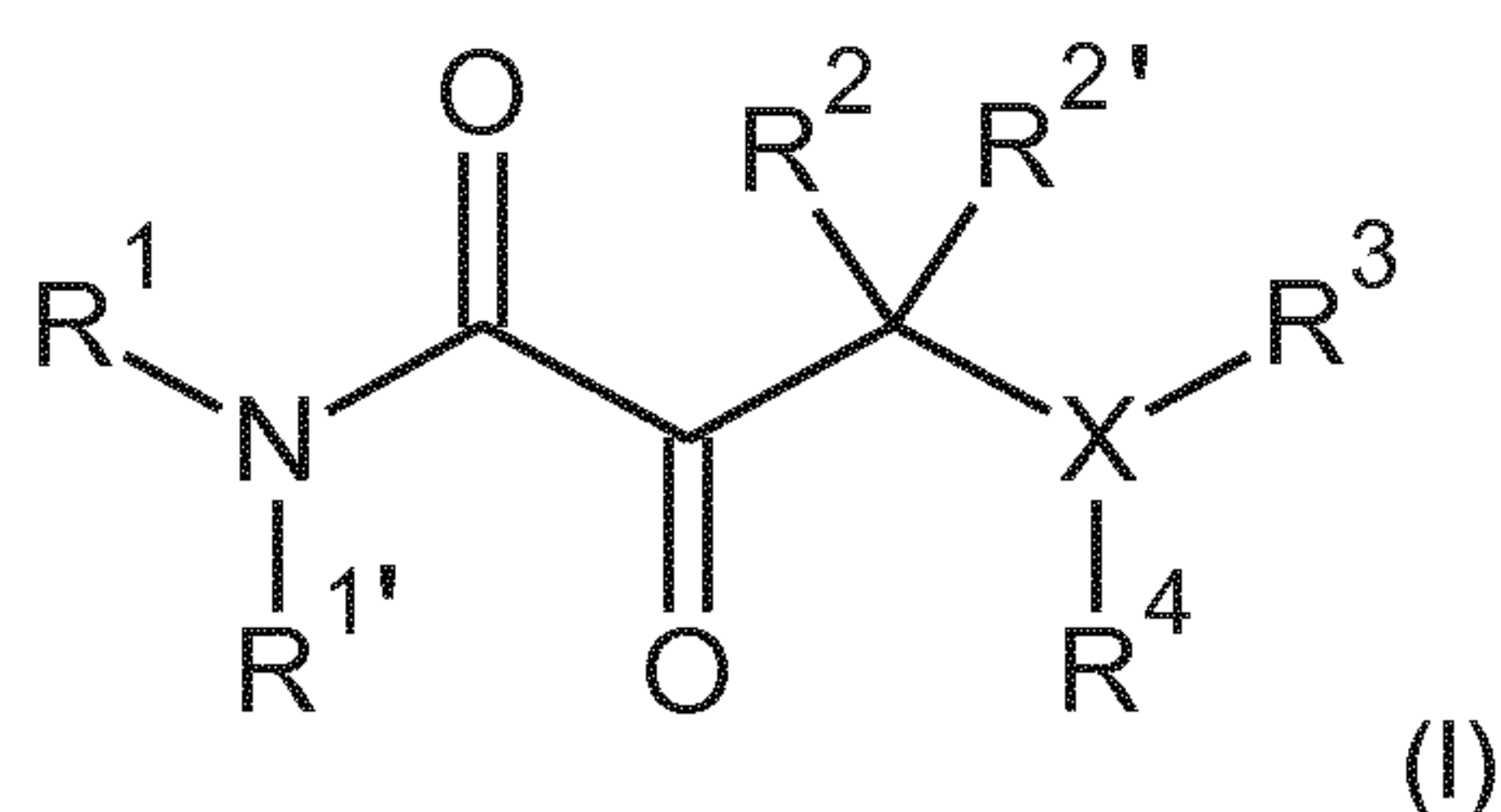
Summary of invention

[010] It has surprisingly been found, that compounds of general formula I, wherein the groups X, and R¹ to R⁴ have the meanings below, act as specific inhibitors against PLA2G16. The compounds according to the invention are specifically useful as antiviral compounds. Thus, the compounds according to the invention may be used for example for treating, preventing, and/or ameliorating viral infections.

[011] Various objects, features, aspects, and advantages of the present invention will become more apparent from the following detailed description of embodiments of the invention.

Description of embodiments

[012] The present invention relates to compounds of general formula I



wherein

R¹ denotes H, -C(O)R^a, -(CH₂)_nC(O)OR^a or a group, optionally substituted by one or more, identical or different R^a and/or R^b, selected independently from one another among C₁₋₈alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₁₀cycloalkyl, C₆₋₁₀aryl, 3-8 membered heterocycloalkyl, and 5-12 membered heteroaryl, and

R^{1'} denotes H or C₁₋₄alkyl,

or **R¹** and **R^{1'}** together with the adjacent nitrogen atom form a 4- to 10-membered heterocyclic group, which optionally may be substituted by one or more, identical or different R^a and/or R^b;

X denotes -(CH₂)_n-N- or O;

R² denotes H, -C(O)R^a or a group, optionally substituted by one or more, identical or different R^a and/or R^b, selected independently from one another among C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₁₀cycloalkyl, C₄₋₁₆cycloalkylalkyl, C₆₋₁₀aryl,

C₇₋₁₆arylalkyl, 3-8 membered heterocycloalkyl, 5-12 membered heteroaryl and 6-18 membered heteroarylalkyl;

or **R**² forms together with **R**³ a 5–7 membered heterocycloalkyl ring when X denotes N, wherein said heterocycloalkyl ring bears an oxo group, and is optionally substituted by one or more, identical or different R^a and/or R^b;

R^{2'} denotes H or C₁₋₆alkyl;

R³ denotes H, –C(O)R^c, or –SO₂R^a; and

R⁴ denotes H, or a group, optionally substituted by one or more, identical or different R^a and/or R^b, selected independently from one another among

C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₁₀cycloalkyl, C₄₋₁₆cycloalkyl, C₆₋₁₀aryl, C₇₋₁₆arylalkyl, 3-8 membered heterocycloalkyl, 4-14 membered heterocycloalkylalkyl, 5-12 membered heteroaryl, and 6-18 membered heteroarylalkyl;

or **R**⁴ form together with R³ a 4-6-membered heterocycloalkyl ring when X denotes -N-, wherein said heterocycloalkyl ring bears an oxo group, and is optionally substituted by one or more, identical or different R^a and/or R^b; and

n denotes 0, 1, 2 or 3;

each **R**^a independently of one another denotes hydrogen or a group, optionally substituted by one or more, identical or different R^b and/or R^c, selected from among C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₁₀cycloalkyl, C₄₋₁₆cycloalkylalkyl,

C₆₋₁₀aryl, C₇₋₁₆arylalkyl, 3-8 membered heterocycloalkyl, 4-14 membered heterocycloalkylalkyl, 5-12 membered heteroaryl and 6-18 membered heteroarylalkyl;

each **R**^b is a suitable substituent and is selected in each case independently of one another from among =O, –OR^c, C₁₋₃haloalkyloxy, –OCF₃, =S, –SR^c, =NR^c, =NOR^c,

=NNR^cR^c, =NN(R^g)C(O)NR^cR^c, –NR^cR^c, –ONR^cR^c, –N(OR^c)R^c, –N(R^g)NR^cR^c, halogen, –CF₃, –CN, –NC, –OCN, –SCN, –NO, –NO₂, =N₂, –N₃, –S(O)R^c, –S(O)OR^c, –S(O)₂R^c,

–S(O)₂OR^c, –S(O)NR^cR^c, –S(O)₂NR^cR^c, –OS(O)R^c, –OS(O)₂R^c, –OS(O)₂OR^c,

–OS(O)NR^cR^c, –OS(O)₂NR^cR^c, –O(CH₂)_p(CH₂)_pR^c, –C(O)R^c, –C(O)OR^c, –C(O)SR^c,

–C(O)NR^cR^c, –C(O)N(R^g)NR^cR^c, –C(O)N(R^g)OR^c, –C(NR^g)NR^cR^c, –C(NOH)R^c,

–C(NOH)NR^cR^c, –OC(O)R^c, –OC(O)OR^c, –OC(O)SR^c, –OC(O)NR^cR^c,

–OC(NR^g)NR^cR^c, –SC(O)R^c, –SC(O)OR^c, –SC(O)NR^cR^c, –SC(NR^g)NR^cR^c,

–N(R^g)C(O)R^c, –N[C(O)R^c]₂, –N(OR^g)C(O)R^c, –N(R^g)C(NR^g)R^c, –N(R^g)N(R^g)C(O)R^c,

–N[C(O)R^c]NR^cR^c, –N(R^g)C(S)R^c, –N(R^g)S(O)R^c, –N(R^g)S(O)OR^c, –N(R^g)S(O)₂R^c,

–N[S(O)₂R^c]₂, –N(R^g)S(O)₂OR^c, –N(R^g)S(O)₂NR^cR^c, –N(R^g)[S(O)₂]₂R^c, –N(R^g)C(O)OR^c,

–N(R^g)C(O)SR^c, –N(R^g)C(O)NR^cR^c, –N(R^g)C(O)NR^gNR^cR^c, –N(R^g)N(R^g)C(O)NR^cR^c,

$-N(R^g)C(S)NR^cR^c$, $-[N(R^g)C(O)]_2R^c$, $-N(R^g)[C(O)]_2R^c$, $-N\{[C(O)]_2R^c\}_2$,
 $-N(R^g)[C(O)]_2OR^c$, $-N(R^g)[C(O)]_2NR^cR^c$, $-N\{[C(O)]_2OR^c\}_2$, $-N\{[C(O)]_2NR^cR^c\}_2$,
 $-[N(R^g)C(O)]_2OR^c$, $-N(R^g)C(NR^g)OR^c$, $-N(R^g)C(NOH)R^c$, $-N(R^g)C(NR^g)SR^c$ and
 $-N(R^g)C(NR^g)NR^cR^c$;

each R^c independently of one another denotes hydrogen or a group, optionally substituted by one or more, identical or different R^d and/or R^e , selected from among C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{4-16} cycloalkylalkyl, C_{6-10} aryl, C_{7-16} arylalkyl, 3-8 membered heterocycloalkyl, 4-14 membered heterocycloalkylalkyl, 5-12 membered heteroaryl and 6-18 membered heteroarylalkyl;

each R^d denotes a suitable substituent and is selected in each case independently of one another from among $=O$, $-OR^e$, C_{1-3} haloalkyloxy, $-OCF_3$, $=S$, $-SR^e$, $=NR^e$, $=NOR^e$, $=NNR^eR^e$, $=NN(R^g)C(O)NR^eR^e$, $-NR^eR^e$, $-ONR^eR^e$, $-N(OR^e)R^e$, $-N(R^g)NR^eR^e$, halogen, $-CF_3$, $-CN$, $-NC$, $-OCN$, $-SCN$, $-NO$, $-NO_2$, $=N_2$, $-N_3$, $-S(O)R^e$, $-S(O)OR^e$, $-S(O)_2R^e$, $-S(O)_2OR^e$, $-S(O)NR^eR^e$, $-S(O)_2NR^eR^e$, $-OS(O)R^e$, $-OS(O)_2R^e$, $-OS(O)_2OR^e$, $-OS(O)NR^eR^e$, $-OS(O)_2NR^eR^e$, $-C(O)R^e$, $-C(O)OR^e$, $-C(O)SR^e$, $-C(O)NR^eR^e$, $-C(O)N(R^g)NR^eR^e$, $-C(O)N(R^g)OR^e$, $-C(NR^g)NR^eR^e$, $-C(NOH)R^e$, $-C(NOH)NR^eR^e$, $-OC(O)R^e$, $-OC(O)OR^e$, $-OC(O)SR^e$, $-OC(O)NR^eR^e$, $-OC(NR^g)NR^eR^e$, $-SC(O)R^e$, $-SC(O)OR^e$, $-SC(O)NR^eR^e$, $-SC(NR^g)NR^eR^e$, $-N(R^g)C(O)R^e$, $-N[C(O)R^e]_2$, $-N(OR^g)C(O)R^e$, $-N(R^g)C(NR^g)R^e$, $-N(R^g)N(R^g)C(O)R^e$, $-N[C(O)R^e]NR^eR^e$, $-N(R^g)C(S)R^e$, $-N(R^g)S(O)R^e$, $-N(R^g)S(O)OR^e$, $-N(R^g)S(O)_2R^e$, $-N[S(O)_2R^e]_2$, $-N(R^g)S(O)_2OR^e$, $-N(R^g)S(O)_2NR^eR^e$, $-N(R^g)[S(O)_2]_2R^e$, $-N(R^g)C(O)OR^e$, $-N(R^g)C(O)SR^e$, $-N(R^g)C(O)NR^eR^e$, $-N(R^g)C(O)NR^gNR^eR^e$, $-N(R^g)N(R^g)C(O)NR^eR^e$, $-N(R^g)C(S)NR^eR^e$, $-[N(R^g)C(O)]_2R^e$, $-N(R^g)[C(O)]_2R^e$, $-N\{[C(O)]_2R^e\}_2$, $-N(R^g)[C(O)]_2OR^e$, $-N(R^g)[C(O)]_2NR^eR^e$, $-N\{[C(O)]_2OR^e\}_2$, $-N\{[C(O)]_2NR^eR^e\}_2$, $-[N(R^g)C(O)]_2OR^e$, $-N(R^g)C(NR^g)OR^e$, $-N(R^g)C(NOH)R^e$, $-N(R^g)C(NR^g)SR^e$ and $-N(R^g)C(NR^g)NR^eR^e$; and

each R^e independently of one another denotes hydrogen or a group selected from among C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{6-10} aryl, 3-8 membered heterocycloalkyl, and 5-12 membered heteroaryl; and

each R^g independently of one another denotes hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{6-10} aryl, 3-8 membered heterocycloalkyl, or 5-12 membered heteroaryl; and

p denotes independently from one another 1, 2, 3, or 4; and
provided that when X denotes O R³ is absent and
provided that when X denotes N- and R¹ and R^{1'} denote hydrogen R³ and R⁴ are other than hydrogen; and
provided that R² is not benzyl, and
optionally in the form of the tautomers, the racemates, the enantiomers, the diastereomers, hydrates, isotopes, and mixtures thereof, and optionally the pharmacologically acceptable salts thereof.

[013] One embodiment of the invention relates to compounds as described herein, wherein X is N.

[014] One embodiment of the invention relates to compounds as described herein, wherein the 4- to 10-membered heterocyclic group formed by R¹ and R^{1'} together with the adjacent nitrogen atom does not contain any additional heteroatom.

[015] One embodiment of the invention relates to compounds as described herein, wherein R³ is -C(O)R^c.

[016] One embodiment of the invention relates to compounds as described herein, wherein X is O.

[017] One embodiment of the invention relates to compounds as described herein, wherein R⁴ is selected from optionally substituted C₁₋₆alkyl, C₃₋₆cycloalkyl, C₆aryl, 3-8 membered heterocycloalkyl, and 5-6 membered heteroaryl.

[018] One embodiment of the invention relates to compounds as described herein, wherein R⁴ is C₁₋₆alkyl.

[019] One embodiment of the invention relates to compounds as described herein, wherein R² forms together with R³ an oxo bearing pyrrolidinyll group.

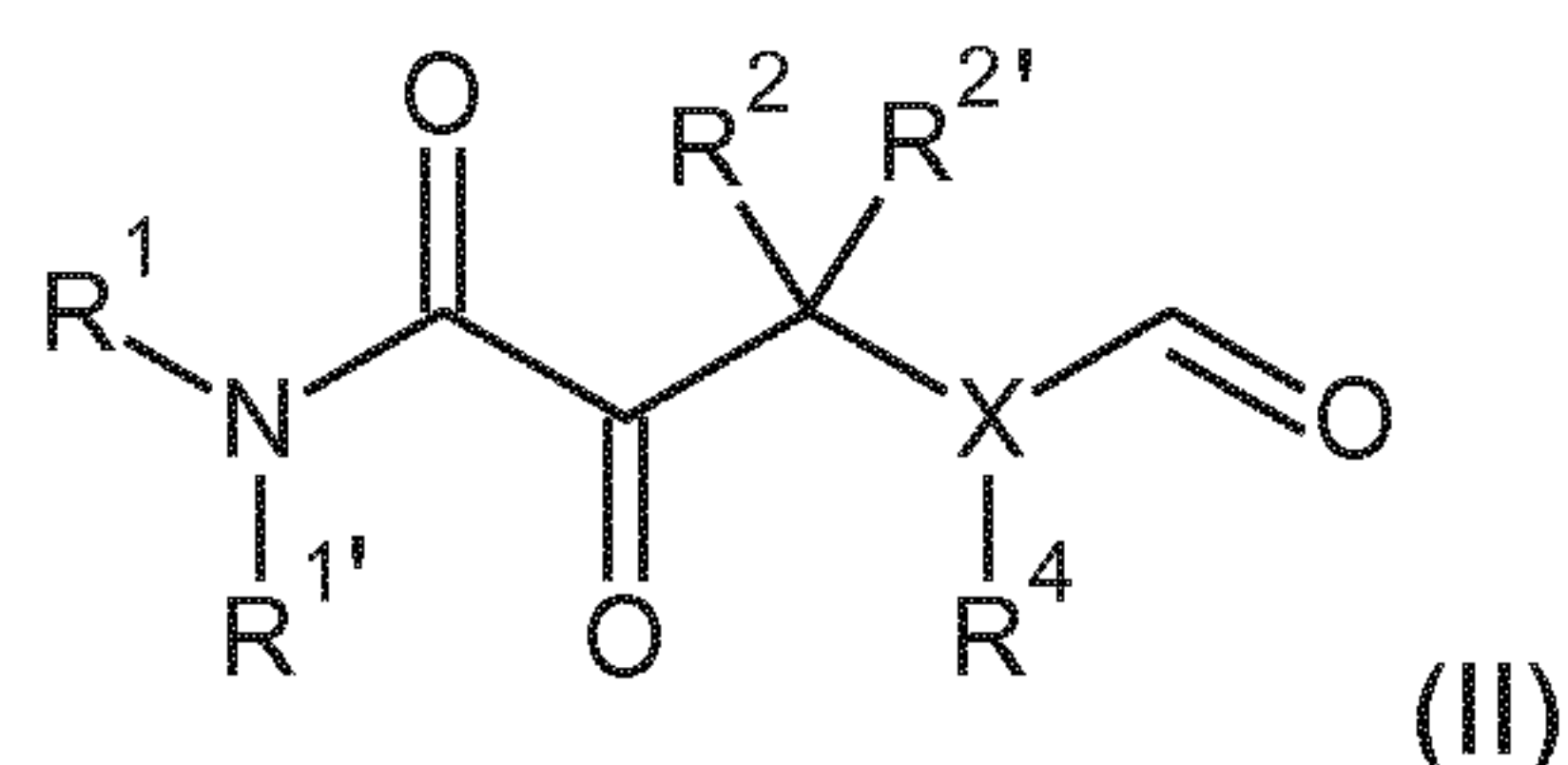
[020] One embodiment of the invention relates to compounds as described herein, wherein R^{1'} is H.

[021] One embodiment of the invention relates to compounds as described herein, wherein R¹ is optionally substituted C₁₋₆alkyl, C₃₋₆cycloalkyl, or C₄₋₁₆cycloalkylalkyl.

[022] One embodiment of the invention relates to compounds as described herein, wherein R^{2'} is H.

[023] One embodiment of the invention relates to compounds as described herein, wherein R² is optionally substituted C₁₋₆alkyl.

[024] One embodiment of the invention relates to compounds of general formula II,



wherein

X denotes $-(CH_2)_n-N-$;

R¹ denotes H, $-C(O)R^a$, $-(CH_2)_nC(O)OR^a$, or a group, optionally substituted by one or more, identical or different R^a and/or R^b , selected independently from one another among C_{1-8} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-10} aryl, 3-8 membered heterocycloalkyl, and 5-12 membered heteroaryl;

R^{1'} denotes H or C_{1-4} alkyl;

or **R¹** and **R^{1'}** together with the adjacent nitrogen atom form a 4- to 10-membered heterocyclic group, which optionally may be substituted by one or more, identical or different R^a and/or R^b ;

R² denotes H, $-C(O)R^a$, or a group, optionally substituted by one or more, identical or different R^a and/or R^b , selected independently from one another among C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{4-16} cycloalkylalkyl, C_{6-10} aryl, C_{7-16} arylalkyl, 3-8 membered heterocycloalkyl, 4-14 membered heterocycloalkylalkyl, 5-12 membered heteroaryl and 6-18 membered heteroarylalkyl;

R^{2'} denotes H or C_{1-6} alkyl;

R⁴ denotes H, $-C(O)R^a$, or a group, optionally substituted by one or more, identical or different R^a and/or R^b , selected independently from one another among C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-10} aryl, 3-8 membered heterocycloalkyl, and 5-12 membered heteroaryl;

each **R^a** independently of one another denotes hydrogen or a group, optionally substituted by one or more, identical or different R^b and/or R^c , selected from among C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{4-16} cycloalkylalkyl, C_{6-10} aryl, C_{7-16} arylalkyl, 3-8 membered heterocycloalkyl, 4-14 membered heterocycloalkylalkyl, 5-12 membered heteroaryl and 6- 18 membered heteroarylalkyl;

each **R^b** is a suitable substituent and is selected in each case independently of one another from among $=O$, $-OR^c$, C_{1-3} haloalkyloxy, $-OCF_3$, $=S$, $-SR^c$, $=NR^c$, $=NOR^c$,

=NNR^cR^c, =NN(R^g)C(O)NR^cR^c, -NR^cR^c, -ONR^cR^c, -N(OR^c)R^c, -N(R^g)NR^cR^c, halogen, -CF₃, -CN, -NC, -OCN, -SCN, -NO, -NO₂, =N₂, -N₃, -S(O)R^c, -S(O)OR^c, -S(O)₂R^c, -S(O)₂OR^c, -S(O)NR^cR^c, -S(O)₂NR^cR^c, -OS(O)R^c, -OS(O)₂R^c, -OS(O)₂OR^c, -OS(O)NR^cR^c, -OS(O)₂NR^cR^c, -C(O)R^c, -C(O)OR^c, -C(O)SR^c, -C(O)NR^cR^c, -C(O)N(R^g)NR^cR^c, -C(O)N(R^g)OR^c, -C(NR^g)NR^cR^c, -C(NOH)R^c, -C(NOH)NR^cR^c, -OC(O)R^c, -OC(O)OR^c, -OC(O)SR^c, -OC(O)NR^cR^c, -OC(NR^g)NR^cR^c, -SC(O)R^c, -SC(O)OR^c, -SC(O)NR^cR^c, -SC(NR^g)NR^cR^c, -N(R^g)C(O)R^c, -N[C(O)R^c]₂, -N(OR^g)C(O)R^c, -N(R^g)C(NR^g)R^c, -N(R^g)N(R^g)C(O)R^c, -N[C(O)R^c]NR^cR^c, -N(R^g)C(S)R^c, -N(R^g)S(O)R^c, -N(R^g)S(O)OR^c, -N(R^g)S(O)₂R^c, -N[S(O)₂R^c]₂, -N(R^g)S(O)₂OR^c, -N(R^g)S(O)₂NR^cR^c, -N(R^g)[S(O)₂]₂R^c, -N(R^g)C(O)OR^c, -N(R^g)C(O)SR^c, -N(R^g)C(O)NR^cR^c, -N(R^g)C(O)NR^gNR^cR^c, -N(R^g)N(R^g)C(O)NR^cR^c, -N(R^g)C(S)NR^cR^c, -[N(R^g)C(O)]₂R^c, -N(R^g)[C(O)]₂R^c, -N{[C(O)]₂R^c}₂, -N(R^g)[C(O)]₂OR^c, -N(R^g)[C(O)]₂NR^cR^c, -N{[C(O)]₂OR^c}₂, -N{[C(O)]₂NR^cR^c}₂, -[N(R^g)C(O)]₂OR^c, -N(R^g)C(NR^g)OR^c, -N(R^g)C(NOH)R^c, -N(R^g)C(NR^g)SR^c and -N(R^g)C(NR^g)NR^cR^c;

each **R^c** independently of one another denotes hydrogen or a group, optionally substituted by one or more, identical or different R^d and/or R^e, selected from among C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₁₀cycloalkyl, C₄₋₁₆cycloalkylalkyl, C₆₋₁₀aryl, C₇₋₁₆arylalkyl, 3-8 membered heterocycloalkyl, 4-14 membered heterocycloalkylalkyl, 5-12 membered heteroaryl and 6-18 membered heteroarylalkyl;

each **R^d** denotes a suitable substituent and is selected in each case independently of one another from among =O, -OR^e, C₁₋₃haloalkyloxy, -OCF₃, =S, -SR^e, =NR^e, =NOR^e, =NNR^eR^e, =NN(R^g)C(O)NR^eR^e, -NR^eR^e, -ONR^eR^e, -N(OR^e)R^e, -N(R^g)NR^eR^e, halogen, -CF₃, -CN, -NC, -OCN, -SCN, -NO, -NO₂, =N₂, -N₃, -S(O)R^e, -S(O)OR^e, -S(O)₂R^e, -S(O)₂OR^e, -S(O)NR^eR^e, -S(O)₂NR^eR^e, -OS(O)R^e, -OS(O)₂R^e, -OS(O)₂OR^e, -OS(O)NR^eR^e, -OS(O)₂NR^eR^e, -C(O)R^e, -C(O)OR^e, -C(O)SR^e, -C(O)NR^eR^e, -C(O)N(R^g)NR^eR^e, -C(O)N(R^g)OR^e, -C(NR^g)NR^eR^e, -C(NOH)R^e, -C(NOH)NR^eR^e, -OC(O)R^e, -OC(O)OR^e, -OC(O)SR^e, -OC(O)NR^eR^e, -OC(NR^g)NR^eR^e, -SC(O)R^e, -SC(O)OR^e, -SC(O)NR^eR^e, -SC(NR^g)NR^eR^e, -N(R^g)C(O)R^e, -N[C(O)R^e]₂, -N(OR^g)C(O)R^e, -N(R^g)C(NR^g)R^e, -N(R^g)N(R^g)C(O)R^e, -N[C(O)R^e]NR^eR^e, -N(R^g)C(S)R^e, -N(R^g)S(O)R^e, -N(R^g)S(O)OR^e, -N(R^g)S(O)₂R^e, -N[S(O)₂R^e]₂, -N(R^g)S(O)₂OR^e, -N(R^g)S(O)₂NR^eR^e, -N(R^g)[S(O)₂]₂R^e,

$-N(R^g)C(O)OR^e$, $-N(R^g)C(O)SR^e$, $-N(R^g)C(O)NR^eR^e$, $-N(R^g)C(O)NR^gNR^eR^e$,
 $-N(R^g)N(R^g)C(O)NR^eR^e$, $-N(R^g)C(S)NR^eR^e$, $-[N(R^g)C(O)]_2R^e$, $-N(R^g)[C(O)]_2R^e$,
 $-N\{[C(O)]_2R^e\}_2$, $-N(R^g)[C(O)]_2OR^e$, $-N(R^g)[C(O)]_2NR^eR^e$, $-N\{[C(O)]_2OR^e\}_2$,
 $-N\{[C(O)]_2NR^eR^e\}_2$, $-[N(R^g)C(O)]_2OR^e$, $-N(R^g)C(NR^g)OR^e$, $-N(R^g)C(NOH)R^e$,
 $-N(R^g)C(NR^g)SR^e$ and $-N(R^g)C(NR^g)NR^eR^e$;

each R^e independently of one another denotes hydrogen or a group selected from among C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{6-10} aryl, 3-8 membered heterocycloalkyl, and 5-12 membered heteroaryl;

each R^g independently of one another denotes hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{6-10} aryl, 3-8 membered heterocycloalkyl, or 5-12 membered heteroaryl;

n denotes 0, 1, 2 or 3;

optionally in the form of the tautomers, the racemates, the enantiomers, the diastereomers, hydrates, isotopes, and the mixtures thereof, and optionally the pharmacologically acceptable salts thereof.

[025] One embodiment of the invention relates to compounds of general formula II as described herein, wherein X is N.

[026] One embodiment of the invention relates to compounds of general formula II as described herein, wherein R^4 is selected from optionally substituted C_{1-6} alkyl, C_{3-6} cycloalkyl, phenyl, 3-8 membered heterocycloalkyl, and 5-6 membered heteroaryl.

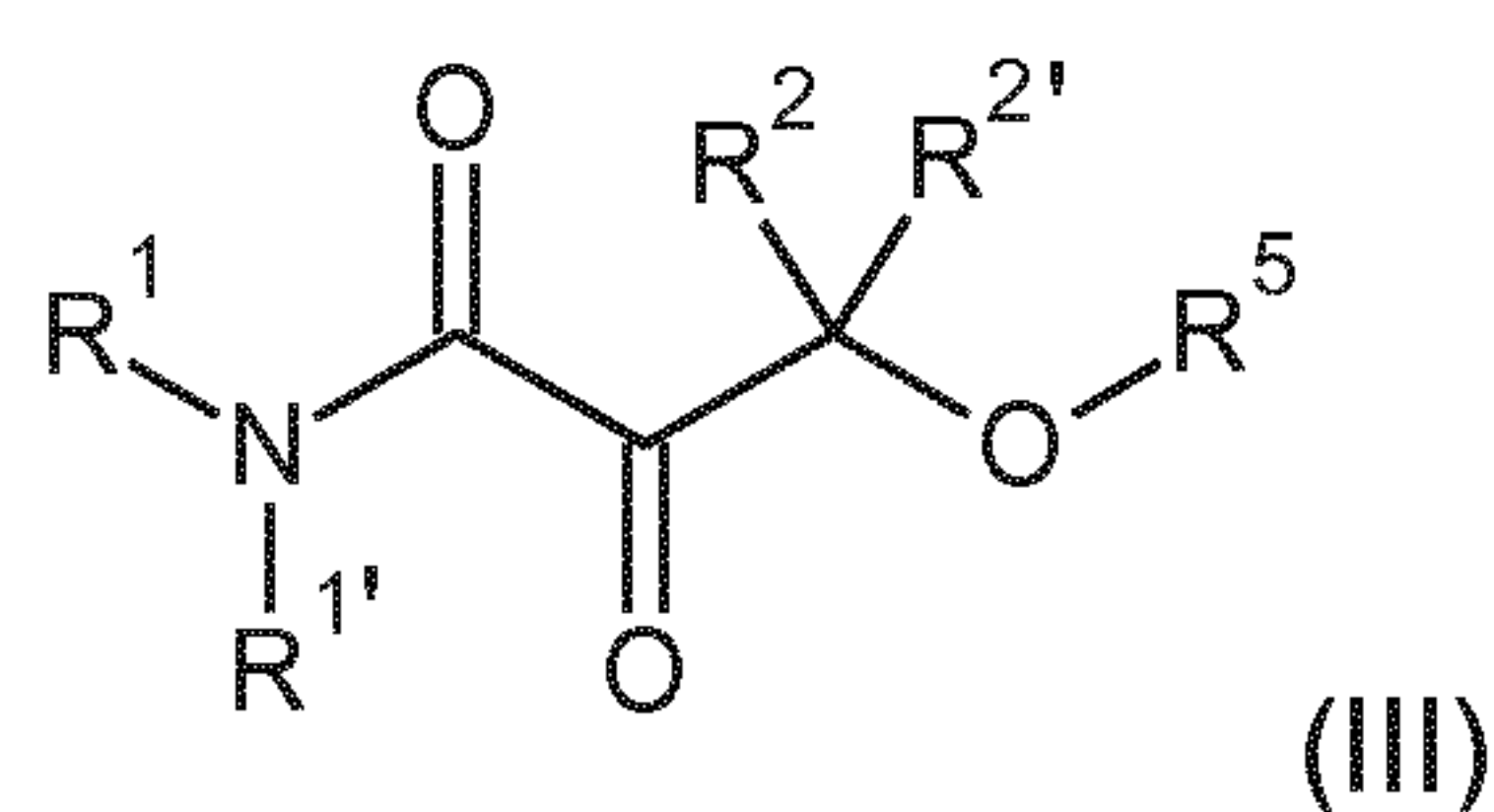
[027] One embodiment of the invention relates to compounds of general formula II as described herein, wherein $R^{1'}$ is H.

[028] One embodiment of the invention relates to compounds of general formula II as described herein, wherein R^1 is optionally substituted C_{1-6} alkyl or C_{3-6} cycloalkyl.

[029] One embodiment of the invention relates to compounds of general formula II as described herein, wherein $R^{2'}$ is H.

[030] One embodiment of the invention relates to compounds of general formula II as described herein, wherein R^2 is optionally substituted C_{1-6} alkyl.

[031] One embodiment of the invention relates to compounds of general formula III,



wherein

R¹ denotes H, $-\text{C}(\text{O})\text{R}^a$, $-(\text{CH}_2)_n\text{C}(\text{O})\text{OR}^a$, or a group, optionally substituted by one or more, identical or different R^a and/or R^b , selected independently from one another among C_{1-8} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-10} aryl, 3-8 membered heterocycloalkyl, and 5-12 membered heteroaryl;

R¹' denotes H or C_{1-4} alkyl;

or **R¹** and **R¹'** together with the adjacent nitrogen atom form a 4- to 10-membered heterocyclic group, which optionally may be substituted by one or more, identical or different R^a and/or R^b ;

R² denotes H, $-\text{C}(\text{O})\text{R}^a$, or a group, optionally substituted by one or more, identical or different R^a and/or R^b , selected independently from one another among C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{4-16} cycloalkylalkyl, C_{6-10} aryl, C_{7-16} arylalkyl, 3-8 membered heterocycloalkyl, 4-14 membered heterocycloalkylalkyl, 5-12 membered heteroaryl and 6- 18 membered heteroarylalkyl;

R²' denotes H or C_{1-6} alkyl;

R⁵ denotes a group, optionally substituted by one or more, identical or different R^a and/or R^b , selected independently from one another among C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-10} aryl, 3-8 membered heterocycloalkyl, and 5-12 membered heteroaryl;

each **R^a** independently of one another denotes hydrogen or a group, optionally substituted by one or more, identical or different R^b and/or R^c , selected from among C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{4-16} cycloalkylalkyl, C_{6-10} aryl, C_{7-16} arylalkyl, 3-8 membered heterocycloalkyl, 4-14 membered heterocycloalkylalkyl, 5-12 membered heteroaryl and 6-18 membered heteroarylalkyl;

each **R^b** is a suitable substituent and is selected in each case independently of one another from among $=\text{O}$, $-\text{OR}^c$, C_{1-3} haloalkyloxy, $-\text{OCF}_3$, $=\text{S}$, $-\text{SR}^c$, $=\text{NR}^c$, $=\text{NOR}^c$, $=\text{NNR}^c\text{R}^c$, $=\text{NN}(\text{R}^g)\text{C}(\text{O})\text{NR}^c\text{R}^c$, $-\text{NR}^c\text{R}^c$, $-\text{ONR}^c\text{R}^c$, $-\text{N}(\text{OR}^c)\text{R}^c$, $-\text{N}(\text{R}^g)\text{NR}^c\text{R}^c$, halogen, $-\text{CF}_3$, $-\text{CN}$, $-\text{NC}$, $-\text{OCN}$, $-\text{SCN}$, $-\text{NO}$, $-\text{NO}_2$, $=\text{N}_2$, $-\text{N}_3$, $-\text{S}(\text{O})\text{R}^c$, $-\text{S}(\text{O})\text{OR}^c$, $-\text{S}(\text{O})_2\text{R}^c$,

$-\text{S}(\text{O})_2\text{OR}^c$, $-\text{S}(\text{O})\text{NR}^c\text{R}^c$, $-\text{S}(\text{O})_2\text{NR}^c\text{R}^c$, $-\text{OS}(\text{O})\text{R}^c$, $-\text{OS}(\text{O})_2\text{R}^c$, $-\text{OS}(\text{O})_2\text{OR}^c$,
 $-\text{OS}(\text{O})\text{NR}^c\text{R}^c$, $-\text{OS}(\text{O})_2\text{NR}^c\text{R}^c$, $-\text{C}(\text{O})\text{R}^c$, $-\text{C}(\text{O})\text{OR}^c$, $-\text{C}(\text{O})\text{SR}^c$, $-\text{C}(\text{O})\text{NR}^c\text{R}^c$,
 $-\text{C}(\text{O})\text{N}(\text{R}^g)\text{NR}^c\text{R}^c$, $-\text{C}(\text{O})\text{N}(\text{R}^g)\text{OR}^c$, $-\text{C}(\text{NR}^g)\text{NR}^c\text{R}^c$, $-\text{C}(\text{NOH})\text{R}^c$, $-\text{C}(\text{NOH})\text{NR}^c\text{R}^c$,
 $-\text{OC}(\text{O})\text{R}^c$, $-\text{OC}(\text{O})\text{OR}^c$, $-\text{OC}(\text{O})\text{SR}^c$, $-\text{OC}(\text{O})\text{NR}^c\text{R}^c$, $-\text{OC}(\text{NR}^g)\text{NR}^c\text{R}^c$, $-\text{SC}(\text{O})\text{R}^c$,
 $-\text{SC}(\text{O})\text{OR}^c$, $-\text{SC}(\text{O})\text{NR}^c\text{R}^c$, $-\text{SC}(\text{NR}^g)\text{NR}^c\text{R}^c$, $-\text{N}(\text{R}^g)\text{C}(\text{O})\text{R}^c$, $-\text{N}[\text{C}(\text{O})\text{R}^c]_2$,
 $-\text{N}(\text{OR}^g)\text{C}(\text{O})\text{R}^c$, $-\text{N}(\text{R}^g)\text{C}(\text{NR}^g)\text{R}^c$, $-\text{N}(\text{R}^g)\text{N}(\text{R}^g)\text{C}(\text{O})\text{R}^c$, $-\text{N}[\text{C}(\text{O})\text{R}^c]\text{NR}^c\text{R}^c$,
 $-\text{N}(\text{R}^g)\text{C}(\text{S})\text{R}^c$, $-\text{N}(\text{R}^g)\text{S}(\text{O})\text{R}^c$, $-\text{N}(\text{R}^g)\text{S}(\text{O})\text{OR}^c$, $-\text{N}(\text{R}^g)\text{S}(\text{O})_2\text{R}^c$, $-\text{N}[\text{S}(\text{O})_2\text{R}^c]_2$,
 $-\text{N}(\text{R}^g)\text{S}(\text{O})_2\text{OR}^c$, $-\text{N}(\text{R}^g)\text{S}(\text{O})_2\text{NR}^c\text{R}^c$, $-\text{N}(\text{R}^g)[\text{S}(\text{O})_2]_2\text{R}^c$, $-\text{N}(\text{R}^g)\text{C}(\text{O})\text{OR}^c$,
 $-\text{N}(\text{R}^g)\text{C}(\text{O})\text{SR}^c$, $-\text{N}(\text{R}^g)\text{C}(\text{O})\text{NR}^c\text{R}^c$, $-\text{N}(\text{R}^g)\text{C}(\text{O})\text{NR}^g\text{NR}^c\text{R}^c$, $-\text{N}(\text{R}^g)\text{N}(\text{R}^g)\text{C}(\text{O})\text{NR}^c\text{R}^c$,
 $-\text{N}(\text{R}^g)\text{C}(\text{S})\text{NR}^c\text{R}^c$, $-\text{N}(\text{R}^g)\text{C}(\text{O})]_2\text{R}^c$, $-\text{N}(\text{R}^g)[\text{C}(\text{O})]_2\text{R}^c$, $-\text{N}\{[\text{C}(\text{O})]_2\text{R}^c\}_2$,
 $-\text{N}(\text{R}^g)[\text{C}(\text{O})]_2\text{OR}^c$, $-\text{N}(\text{R}^g)[\text{C}(\text{O})]_2\text{NR}^c\text{R}^c$, $-\text{N}\{[\text{C}(\text{O})]_2\text{OR}^c\}_2$, $-\text{N}\{[\text{C}(\text{O})]_2\text{NR}^c\text{R}^c\}_2$,
 $-\text{N}(\text{R}^g)\text{C}(\text{O})]_2\text{OR}^c$, $-\text{N}(\text{R}^g)\text{C}(\text{NR}^g)\text{OR}^c$, $-\text{N}(\text{R}^g)\text{C}(\text{NOH})\text{R}^c$, $-\text{N}(\text{R}^g)\text{C}(\text{NR}^g)\text{SR}^c$ and
 $-\text{N}(\text{R}^g)\text{C}(\text{NR}^g)\text{NR}^c\text{R}^c$;

each R^c independently of one another denotes hydrogen or a group, optionally substituted by one or more, identical or different R^d and/or R^e , selected from among C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{4-16} cycloalkylalkyl, C_{6-10} aryl, C_{7-16} arylalkyl, 3-8 membered heterocycloalkyl, 4-14 membered heterocycloalkylalkyl, 5-12 membered heteroaryl and 6-18 membered heteroarylalkyl;

each R^d denotes a suitable substituent and is selected in each case independently of one another from among $=\text{O}$, $-\text{OR}^e$, C_{1-3} haloalkyloxy, $-\text{OCF}_3$, $=\text{S}$, $-\text{SR}^e$, $=\text{NR}^e$, $=\text{NOR}^e$, $=\text{NNR}^e\text{R}^e$, $=\text{NN}(\text{R}^g)\text{C}(\text{O})\text{NR}^e\text{R}^e$, $-\text{NR}^e\text{R}^e$, $-\text{ONR}^e\text{R}^e$, $-\text{N}(\text{OR}^e)\text{R}^e$, $-\text{N}(\text{R}^g)\text{NR}^e\text{R}^e$, halogen, $-\text{CF}_3$, $-\text{CN}$, $-\text{NC}$, $-\text{OCN}$, $-\text{SCN}$, $-\text{NO}$, $-\text{NO}_2$, $=\text{N}_2$, $-\text{N}_3$, $-\text{S}(\text{O})\text{R}^e$, $-\text{S}(\text{O})\text{OR}^e$, $-\text{S}(\text{O})_2\text{R}^e$, $-\text{S}(\text{O})_2\text{OR}^e$, $-\text{S}(\text{O})\text{NR}^e\text{R}^e$, $-\text{S}(\text{O})_2\text{NR}^e\text{R}^e$, $-\text{OS}(\text{O})\text{R}^e$, $-\text{OS}(\text{O})_2\text{R}^e$, $-\text{OS}(\text{O})_2\text{OR}^e$, $-\text{OS}(\text{O})\text{NR}^e\text{R}^e$, $-\text{OS}(\text{O})_2\text{NR}^e\text{R}^e$, $-\text{C}(\text{O})\text{R}^e$, $-\text{C}(\text{O})\text{OR}^e$, $-\text{C}(\text{O})\text{SR}^e$, $-\text{C}(\text{O})\text{NR}^e\text{R}^e$, $-\text{C}(\text{O})\text{N}(\text{R}^g)\text{NR}^e\text{R}^e$, $-\text{C}(\text{O})\text{N}(\text{R}^g)\text{OR}^e$, $-\text{C}(\text{NR}^g)\text{NR}^e\text{R}^e$, $-\text{C}(\text{NOH})\text{R}^e$, $-\text{C}(\text{NOH})\text{NR}^e\text{R}^e$, $-\text{OC}(\text{O})\text{R}^e$, $-\text{OC}(\text{O})\text{OR}^e$, $-\text{OC}(\text{O})\text{SR}^e$, $-\text{OC}(\text{O})\text{NR}^e\text{R}^e$, $-\text{OC}(\text{NR}^g)\text{NR}^e\text{R}^e$, $-\text{SC}(\text{O})\text{R}^e$, $-\text{SC}(\text{O})\text{OR}^e$, $-\text{SC}(\text{O})\text{NR}^e\text{R}^e$, $-\text{SC}(\text{NR}^g)\text{NR}^e\text{R}^e$, $-\text{N}(\text{R}^g)\text{C}(\text{O})\text{R}^e$, $-\text{N}[\text{C}(\text{O})\text{R}^e]_2$, $-\text{N}(\text{OR}^g)\text{C}(\text{O})\text{R}^e$, $-\text{N}(\text{R}^g)\text{C}(\text{NR}^g)\text{R}^e$, $-\text{N}(\text{R}^g)\text{N}(\text{R}^g)\text{C}(\text{O})\text{R}^e$, $-\text{N}[\text{C}(\text{O})\text{R}^e]\text{NR}^e\text{R}^e$, $-\text{N}(\text{R}^g)\text{C}(\text{S})\text{R}^e$, $-\text{N}(\text{R}^g)\text{S}(\text{O})\text{R}^e$, $-\text{N}(\text{R}^g)\text{S}(\text{O})\text{OR}^e$, $-\text{N}(\text{R}^g)\text{S}(\text{O})_2\text{R}^e$, $-\text{N}[\text{S}(\text{O})_2\text{R}^e]_2$, $-\text{N}(\text{R}^g)\text{S}(\text{O})_2\text{OR}^e$, $-\text{N}(\text{R}^g)\text{S}(\text{O})_2\text{NR}^e\text{R}^e$, $-\text{N}(\text{R}^g)[\text{S}(\text{O})_2]_2\text{R}^e$, $-\text{N}(\text{R}^g)\text{C}(\text{O})\text{OR}^e$, $-\text{N}(\text{R}^g)\text{C}(\text{O})\text{SR}^e$, $-\text{N}(\text{R}^g)\text{C}(\text{O})\text{NR}^e\text{R}^e$, $-\text{N}(\text{R}^g)\text{C}(\text{O})\text{NR}^g\text{NR}^e\text{R}^e$, $-\text{N}(\text{R}^g)\text{N}(\text{R}^g)\text{C}(\text{O})\text{NR}^e\text{R}^e$, $-\text{N}(\text{R}^g)\text{C}(\text{S})\text{NR}^e\text{R}^e$, $-\text{N}(\text{R}^g)\text{C}(\text{O})]_2\text{R}^e$, $-\text{N}(\text{R}^g)[\text{C}(\text{O})]_2\text{R}^e$,

$-N\{[C(O)]_2R^e\}_2$, $-N(R^g)[C(O)]_2OR^e$, $-N(R^g)[C(O)]_2NR^eR^e$, $-N\{[C(O)]_2OR^e\}_2$,
 $-N\{[C(O)]_2NR^eR^e\}_2$, $-[N(R^g)C(O)]_2OR^e$, $-N(R^g)C(NR^g)OR^e$, $-N(R^g)C(NOH)R^e$,
 $-N(R^g)C(NR^g)SR^e$ and $-N(R^g)C(NR^g)NR^eR^e$;

each R^e independently of one another denotes hydrogen or a group selected from among C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{6-10} aryl, 3-8 membered heterocycloalkyl, and 5-12 membered heteroaryl; and

each R^g independently of one another denotes hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{6-10} aryl, 3-8 membered heterocycloalkyl, or 5-12 membered heteroaryl;

n denotes 0, 1, 2, or 3;

optionally in the form of the tautomers, the racemates, the enantiomers, the diastereomers, hydrates, isotopes, and the mixtures thereof, and optionally the pharmacologically acceptable salts thereof.

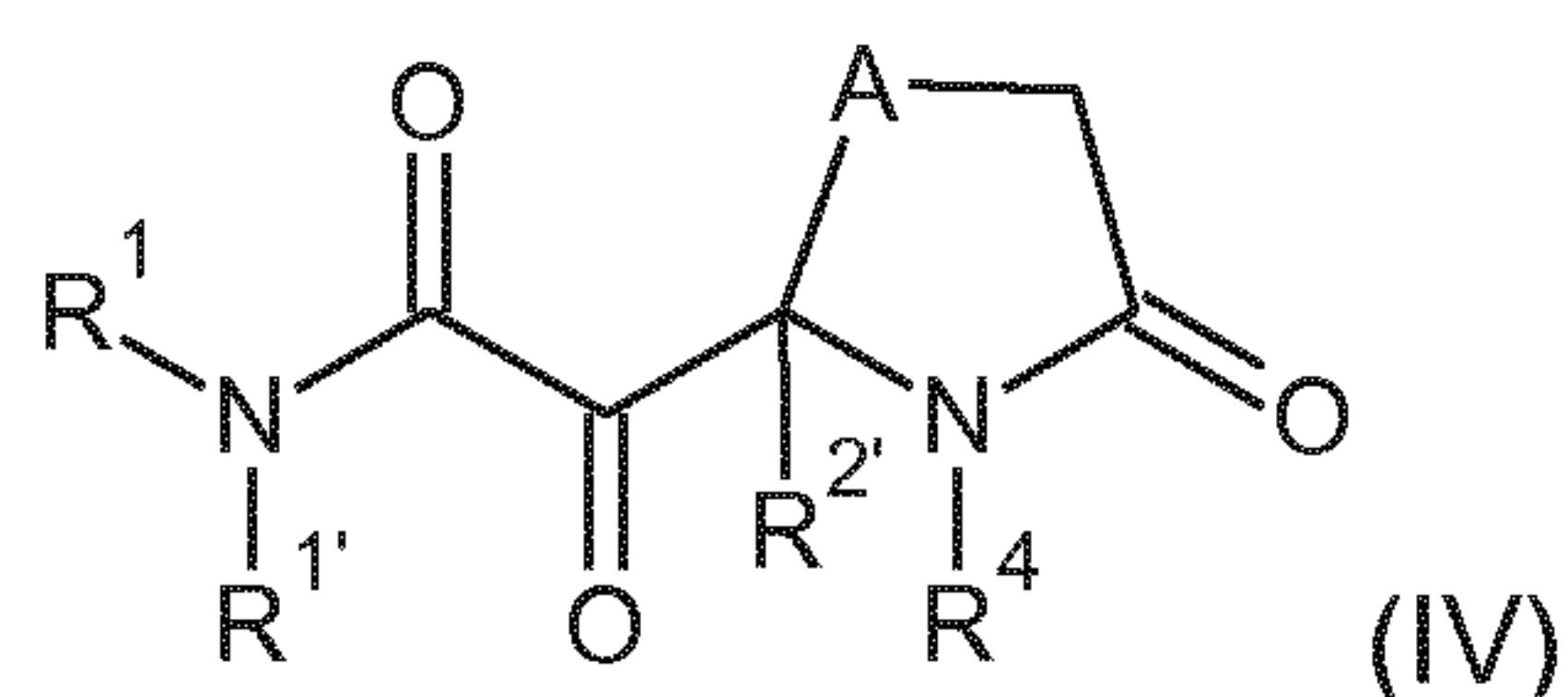
[032] One embodiment of the invention relates to compounds of general formula III as described herein, wherein $R^{1'}$ is H.

[033] One embodiment of the invention relates to compounds of general formula III as described herein, wherein R^1 is optionally substituted C_{1-6} alkyl or C_{3-6} cycloalkyl.

[034] One embodiment of the invention relates to compounds of general formula III as described herein, wherein $R^{2'}$ is H.

[035] One embodiment of the invention relates to compounds of general formula III as described herein, wherein R^2 is optionally substituted C_{1-6} alkyl.

[036] One embodiment of the invention relates to compounds of general formula IV,



wherein

A denotes N, O, S, or $-(CH_2)_m-$ and is optionally substituted by R^e ;

R^1 denotes H, $-C(O)R^a$, $-(CH_2)_nC(O)OR^a$, or a group, optionally substituted by one or more, identical or different R^a and/or R^b , selected independently from one another among C_{1-8} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-10} aryl, 3-8 membered heterocycloalkyl, and 5-12 membered heteroaryl;

$R^{1'}$ denotes H or C_{1-4} alkyl;

or **R**¹ and **R**^{1'} together with the adjacent nitrogen atom form a 4- to 10-membered heterocyclic group, which optionally may be substituted by one or more, identical or different **R**^a and/or **R**^b;

R^{2'} denotes H or C₁₋₆alkyl;

R⁴ denotes H, -C(O)**R**^a, or a group, optionally substituted by one or more, identical or different **R**^a and/or **R**^b, selected independently from one another among C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₁₀cycloalkyl, C₆₋₁₀aryl, 3-8 membered heterocycloalkyl, and 5-12 membered heteroaryl;

each **R**^a independently of one another denotes hydrogen or a group, optionally substituted by one or more, identical or different **R**^b and/or **R**^c, selected from among C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₁₀cycloalkyl, C₄₋₁₆cycloalkylalkyl, C₆₋₁₀aryl, C₇₋₁₆arylalkyl, 3-8 membered heterocycloalkyl, 4-14 membered heterocycloalkylalkyl, 5-12 membered heteroaryl and 6-18 membered heteroarylalkyl;

each **R**^b is a suitable substituent and is selected in each case independently of one another from among =O, -OR^c, C₁₋₃haloalkyloxy, -OCF₃, =S, -SR^c, =NR^c, =NOR^c, =NNR^cR^c, =NN(R^g)C(O)NR^cR^c, -NR^cR^c, -ONR^cR^c, -N(OR^c)R^c, -N(R^g)NR^cR^c, halogen, -CF₃, -CN, -NC, -OCN, -SCN, -NO, -NO₂, =N₂, -N₃, -S(O)R^c, -S(O)OR^c, -S(O)₂R^c, -S(O)₂OR^c, -S(O)NR^cR^c, -S(O)₂NR^cR^c, -OS(O)R^c, -OS(O)₂R^c, -OS(O)₂OR^c, -OS(O)NR^cR^c, -OS(O)₂NR^cR^c, -C(O)R^c, -C(O)OR^c, -C(O)SR^c, -C(O)NR^cR^c, -C(O)N(R^g)NR^cR^c, -C(O)N(R^g)OR^c, -C(NR^g)NR^cR^c, -C(NOH)R^c, -C(NOH)NR^cR^c, -OC(O)R^c, -OC(O)OR^c, -OC(O)SR^c, -OC(O)NR^cR^c, -OC(NR^g)NR^cR^c, -SC(O)R^c, -SC(O)OR^c, -SC(O)NR^cR^c, -SC(NR^g)NR^cR^c, -N(R^g)C(O)R^c, -N[C(O)R^c]₂, -N(OR^g)C(O)R^c, -N(R^g)C(NR^g)R^c, -N(R^g)N(R^g)C(O)R^c, -N[C(O)R^c]NR^cR^c, -N(R^g)C(S)R^c, -N(R^g)S(O)R^c, -N(R^g)S(O)OR^c, -N(R^g)S(O)₂R^c, -N[S(O)₂R^c]₂, -N(R^g)S(O)₂OR^c, -N(R^g)S(O)₂NR^cR^c, -N(R^g)[S(O)₂]₂R^c, -N(R^g)C(O)OR^c, -N(R^g)C(O)SR^c, -N(R^g)C(O)NR^cR^c, -N(R^g)C(O)NR^gNR^cR^c, -N(R^g)N(R^g)C(O)NR^cR^c, -N(R^g)C(S)NR^cR^c, -[N(R^g)C(O)]₂R^c, -N(R^g)[C(O)]₂R^c, -N{[C(O)]₂R^c}₂, -N(R^g)[C(O)]₂OR^c, -N(R^g)[C(O)]₂NR^cR^c, -N{[C(O)]₂OR^c}₂, -N{[C(O)]₂NR^cR^c}₂, -[N(R^g)C(O)]₂OR^c, -N(R^g)C(NR^g)OR^c, -N(R^g)C(NOH)R^c, -N(R^g)C(NR^g)SR^c and -N(R^g)C(NR^g)NR^cR^c;

each **R**^c independently of one another denotes hydrogen or a group, optionally substituted by one or more, identical or different **R**^d and/or **R**^e, selected from among

C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₁₀cycloalkyl, C₄₋₁₆cycloalkylalkyl, C₆₋₁₀aryl, C₇₋₁₆arylalkyl, 3-8 membered heterocycloalkyl, 4-14 membered heterocycloalkylalkyl, 5-12 membered heteroaryl and 6-18 membered heteroarylalkyl;

each **R^d** denotes a suitable substituent and is selected in each case independently of one another from among =O, -OR^e, C₁₋₃haloalkyloxy, -OCF₃, =S, -SR^e, =NR^e, =NOR^e, =NNR^eR^e, =NN(R^g)C(O)NR^eR^e, -NR^eR^e, -ONR^eR^e, -N(OR^e)R^e, -N(R^g)NR^eR^e, halogen, -CF₃, -CN, -NC, -OCN, -SCN, -NO, -NO₂, =N₂, -N₃, -S(O)R^e, -S(O)OR^e, -S(O)₂R^e, -S(O)₂OR^e, -S(O)NR^eR^e, -S(O)₂NR^eR^e, -OS(O)R^e, -OS(O)₂R^e, -OS(O)₂OR^e, -OS(O)NR^eR^e, -OS(O)₂NR^eR^e, -C(O)R^e, -C(O)OR^e, -C(O)SR^e, -C(O)NR^eR^e, -C(O)N(R^g)NR^eR^e, -C(O)N(R^g)OR^e, -C(NR^g)NR^eR^e, -C(NOH)R^e, -C(NOH)NR^eR^e, -OC(O)R^e, -OC(O)OR^e, -OC(O)SR^e, -OC(O)NR^eR^e, -OC(NR^g)NR^eR^e, -SC(O)R^e, -SC(O)OR^e, -SC(O)NR^eR^e, -SC(NR^g)NR^eR^e, -N(R^g)C(O)R^e, -N[C(O)R^e]₂, -N(OR^g)C(O)R^e, -N(R^g)C(NR^g)R^e, -N(R^g)N(R^g)C(O)R^e, -N[C(O)R^e]NR^eR^e, -N(R^g)C(S)R^e, -N(R^g)S(O)R^e, -N(R^g)S(O)OR^e, -N(R^g)S(O)₂R^e, -N[S(O)₂R^e]₂, -N(R^g)S(O)₂OR^e, -N(R^g)S(O)₂NR^eR^e, -N(R^g)[S(O)₂]₂R^e, -N(R^g)C(O)OR^e, -N(R^g)C(O)SR^e, -N(R^g)C(O)NR^eR^e, -N(R^g)C(O)NR^gNR^eR^e, -N(R^g)N(R^g)C(O)NR^eR^e, -N(R^g)C(S)NR^eR^e, -[N(R^g)C(O)]₂R^e, -N(R^g)[C(O)]₂R^e, -N{[C(O)]₂R^e}₂, -N(R^g)[C(O)]₂OR^e, -N(R^g)[C(O)]₂NR^eR^e, -N{[C(O)]₂OR^e}₂, -N{[C(O)]₂NR^eR^e}₂, -[N(R^g)C(O)]₂OR^e, -N(R^g)C(NR^g)OR^e, -N(R^g)C(NOH)R^e, -N(R^g)C(NR^g)SR^e and -N(R^g)C(NR^g)NR^eR^e;

each **R^e** independently of one another denotes hydrogen or a group selected from among C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₈cycloalkyl, C₆₋₁₀aryl, 3-8 membered heterocycloalkyl, and 5-12 membered heteroaryl;

each **R^g** independently of one another denotes hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₈cycloalkyl, C₆₋₁₀aryl, 3-8 membered heterocycloalkyl, or 5-12 membered heteroaryl;

m denotes 1, 2 or 3;

n denotes 0, 1, 2, or 3;

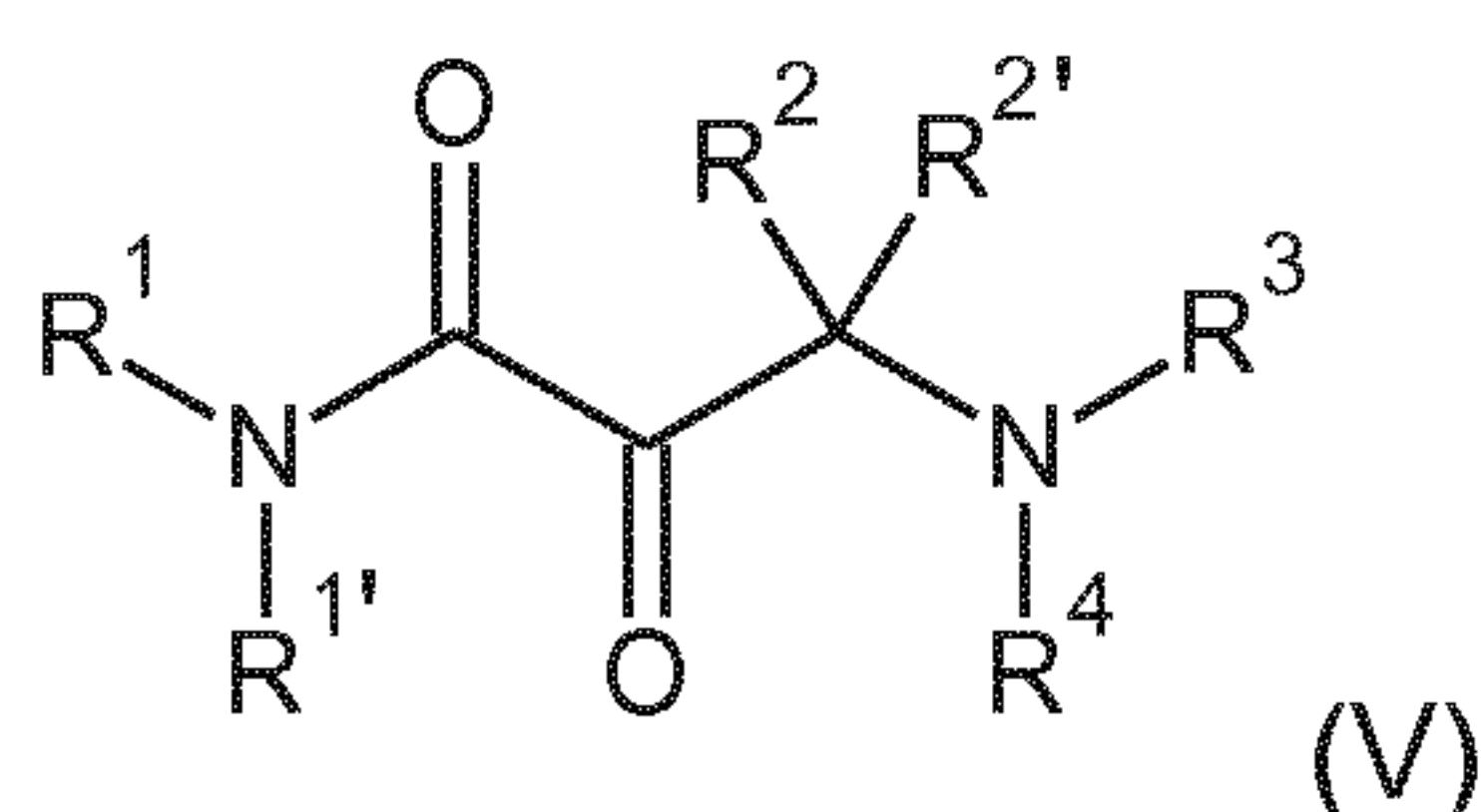
optionally in the form of the tautomers, the racemates, the enantiomers, the diastereomers, hydrates, isotopes, and the mixtures thereof, and optionally the pharmacologically acceptable salts thereof.

[037] One embodiment of the invention relates to compounds of general formula IV as described herein, wherein A is $-(CH_2)-$.

[038] One embodiment of the invention relates to compounds of general formula IV as described herein, wherein R^1 is optionally substituted C_{1-6} alkyl or C_{3-6} cycloalkyl.

[039] One embodiment of the invention relates to compounds of general formula IV as described herein, wherein R^4 is selected from optionally substituted C_{1-6} alkyl, C_{3-6} cycloalkyl, C_6 aryl, 3-8 membered heterocycloalkyl, and 5-6 membered heteroaryl.

[040] One embodiment of the invention relates to compounds of general formula V



wherein

R^1 denotes H, $-C(O)R^a$, $-(CH_2)_nC(O)OR^a$, or a group, optionally substituted by one or more, R^a and/or R^b , selected independently from one another among C_{1-8} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-10} aryl, 3-8 membered heterocycloalkyl, and 5-12 membered heteroaryl;

$R^{1'}$ denotes H or C_{1-4} alkyl;

or R^1 and $R^{1'}$ together with the adjacent nitrogen atom form a 4- to 10-membered heterocyclic group; which optionally may be substituted by one or more, identical or different R^a and/or R^b ;

R^2 denotes H, $-C(O)R^a$, or a group, optionally substituted by one or more, identical or different R^a and/or R^b , selected independently from one another among C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{4-16} cycloalkylalkyl, C_{6-10} aryl, C_{7-16} arylalkyl, 3-8 membered heterocycloalkyl, 4-14 membered heterocycloalkylalkyl, 5-12 membered heteroaryl and 6-18 membered heteroarylalkyl;

or R^2 forms together with R^3 and the adjacent nitrogen a 5–7 membered heterocycloalkyl ring, wherein said heterocycloalkyl ring bears an oxo group, and optionally is substituted by one or more, identical or different R^a and/or R^b ;

$R^{2'}$ denotes H or C_{1-6} alkyl;

R^3 denotes H, $-C(O)R^c$, $-C(O)OR^a$, $-SO_2R^a$ or a group, optionally substituted by one or more, identical or different R^a and/or R^b , selected independently from one another

among C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₁₀cycloalkyl, C₄₋₁₆cycloalkylalkyl, C₆₋₁₀aryl, C₇₋₁₆arylalkyl, 4-14 membered heterocycloalkylalkyl, 5-12 membered heteroaryl and 6-18 membered heteroarylalkyl;

R⁴ denotes H, -C(O)**R**^a, or a group, optionally substituted by one or more, identical or different **R**^a and/or **R**^b, selected independently from one another among C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₁₀cycloalkyl, C₆₋₁₀aryl, 3-8 membered heterocycloalkyl, and 5-12 membered heteroaryl;

or **R**⁴ and **R**³ form together with the adjacent nitrogen atom a 4- to 6-membered heterocycloalkyl ring, wherein said heterocycloalkyl ring bears an oxo group, and optionally is substituted by one or more, identical or different **R**^a and/or **R**^b;

each **R**^a independently of one another denotes hydrogen or a group, optionally substituted by one or more, identical or different **R**^b and/or **R**^c, selected from among C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₁₀cycloalkyl, C₄₋₁₆cycloalkylalkyl, C₆₋₁₀aryl, C₇₋₁₆arylalkyl, 3-8 membered heterocycloalkyl, 4-14 membered heterocycloalkylalkyl, 5-12 membered heteroaryl and 6-18 membered heteroarylalkyl;

each **R**^b is a suitable substituent and is selected in each case independently of one another from among =O, -OR^c, C₁₋₃haloalkyloxy, -OCF₃, =S, -SR^c, =NR^c, =NOR^c, =NNR^cR^c, =NN(R^g)C(O)NR^cR^c, -NR^cR^c, -ONR^cR^c, -N(OR^c)R^c, -N(R^g)NR^cR^c, halogen, -CF₃, -CN, -NC, -OCN, -SCN, -NO, -NO₂, =N₂, -N₃, -S(O)R^c, -S(O)OR^c, -S(O)₂R^c, -S(O)₂OR^c, -S(O)NR^cR^c, -S(O)₂NR^cR^c, -OS(O)R^c, -OS(O)₂R^c, -OS(O)₂OR^c, -OS(O)NR^cR^c, -OS(O)₂NR^cR^c, -C(O)R^c, -C(O)OR^c, -C(O)SR^c, -C(O)NR^cR^c, -C(O)N(R^g)NR^cR^c, -C(O)N(R^g)OR^c, -C(NR^g)NR^cR^c, -C(NOH)R^c, -C(NOH)NR^cR^c, -OC(O)R^c, -OC(O)OR^c, -OC(O)SR^c, -OC(O)NR^cR^c, -OC(NR^g)NR^cR^c, -SC(O)R^c, -SC(O)OR^c, -SC(O)NR^cR^c, -SC(NR^g)NR^cR^c, -N(R^g)C(O)R^c, -N[C(O)R^c]₂, -N(OR^g)C(O)R^c, -N(R^g)C(NR^g)R^c, -N(R^g)N(R^g)C(O)R^c, -N[C(O)R^c]NR^cR^c, -N(R^g)C(S)R^c, -N(R^g)S(O)R^c, -N(R^g)S(O)OR^c, -N(R^g)S(O)₂R^c, -N[S(O)₂R^c]₂, -N(R^g)S(O)₂OR^c, -N(R^g)S(O)₂NR^cR^c, -N(R^g)[S(O)₂]₂R^c, -N(R^g)C(O)OR^c, -N(R^g)C(O)SR^c, -N(R^g)C(O)NR^cR^c, -N(R^g)C(O)NR^gNR^cR^c, -N(R^g)N(R^g)C(O)NR^cR^c, -N(R^g)C(S)NR^cR^c, -[N(R^g)C(O)]₂R^c, -N(R^g)[C(O)]₂R^c, -N{[C(O)]₂R^c}₂, -N(R^g)[C(O)]₂OR^c, -N(R^g)[C(O)]₂NR^cR^c, -N{[C(O)]₂OR^c}₂, -N{[C(O)]₂NR^cR^c}₂, -[N(R^g)C(O)]₂OR^c, -N(R^g)C(NR^g)OR^c, -N(R^g)C(NOH)R^c, -N(R^g)C(NR^g)SR^c and -N(R^g)C(NR^g)NR^cR^c;

each R^c independently of one another denotes hydrogen or a group, optionally substituted by one or more, identical or different R^d and/or R^e , selected from among C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{4-16} cycloalkylalkyl, C_{6-10} aryl, C_{7-16} arylalkyl, 3-8 membered heterocycloalkyl, 4-14 membered heterocycloalkylalkyl, 5-12 membered heteroaryl and 6-18 membered heteroarylalkyl; each R^d denotes a suitable substituent and is selected in each case independently of one another from among $=O$, $-OR^e$, C_{1-3} haloalkyloxy, $-OCF_3$, $=S$, $-SR^e$, $=NR^e$, $=NOR^e$, $=NNR^eR^e$, $=NN(R^g)C(O)NR^eR^e$, $-NR^eR^e$, $-ONR^eR^e$, $-N(OR^e)R^e$, $-N(R^g)NR^eR^e$, halogen, $-CF_3$, $-CN$, $-NC$, $-OCN$, $-SCN$, $-NO$, $-NO_2$, $=N_2$, $-N_3$, $-S(O)R^e$, $-S(O)OR^e$, $-S(O)_2R^e$, $-S(O)_2OR^e$, $-S(O)NR^eR^e$, $-S(O)_2NR^eR^e$, $-OS(O)R^e$, $-OS(O)_2R^e$, $-OS(O)_2OR^e$, $-OS(O)NR^eR^e$, $-OS(O)_2NR^eR^e$, $-C(O)R^e$, $-C(O)OR^e$, $-C(O)SR^e$, $-C(O)NR^eR^e$, $-C(O)N(R^g)NR^eR^e$, $-C(O)N(R^g)OR^e$, $-C(NR^g)NR^eR^e$, $-C(NOH)R^e$, $-C(NOH)NR^eR^e$, $-OC(O)R^e$, $-OC(O)OR^e$, $-OC(O)SR^e$, $-OC(O)NR^eR^e$, $-OC(NR^g)NR^eR^e$, $-SC(O)R^e$, $-SC(O)OR^e$, $-SC(O)NR^eR^e$, $-SC(NR^g)NR^eR^e$, $-N(R^g)C(O)R^e$, $-N[C(O)R^e]_2$, $-N(OR^g)C(O)R^e$, $-N(R^g)C(NR^g)R^e$, $-N(R^g)N(R^g)C(O)R^e$, $-N[C(O)R^e]NR^eR^e$, $-N(R^g)C(S)R^e$, $-N(R^g)S(O)R^e$, $-N(R^g)S(O)OR^e$, $-N(R^g)S(O)_2R^e$, $-N[S(O)_2R^e]_2$, $-N(R^g)S(O)_2OR^e$, $-N(R^g)S(O)_2NR^eR^e$, $-N(R^g)[S(O)_2]_2R^e$, $-N(R^g)C(O)OR^e$, $-N(R^g)C(O)SR^e$, $-N(R^g)C(O)NR^eR^e$, $-N(R^g)C(O)NR^gNR^eR^e$, $-N(R^g)N(R^g)C(O)NR^eR^e$, $-N(R^g)C(S)NR^eR^e$, $-[N(R^g)C(O)]_2R^e$, $-N(R^g)[C(O)]_2R^e$, $-N\{[C(O)]_2R^e\}_2$, $-N(R^g)[C(O)]_2OR^e$, $-N(R^g)[C(O)]_2NR^eR^e$, $-N\{[C(O)]_2OR^e\}_2$, $-N\{[C(O)]_2NR^eR^e\}_2$, $-[N(R^g)C(O)]_2OR^e$, $-N(R^g)C(NR^g)OR^e$, $-N(R^g)C(NOH)R^e$, $-N(R^g)C(NR^g)SR^e$ and $-N(R^g)C(NR^g)NR^eR^e$;

each R^e independently of one another denotes hydrogen or a group selected from among C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{6-10} aryl, 3-8 membered heterocycloalkyl, and 5-12 membered heteroaryl;

each R^g independently of one another denotes hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{6-10} aryl, 3-8 membered heterocycloalkyl, or 5-12 membered heteroaryl;

n denotes 0, 1, 2 or 3;

optionally in the form of the tautomers, the racemates, the enantiomers, the diastereomers, hydrates, isotopes, and the mixtures thereof, and optionally the pharmacologically acceptable salts thereof.

[041] One embodiment of the invention relates to compounds of general formula V as described herein, wherein R¹ is optionally substituted C₁₋₆alkyl or C₃₋₆cycloalkyl.

[042] One embodiment of the invention relates to compounds of general formula V as described herein, wherein R³ is -C(O)R^c, or -SO₂R^a.

[043] One embodiment of the invention relates to compounds of general formula V as described herein, wherein R⁴ is H or optionally substituted C₁₋₆alkyl, C₃₋₆cycloalkyl, or phenyl.

[044] One embodiment of the invention relates to compounds as described herein, wherein the compounds are selected from Table 2.

[045] One embodiment of the invention relates to compounds as described herein, optionally in the form of the tautomers, the racemates, the enantiomers, the diastereomers, hydrates, isotopes, and mixtures thereof, or the pharmacologically acceptable salt thereof, for use as medicament.

[046] The invention contemplates treatment of a wide variety of viral infections in human and/or animal subjects, e.g., infection due to any virus. In some embodiments, the virus is a picornavirus, e.g., a cardiovirus, enterovirus (e.g. a coxsackievirus, a rhinovirus, a poliovirus or echovirus), or hepatovirus. In some embodiments, the virus clusters phylogenetically within the enterovirus genus. In some embodiments, the picornavirus is classified with a species selected from the group consisting of: human enterovirus A, human enterovirus B, human enterovirus C, human enterovirus D, simian enterovirus A, bovine enterovirus, porcine enterovirus B, human rhinovirus A, human rhinovirus B and human rhinovirus C. In some embodiments, the picornavirus is classified with a species selected from the group consisting of: human enterovirus A, human enterovirus B, human enterovirus C, human enterovirus D, human rhinovirus A, human rhinovirus B and human rhinovirus C.

[047] The invention provides use of the compounds for treating diseases and medical conditions resulting from viral infection, e.g., by a picornavirus. Exemplary diseases and conditions include, e.g., asthma exacerbation, bronchiolitis, colitis, common cold, COPD exacerbation, encephalitis, encephalomyelitis, enterocolitis, foot-and-mouth disease, hand-foot-and-mouth disease, gastroenteritis, herpangina, hepatitis, meningitis, meningoencephalitis, myocarditis, pancreatitis, poliomyelitis, and

pneumonia. In some aspects, the invention contemplates *ex vivo* uses of the PLA2G16 inhibitors.

[048] Thus, one embodiment of the invention relates to compounds as described herein, optionally in the form of the tautomers, the racemates, the enantiomers, the diastereomers, hydrates, isotopes, and mixtures thereof, or the pharmacologically acceptable salt thereof, for use as antiviral agents.

[049] A further embodiment of the invention relates to compounds as described herein, optionally in the form of the tautomers, the racemates, the enantiomers, the diastereomers, hydrates, isotopes, and mixtures thereof, or the pharmacologically acceptable salt thereof, for use in the treatment or prevention of infectious diseases, cancer or obesity.

[050] One embodiment of the invention relates to compounds as described herein, optionally in the form of the tautomers, the racemates, the enantiomers, the diastereomers, hydrates, isotopes, and mixtures thereof, or the pharmacologically acceptable salt thereof, for use in treating, preventing, and/or ameliorating viral infections.

[051] One embodiment of the invention relates to compounds as described herein, optionally in the form of the tautomers, the racemates, the enantiomers, the diastereomers, hydrates, isotopes, and mixtures thereof, or the pharmacologically acceptable salt thereof, for use in treating, preventing, and/or ameliorating viral infections caused by a picornavirus, e.g. by a rhinovirus.

[052] One embodiment of the invention relates to pharmaceutical preparations containing as active substance one or more compounds of general formula I as described herein, optionally in the form of the tautomers, the racemates, the enantiomers, the diastereomers, hydrates, isotopes, and mixtures thereof, or the pharmacologically acceptable salt thereof, or the pharmacologically acceptable salts thereof, optionally in combination with conventional excipients and/or carriers.

[053] One embodiment of the invention relates to pharmaceutical preparations comprising a compound of general formula I as described herein, wherein the compounds are optionally present in the form of the tautomers, racemates, enantiomers, diastereomers, hydrates, isotopes, and mixtures thereof, or also as the

respective pharmacologically acceptable salts of all the above mentioned forms, and at least one further active substance different from formula I.

Definitions

[054] As used herein, the following definitions apply, unless stated otherwise:

[055] Unless specified otherwise, the term “alkyl”, when used alone or in combination with other groups or atoms, refers to a saturated straight or branched chain consisting solely of 1 to 6 hydrogen-substituted carbon atoms, and includes methyl, ethyl, propyl, isopropyl, n-butyl, 1-methylpropyl, isobutyl, *tert*-butyl, 2,2-dimethylbutyl, 2,2-dimethylpropyl, n-pentyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, n-hexyl and the like.

[056] Unless specified otherwise, the term “alkenyl” refers to a partially unsaturated straight or branched chain consisting solely of 2 to 6 hydrogen-substituted carbon atoms that contains at least one double bond, and includes vinyl, allyl, 2-methylprop-1-enyl, but-1-enyl, but-2-enyl, but-3-enyl, buta-1,3-dienyl, penta-1,3-dienyl, penta-2,4-dienyl, 2-methylbut-1-enyl, 2-methylpent-1-enyl, 4-methylpent-1-enyl, 4-methylpent-2-enyl, 2-methylpent-2-enyl, 4-methylpenta-1,3-dienyl, hexen-1-yl and the like.

[057] Unless specified otherwise, the term “alkynyl” refers to a partially unsaturated straight or branched chain consisting solely of 2 to 6 hydrogen-substituted carbon atoms that contains at least one triple bond, and includes ethynyl, 1-propynyl, 2-propynyl, 2-methylprop-1-ynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1,3-butadiynyl, 3-methylbut-1-ynyl, 4-methylbut-ynyl, 4-methylbut-2-ynyl, 2-methylbut-1-ynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1,3-pentadiynyl, 1,4-pentadiynyl, 3-methylpent-1-ynyl, 4-methylpent-2-ynyl, 4-methylpent-2-ynyl, 1-hexynyl, and the like.

[058] Unless specified otherwise, the term “cycloalkyl”, when used alone or in combination with other groups or atoms, refers to monocyclic hydrocarbon rings, bicyclic hydrocarbon rings or spirohydrocarbon rings, which each may be either saturated or unsaturated (cycloalkenyl). The term unsaturated means that in the ring system in question there is at least one double bond, but no aromatic system is formed. In bicyclic hydrocarbon rings two rings are linked such that they have at least two carbon atoms in common. In spirohydrocarbon rings one carbon atom (spiroatom) is shared by two rings. If a cycloalkyl is substituted, the substitution may be mono- or polysubstitution in each case, at all the hydrogen-carrying carbon atoms,

independently of one another. Cycloalkyl itself may be linked to the molecule as substituent via any suitable position of the ring system.

[059] Typical examples of individual sub-groups are listed below.

Monocyclic saturated hydrocarbon rings: cyclopropyl; cyclobutyl; cyclopentyl; cyclohexyl; cycloheptyl, etc.

Monocyclic unsaturated hydrocarbon rings: cycloprop-1-enyl; cycloprop-2-enyl; cyclobut-1-enyl; cyclobut-2-enyl; cyclopent-1-enyl; cyclopent-2-enyl; cyclopent-3-enyl; cyclohex-1-enyl; cyclohex-2-enyl; cyclohex-3-enyl; cyclohept-1-enyl; cyclohept-2-enyl; cyclohept-3-enyl; cyclohept-4-enyl; cyclobuta-1,3- dienyl; cyclopenta-1,4-dienyl; cyclopenta-1,3-dienyl; cyclopenta-2,4-dienyl; cyclohexa-1,3- dienyl; cyclohexa-1,5- dienyl; cyclohexa-2,4-dienyl; cyclohexa-1,4-dienyl; cyclohexa-2,5- dienyl, etc.

Saturated and unsaturated bicyclic hydrocarbon rings: bicyclo[1.1.1]pentyl, bicyclo[2.2.0]hexyl; bicyclo[3.2.0]heptyl; bicyclo[3.2.1]octyl; bicyclo[2.2.2]octyl; bicyclo[4.3.0]nonyl (octahydroindenyl); bicyclo[4.4.0]decyl (decahydronaphthalene); bicyclo[2.2.1]heptyl (norbornyl); (bicyclo[2.2.1]hepta-2,5-dienyl (norborna-2,5-dienyl); bicyclo[2.2.1]hept-2-enyl (norbornenyl); bicyclo[4.1.0]heptyl (norcaranyl); bicyclo-[3.1.1]heptyl (pinanyl), etc.

Saturated and unsaturated spirohydrocarbon rings: spiro[2.5]octyl, spiro[3.3]heptyl, spiro[4.5]dec-2-ene, etc.

[060] "Cycloalkylalkyl" denotes the combination of the above-defined groups alkyl, alkenyl, alkynyl, and cycloalkyl, in each case in their broadest sense. The alkyl group as substituent is directly linked to the molecule and is in turn substituted by a cycloalkyl group. The alkyl and cycloalkyl may be linked in both groups via any carbon atoms suitable for this purpose. The respective sub-groups of alkyl and cycloalkyl are also included in the combination of the two groups.

[061] Unless specified otherwise, the term "aryl" refers to an aromatic mono- or bicyclic group containing from 6 to 14 carbon atoms, preferably 6 to 10 carbon atoms, that may be optionally fused with a fully or partially saturated or unsaturated carbocyclic ring and may optionally be substituted with one or more, identical or different substituents, suitably one to three substituents. Examples of aryl groups include phenyl, naphthyl, indanyl, and the like.

[062] "Arylalkyl" denotes the combination of the groups alkyl, alkenyl, alkynyl and aryl as hereinbefore defined, in each case in their broadest sense. The alkyl group as substituent is directly linked to the molecule and is in turn substituted by an aryl group. The alkyl and aryl may be linked in both groups via any carbon atoms suitable for this purpose. Typical examples include benzyl, 1-phenylethyl, 2-phenylethyl, phenylvinyl, phenylallyl, etc.

[063] Unless specified otherwise, the term "heteroaryl" refers to an aromatic mono- or bicyclic group containing from 5 to 14 carbon atoms, preferably 5 to 12 carbon atoms, of which one to five is replaced with a heteroatom selected from N, S and O, that may optionally be reduced to a non-aromatic heterocycle and may optionally be substituted with one or more, identical or different substituents. Examples of heteroaryl groups include pyrrolyl, dihydropyrrolyl, pyrrolidinyl, oxopyrrolidinyl, indolyl, isoindolyl, indoliziny, imidazolyl, pyrazolyl, benzimidazolyl, imidazo(1,2-a)pyridinyl, indazolyl, purinyl, pyrrolo(2,3-c)pyridinyl, pyrrolo(3,2-c)pyridinyl, pyrrolo(2,3-b)pyridinyl, pyrazolo(1,5-a)pyridinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, oxazolyl, 1,2-oxazolyl, isoxazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,3-oxadiazolyl, thiazolyl, isothiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,3-thiadiazolyl, furanyl, dihydrofuranyl, tetrahydrofuranyl, benzofuranyl, isobenzofuranyl, thiophenyl, dihydrothiophenyl, tetrahydrothiophenyl, benzothiophenyl, benzoisothiophenyl, pyridyl, piperidinyl, quinolinyl, isoquinolinyl, tetrahydroisoquinolinyl, quinoliziny, pyrazinyl, pyridazinyl, pyrimidinyl, pyranyl, tetrahydropyranyl, 1,2,3-triazinyl, 1,2,4-triazinyl, 1,3,5-triazinyl, chromenyl, morpholinyl, diazepinyl, benzodiazepinyl, and the like.

[064] "Heteroarylalkyl" denotes the combination of the alkyl, alkenyl, alkynyl, and heteroaryl groups defined hereinbefore, in each case in their broadest sense. The alkyl group as substituent is directly linked to the molecule and is in turn substituted by a heteroaryl group. The linking of the alkyl and heteroaryl may be achieved on the alkyl side via any carbon atoms suitable for this purpose and on the heteroaryl side by any carbon or nitrogen atoms suitable for this purpose.

[065] By the term "heterocycloalkyl" are meant groups which are derived from cycloalkyl as hereinbefore defined if in the hydrocarbon rings one or more of the groups -CH₂- are replaced independently of one another by the groups -O-, -S- or -NH-

or one or more of the groups =CH- are replaced by the group =N-, while not more than five heteroatoms may be present in total, there must be at least one carbon atom between two oxygen atoms and between two sulphur atoms or between one oxygen and one sulphur atom and the group as a whole must be chemically stable.

Heteroatoms may simultaneously be present in all the possible oxidation stages (sulphur -> sulfoxide -SO-, sulphone -SO₂-; nitrogen -> N-oxide). It is immediately apparent from the indirect definition/derivation from cycloalkyl that heterocycloalkyl is made up of the sub-groups monocyclic hetero-rings, bicyclic hetero-rings and spirohetero-rings, while each sub-group can also be further subdivided into saturated and unsaturated (heterocycloalkenyl). The term unsaturated means that in the ring system in question there is at least one double bond, but no aromatic system is formed. In bicyclic hetero-rings two rings are linked such that they have at least two atoms in common. In spirohetero-rings one carbon atom (spiroatom) is shared by two rings. If a heterocycloalkyl is substituted, the substitution may be mono- or polysubstitution in each case, at all the hydrogen-carrying carbon and/or nitrogen atoms, independently of one another. Heterocycloalkyl itself as substituent may be linked to the molecule via any suitable position of the ring system.

[066] The term "heterocyclic group" as used herein refers to a heterocycloalkyl group which optionally may be fused to an aromatic aryl or heteroaryl group.

[067] Typical examples of individual sub-groups are listed below:

Monocyclic heterorings (saturated and unsaturated): oxolane, pyrrolidiny, pyrrolinyl, imidazolidinyl, thiazolidinyl, imidazolinyl, pyrazolidinyl, pyrazolinyl, piperidiny, piperazinyl, oxiranyl, aziridinyl, azetidiny, 1,4-dioxanyl, azepanyl, diazepanyl, morpholinyl, thiomorpholinyl, homomorpholinyl, homopiperidiny, homopiperazinyl, homothiomorpholinyl, thiomorpholinyl-S-oxide, thiomorpholinyl-S,S-dioxide, 1,3-dioxolanyl, oxane, tetrahydrothiopyranyl, 1,4-oxazepanyl, tetrahydrothienyl, homothiomorpholinyl-S,S-dioxide, oxazolidinonyl, dihydropyrazolyl, dihydropyrrolyl, dihydropyrazinyl, dihydropyridyl, dihydro-pyrimidinyl, dihydrofuryl, dihydropyranyl, tetrahydrothienyl-S-oxide, tetrahydrothienyl-S,S-dioxide, homothiomorpholinyl-S-oxide, 2,3-dihydroazet, 2*H*-pyrrolyl, 4*H*-pyranyl, 1,4- dihydropyridinyl, etc;

Bicyclic heterorings (saturated and unsaturated): 8-azabicyclo[3.2.1]octyl, 8-azabicyclo[5.1.0]octyl, 2-oxa-5-azabicyclo[2.2.1]heptyl, 8-oxa- 3-aza-

bicyclo[3.2.1]octyl, 3,8-diaza-bicyclo[3.2.1]octyl, 2,5-diaza-bicyclo-[2.2.1]heptyl, 1-aza-bicyclo[2.2.2]octyl, 3,8-diaza-bicyclo[3.2.1]octyl, 3,9-diaza-bicyclo[4.2.1]nonyl, 2,6-diaza-bicyclo[3.2.2]nonyl, hexahydro-furo[3,2-b]furyl, etc;

Spiro-heterorings (saturated and unsaturated): 1,4-dioxa-spiro[4.5]decyl; 1-oxa-3,8-diaza-spiro[4.5]decyl; 2-oxaspiro[3.3]heptyl, 5-azaspiro[2.4]heptyl, 2,6-diaza-spiro[3.3]heptyl; 2,7-diaza-spiro[4.4]nonyl; 2,6-diaza-spiro[3.4]octyl; 3,9-diaza-spiro[5.5]undecyl; 2,8-diaza- spiro[4.5]decyl, etc.

[068] "Heterocycloalkylalkyl" denotes the combination of the alkyl, alkenyl, alkynyl, and heterocycloalkyl groups defined hereinbefore, in each case in their broadest sense. The alkyl group as substituent is directly linked to the molecule and is in turn substituted by a heterocycloalkyl group. The linking of the alkyl and heterocycloalkyl may be achieved on the alkyl side via any carbon atoms suitable for this purpose and on the heterocycloalkyl side by any carbon or nitrogen atoms suitable for this purpose.

[069] By the term "suitable substituent" is meant a substituent that on the one hand is fitting on account of its valency and on the other hand leads to a system with chemical stability.

[070] It is intended that the definition of any substituent or variable at a particular location in a molecule be independent of its definitions elsewhere in that molecule. It is understood that substituents and substitution patterns on the compounds of this invention can be selected by one of ordinary skill in the art to provide compounds that are chemically stable and that can be readily synthesized by techniques known in the art as well as those methods set forth herein.

[071] The term "tautomers" refer to compounds that are interchangeable forms of a particular compound structure, and that vary in the displacement of hydrogen atoms and electrons. Thus, two structures may be in equilibrium through the movement of π electrons and an atom (usually H). For example, enols and ketones are tautomers because they are rapidly interconverted by treatment with either acid or base.

[072] It is also to be understood that compounds (e.g., dihydro bases described herein) that have the same molecular formula but differ in the nature or sequence of bonding of their atoms or the arrangement of their atoms in space are termed "isomers". Isomers that differ in the arrangement of their atoms in space are termed "stereoisomers".

[073] Stereoisomers that are not mirror images of one another are termed "diastereomers" and those that are non-superimposable mirror images of each other are termed "enantiomers". When a compound has an asymmetric center, for example, it is bonded to four different groups, a pair of enantiomers is possible. An enantiomer can be characterized by the absolute configuration of its asymmetric center and is described by the R- and S-sequencing rules of Cahn and Prelog, or by the manner in which the molecule rotates the plane of polarized light and designated as dextrorotatory or levorotatory (i.e., as (+) or (-)-isomers respectively).

[074] A 50:50 mixture of enantiomers is referred to as a racemic mixture or a racemate, which may occur where there has been no stereoselection or stereospecificity in a chemical reaction or process. The terms "racemic mixture" and "racemate" refer to an equimolar mixture of two enantiomeric species, devoid of optical activity.

[075] The term "hydrate" refers to a compound which is associated with water. Typically, the number of the water molecules contained in a hydrate of a compound is in a definite ratio to the number of the compound molecules in the hydrate.

[076] Any formula or structure given herein, including Formula I compounds, is also intended to represent unlabeled forms as well as isotopically-labeled forms of the compounds. Isotopically-labeled compounds have structures depicted by the formulas given herein except that one or more atoms are replaced by an atom having a selected atomic mass or mass number. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, and chlorine, such as, but not limited to ^2H (deuterium, D), ^3H (tritium), ^{11}C , ^{13}C , ^{14}C , ^{15}N , ^{18}F , ^{31}P , ^{32}P , ^{35}S , ^{36}Cl , and ^{125}I .

[077] The term "pharmacologically acceptable" means compatible with the treatment of animals, in particular, humans. The term pharmacologically acceptable salt includes both pharmacologically acceptable acid addition salts and pharmacologically acceptable basic addition salts.

[078] The term "pharmacologically acceptable acid addition salt" as used herein means any non-toxic organic or inorganic salt of any base compound of the disclosure, or any of its intermediates. Basic compounds of the disclosure that may form an acid addition salt include, for example, compounds that contain a basic nitrogen atom.

Illustrative inorganic acids which form suitable salts include hydrochloric, hydrobromic, sulfuric and phosphoric acids, as well as metal salts such as sodium monohydrogen orthophosphate and potassium hydrogen sulfate. Illustrative organic acids that form suitable salts include mono-, di-, and tricarboxylic acids such as glycolic, lactic, pyruvic, malonic, succinic, glutaric, fumaric, malic, tartaric, citric, ascorbic, maleic, benzoic, phenylacetic, cinnamic and salicylic acids, as well as sulfonic acids such as p-toluene sulfonic and methanesulfonic acids. Either the mono-, di- or the triacid salts can be formed, and such salts may exist in either a hydrated, solvated or substantially anhydrous form. In general, the acid addition salts of the compounds of the disclosure are more soluble in water and various hydrophilic organic solvents, and generally demonstrate higher melting points in comparison to their free base forms. The selection of the appropriate salt will be known to one skilled in the art. Other non-pharmacologically acceptable acid addition salts, e.g. oxalates, may be used, for example, in the isolation of the compounds of the disclosure, for laboratory use, or for subsequent conversion to a pharmacologically acceptable acid addition salt.

[079] The term “pharmacologically acceptable basic salt” as used herein means any non-toxic organic or inorganic basic addition salt of any acid compound of the invention, or any of its intermediates, which are suitable for or compatible with the treatment of animals, in particular humans. Acidic compounds of the invention that may form a basic addition salt include, for example compounds that contain carboxylic acid, sulfonic acid, sulfinic acid, sulfonamide, N-unsubstituted tetrazole, phosphoric acid ester, or sulfuric acid ester. Illustrative inorganic bases which form suitable salts include lithium, sodium, potassium, calcium, magnesium, or barium hydroxide. Illustrative organic bases which form suitable salts include aliphatic, alicyclic or aromatic organic amines such as methylamine, trimethylamine and picoline or ammonia. The selection of the appropriate salt will be known to a person skilled in the art. Other non-pharmacologically acceptable basic addition salts, may be used, for example, in the isolation of the compounds of the invention, for laboratory use, or for subsequent conversion to a pharmacologically acceptable basic addition salt. The formation of a desired compound salt is achieved using standard techniques. For example, the neutral compound is treated with a base in a suitable solvent and the formed salt is isolated by filtration, extraction or any other suitable method.

[080] The term “therapeutically effective amount”, “effective amount” or “sufficient amount” of a compound of the present invention is a quantity sufficient to, when administered to the subject, including a mammal, for example a human, effect beneficial or desired results, including clinical results, and, as such, an effective amount or synonym thereof depends upon the context in which it is being applied.

Abbreviations

AcOH	acetic acid
atm	atmosphere
Boc	<i>tert</i> -butyloxycarbonyl
CHCl ₃	chloroform
CO ₂	carbon dioxide
conc	concentrated
CV	column volume
1,2-DCE	1,2-dichloroethane
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DIPEA	<i>N,N</i> -diisopropyl- <i>N</i> -ethylamine
DMF	<i>N,N</i> -dimethylformamide
DMP	Dess-Martin periodinane (1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1 <i>H</i>)-one)
DMSO	dimethylsulfoxide
ee	enantiomeric excess
ESI	electron-spray ionisation
Et ₂ O	diethyl ether
EtOAc	ethyl acetate
EtOH	ethanol
g	gram
h	hour
H ₂ O	water
H ₂ SO ₄	sulfuric acid
HATU	1-[bis(dimethylamino)methylene]-1 <i>H</i> -1,2,3-triazolo[4,5- <i>b</i>]pyridinium

	3-oxid hexafluorophosphate
HBr	hydrogen bromide
HCl	hydrochloric acid
HPLC	high-performance liquid chromatography
I	intermediate
IBX	2-iodoxybenzoic acid
IPA	isopropanol
K ₂ CO ₃	potassium carbonate
KI	potassium iodide
LC	liquid chromatography
LiOH	lithium hydroxide
<i>m</i> -CPBA	meta-chloroperoxybenzoic acid
MeCN	acetonitrile
MeOH	methanol
MgSO ₄	magnesium sulfate
mHz	mega Hertz
min	minute
mL	milliliter
NaBH ₄	sodium borohydride
NaCNBH ₃	sodium cyanoborohydride
NaH	sodium hydride
NaHCO ₃	sodium bicarbonate
NaOEt	sodium ethoxide
NaOH	sodium hydroxide
Na ₂ S ₂ O ₃	sodium thiosulfate
Na ₂ SO ₄	sodium sulfate
NH ₄ Cl	ammonium chloride
NMR	nuclear magnetic resonance
Pc/C	palladium on carbon
ppm	parts per million
RT	room temperature
Rt	retention time

sec	second
SFC	supercritical fluid chromatography
STAB	sodium triacetoxyborohydride
T3P	propylphosphonic anhydride
TBME	<i>tert</i> -butyl methyl ether
TEA	<i>N,N,N</i> -triethylamine
TFA	trifluoroacetic acid
THF	tetrahydrofuran
UV	ultraviolet

Examples

[081] The Examples which follow are set forth to aid in the understanding of the invention but are not intended to, and should not be construed to limit the scope of the invention in any way. The Examples do not include detailed descriptions of conventional methods. Such methods are well known to those of ordinary skill in the art.

GENERAL EXPERIMENTAL DETAILS

[082] Commercially available reagents and solvents (HPLC grade) were used without further purification. ¹H NMR spectra were recorded on a Bruker DRX 500 MHz spectrometer or a Bruker DPX 250 MHz spectrometer in deuterated solvents. Chemical shifts (δ) are in parts per million.

[083] Compounds were purified by flash column chromatography on normal phase silica on Biotage Isolera systems using the appropriate SNAP cartridge and gradient. Alternatively, compounds were purified on reverse phase silica using Biotage Isolera systems with the appropriate SNAP C18 cartridges and reverse phase eluent or by preparative LC (if stated otherwise).

Reverse phase chromatography using acidic pH, standard elution method

[084] Purifications by flash column chromatography on reverse phase silica (acidic pH, standard elution method) were performed on Biotage Isolera systems using the appropriate SNAP C18 cartridge and a gradient of 10% B (A= 0.1% formic acid in water; B= 0.1% formic acid in acetonitrile) over 1.7 CV then 10-100% B over 19.5 CV and 100% B for 2 CV.

Reverse phase chromatography using basic pH, standard elution method

[085] Purifications by flash column chromatography on reverse phase silica (basic pH, standard elution method) were performed on Biotage Isolera systems using the appropriate SNAP C18 cartridge and a gradient of 10% B (A= 0.1% ammonia hydroxide in water; B= 0.1 ammonia hydroxide in acetonitrile) over 2 CV then 10-100% B over 19.5 CV and 100% B for 2 CV.

Preparative LC using acidic pH, standard elution method

[086] Purifications by preparative LC (acidic pH, standard elution method) were performed on a Gilson LC system using a Waters Sunfire C18 column (30 mm x 10 mm, 10 μ M; temperature: RT) and a gradient of 30-95% B (A= 0.1% formic acid in water; B= 0.1% formic acid in acetonitrile) over 11.00 min then 95% B for 2.10 min, with an injection volume of 1500 μ L and a flow rate of 40 mL/min. UV spectra were recorded at 215 nm using a Gilson detector.

Preparative LC using acidic pH, early elution method

[087] Purifications by preparative LC (acidic pH, early elution method) were performed on a Gilson LC system using a Waters Sunfire C18 column (30 mm x 100 mm, 10 μ M; temperature: RT) and a gradient of 10-95% B (A= 0.1% formic acid in water; B= 0.1% formic acid in acetonitrile) over 14.44 min then 95% B for 2.11 min, with an injection volume of 1500 μ L and a flow rate of 40 mL/min. UV spectra were recorded at 215 nm using a Gilson detector.

Preparative LC using basic pH, standard elution method

[088] Purifications by preparative LC (basic pH, standard elution method) were performed on a Gilson LC system using Waters Xbridge C18 columns (30 mm x 100 mm, 10 μ M; temperature: RT) and a gradient of 30-95% (A= 0.2% ammonium hydroxide in water; B= 0.2% ammonium hydroxide in acetonitrile) over 11.00 min then 100% B for 2.10 min, with an injection volume of 1500 μ L and a flow rate of 40 mL/min. UV spectra were recorded at 215 nm using a Gilson detector.

Preparative LC using basic pH, early elution method

[089] Purifications by preparative LC (basic pH, early elution method) were performed on a Gilson LC system using a Waters Xbridge C18 column (30 mm x 100 mm, 10 μ M; temperature: RT) and a gradient of 10-95% (A= 0.2% ammonium hydroxide in water; B= 0.2% ammonium hydroxide in acetonitrile) over 14.44 min then

100% B for 2.11 min, with an injection volume of 1500 μ L and a flow rate of 40 mL/min. UV spectra were recorded at 215 nm using a Gilson detector.

Preparative LC using neutral pH, standard elution method

[090] Purifications by preparative LC (acidic pH, standard elution method) were performed on a Gilson LC system using Waters Sunfire C18 columns (30 mm x 10 mm, 10 μ M; temperature: RT) and a gradient of 10-100% B (A= water; B= acetonitrile) over 14.5 min then 100% B for 1.0 min, with an injection volume of 1500 μ L and a flow rate of 40 mL/min. UV spectra were recorded at 215 nm using a Gilson detector.

Method METCR0990

[091] Analytical METCR0990 HPLC-MS were performed on a Agilent G1312A system with Waters PDA and ELS detectors using a Phenomenex Gemini-NX C18 column (2.0 mm x 50 mm, 3 μ M; temperature: 40 °C) and a gradient of 1-100% (A= 2 mM ammonium bicarbonate, buffered to pH 10 with ammonium hydroxide solution; B = acetonitrile) over 1.8 min then 100% B for 0.3 min, with an injection volume of 3 μ L and a flow rate of 1.0 mL/min. UV spectra were recorded at 215 nm using a Waters 2996 photo diode array detector. Mass spectra were obtained over the range m/z 150 to 850 at a sampling rate of 5 scans per sec using a Waters ZQ. Data were integrated and reported using Waters MassLynx and OpenLynx software.

Method METCR1278

[092] Analytical METCR1278 HPLC-MS were performed on Waters HPLC system systems using reverse phase Water Atlantis dC18 columns (2.1 mm x 50 mm, 3 μ m; temperature: 40 °C) and a gradient of 5-100% B (A= 0.1% formic acid in water; B= 0.1% formic acid in acetonitrile) over 2.5 min then 100% B for 0.2 min, with an injection volume of 3 μ L and a flow rate of 1.0 mL/min. UV spectra were recorded at 215 nm using a Waters UV detector. Mass spectra were obtained over the range m/z 150 to 850 at a sampling rate of 2 scans per sec using a Waters ZQ. Data were integrated and reported using Waters MassLynx and OpenLynx software.

Method METCR1410

[093] Analytical METCR1410 HPLC-MS were performed on Shimadzu LCMS-2010EV systems using reverse phase Kinetex Core shell C18 columns (2.1 mm x 50 mm, 5 μ m; temperature: 40 °C) and a gradient of 5-100% B (A= 0.1% formic acid in water; B= 0.1% formic acid in acetonitrile) over 1.2 min then 100% B for 0.1 min, with

an injection volume of 3 μ L and a flow rate of 1.2 mL/min. UV spectra were recorded at 215 nm using a SPD-M20A photo diode array detector. Mass spectra were obtained over the range m/z 150 to 850 at a sampling rate of 2 scans per sec using a LCMS2010EV. Data were integrated and reported using Shimadzu LCMS-Solutions and PsiPort software.

Method METCR1416

[094] Analytical METCR1416HPLC-MS were performed on Shimadzu LCMS-2010EV systems using reverse phase Water Atlantis dC18 columns (2.1 mm x 50 mm, 3 μ m; temperature: 40 °C) and a gradient of 5-100% B (A= 0.1% formic acid in water; B= 0.1% formic acid in acetonitrile) over 5.0 min then 100% B for 0.4 min, with an injection volume of 3 μ L and a flow rate of 0.6 mL/min. UV spectra were recorded at 215 nm using a SPD-M20A photo diode array detector. Mass spectra were obtained over the range m/z 150 to 850 at a sampling rate of 2 scans per sec using a LCMS2010EV. Data were integrated and reported using Shimadzu LCMS-Solutions and PsiPort software.

Method METCR1600

[095] Analytical METCR1600I HPLC-MS were performed on a Agilent G1312A system with Waters PDA and ELS detectors using a Phenomenex Gemini-NX C18 column (2.0 mm x 100 mm, 3 μ M; temperature: 50 °C) and a gradient of 5-100% (A = 2 mM ammonium bicarbonate, buffered to pH 10 with ammonium hydroxide solution; B = acetonitrile) over 5.5 min then 100% B for 0.4 min, with an injection volume of 3 μ L and a flow rate of 0.5 mL/min. UV spectra were recorded at 215 nm using a Waters 2996 photo diode array detector. Mass spectra were obtained over the range m/z 100 to 1000 at a sampling rate of 5 scans per sec using a Waters ZQ. Data were integrated and reported using Waters MassLynx and OpenLynxsoftware.

Method METCR1602

[096] Analytical METCR1602 HPLC-MS were performed on a Waters Acquity UPLC system with Waters Acquity PDA detector using a Waters BEH C18 column (30 x 2 mm, 1.7 μ m column; temperature: 40 °C) and a gradient of 5-100% (A= 2 mM ammonium bicarbonate, buffered to pH 10; B = acetonitrile) over 0.75 min then 100% B for 0.1 min, with an injection volume of 2 μ L and a flow rate of 1.0 mL/min. UV spectra were recorded at 215 nm using a Waters Acquity photo diode array detector.

Mass spectra were obtained over the range m/z 100 to 1000 at a sampling rate of 5 scans per sec using a Water QDa mass detector. Data were integrated and reported using Waters MassLynx and OpenLynx software.

Method METCR1603

[097] Analytical METCR1603 HPLC-MS were performed on a Agilent G1312A system with Waters 2996 PDA detector and Waters 2420 ELS detector using a Phenomenex Gemini –NX C18 column (2.0 x 100mm, 3 μ m column; temperature: 40 °C) and a gradient of 5-100% (A= 2 mM ammonium bicarbonate, buffered to pH 10; B = acetonitrile) over 5.5 min then 100% B for 0.4 min, with an injection volume of 3 μ L and a flow rate of 0.6 mL/min. UV spectra were recorded at 215 nm using a Waters Acquity photo diode array detector. Mass spectra were obtained over the range m/z 150 to 850 at a sampling rate of 5 scans per sec using a Waters ZQ mass detector. Data were integrated and reported using Waters MassLynx and OpenLynx software.

Method METCR1673

[098] Analytical METCR1673 HPLC-MS were performed on a Waters 2795 system with Waters PDA and ELS detectors using a Supelco Ascentis Express column (2.1 x 30 mm, 2.7 μ m; temperature: 40 °C) and a gradient of 5-100% (A= water + 0.1% formic acid; B = acetonitrile + 0.1% formic acid) over 1.5 min then 100% B for 0.1 min, with an injection volume of 3 μ L and a flow rate of 1.0 mL/min. UV spectra were recorded at 215 nm using a Waters 2996 photo diode array detector. Mass spectra were obtained over the range m/z 100 to 1000 at a sampling rate of 5 scans per sec using a Shimadzu LCMS2010EV. Data were integrated and reported using the PsiPort data browser.

Method MET-uHPLC-AB-101

[099] Analytical MET-uHPLC-AB-101 HPLC-MS were performed on a Waters Acquity uPLC system with Waters PDA and ELS detectors using a Phenomenex Kinetex-XB C18 column (2.1 mm x 100 mm, 1.7 μ M; temperature: 40 °C) and a gradient of 5-100% B (A = 0.1% formic acid in water; B = 0.1% formic acid in acetonitrile) over 5.3 min then 100% B for 0.5 min, with an injection solution of 3 μ L and a flow rate of 0.6 mL/min. UV spectra were recorded at 215 nm using a Waters Acquity photo diode array detector. Mass spectra were obtained over the range m/z

150 to 850 at a sampling rate of 5 scans per sec using a Waters SQD. Data were integrated and reported using Waters MassLynx and OpenLynx software.

Method MET-uHPLC-AB-102

[0100] Analytical MET-uHPLC-AB-102 HPLC-MS were performed on a Waters Acquity uPLC system with Waters PDA and ELS detectors using a Waters uPLC CSH C18 column (2.1 mm x 100 mm, 1.7 μ M; temperature: 40 °C) and a gradient of 5-100% (A= 2 mM ammonium bicarbonate, buffered to pH 10 with ammonium hydroxide solution; B = acetonitrile) over 5.3 min then 100% B for 0.5 min a flow rate of 0.6 mL/min. UV spectra were recorded at 215 nm using a Waters Acquity photo diode array detector. Mass spectra were obtained over the range m/z 150 to 850 at a sampling rate of 5 scans per sec using a Waters Quatro Premier XE. Data were integrated and reported using Waters MassLynx and OpenLynx software.

Method Achiral SFC

[0101] Analytical Achiral SFC HPLC-MS were performed on Waters SFC system using Waters Viridis 2-EP columns (4.6 mm x 250 mm, 5 μ m; temperature: 40 °C) and an isocratic eluent of 1:4 ACN/CO₂ over 10 min, with an injection volume of 10 μ L and a flow rate of 4.0 mL/min. UV spectra were recorded at 215 nm using a Waters 2998 photo diode array detector. Mass spectra were obtained over the range m/z 150 to 850 at a sampling rate of 5 scans per sec using a Waters 3100. Data were integrated and reported using Waters MassLynx and OpenLynx software.

Method CAM-A1

[0102] Analytical CAM-A1 chiral HPLC were performed on Waters LC system using Chiralcel OJ-H columns (4.6 mm x 250 mm, 5 μ m; temperature: RT) and an isocratic eluent of 7/3 heptane/IPA over 15 min, with an injection volume of 20 μ L and a flow rate of 0.5 mL/min. UV spectra were recorded at 215 nm using a Waters 2996 photo diode array detector. Data were integrated and reported using Waters MassLynx and OpenLynx software.

Method CAM-A2

[0103] Analytical CAM-A2 chiral HPLC were performed on Waters LC system using Chiralcel OJ-H columns (4.6 mm x 250 mm, 5 μ m; temperature: RT) and an isocratic eluent of 9/1 heptane/IPA over 10 min, with an injection volume of 20 μ L and a flow rate of 1 mL/min. UV spectra were recorded at 215 nm using a Waters 2996 photo

diode array detector. Data were integrated and reported using Waters MassLynx and OpenLynx software.

Method CAM-F1

[0104] Analytical CAM-F1 chiral HPLC were performed on Waters SFC system using Chiralpak AD-H columns (4.6 mm x 250 mm, 5 μ m; temperature: 40 °C) and an isocratic eluent of 1:4 MeOH/CO₂ over 10 min, with an injection volume of 10 μ L and a flow rate of 4.0 mL/min. UV spectra were recorded at 215 nm using a Waters 2998 photo diode array detector. Data were integrated and reported using Waters MassLynx and OpenLynx software.

Method CAM-F2

[0105] Analytical CAM-F2 chiral HPLC were performed on Waters LC system using Chiralpak AS-H columns (4.6 mm x 250 mm, 5 μ m; temperature: RT) and an isocratic eluent of 85/15 heptane/EtOH over 40 min, with an injection volume of 20 μ L and a flow rate of 0.5 mL/min. UV spectra were recorded at 254 nm using a Waters 2996 photo diode array detector. Data were integrated and reported using Waters MassLynx and OpenLynx software.

Method CAM-F3

[0106] Analytical CAM-F3 chiral LC were performed on Waters LC system using Chiralpak AS-H columns (4.6 mm x 250 mm, 5 μ m; temperature: RT) and an isocratic eluent of 2/3 heptane/EtOH over 30 min, with an injection volume of 20 μ L and a flow rate of 1 mL/min. UV spectra were recorded at 254 nm using a Waters 2996 photo diode array detector. Data were integrated and reported using Waters MassLynx and OpenLynx software.

Method CAM-F4

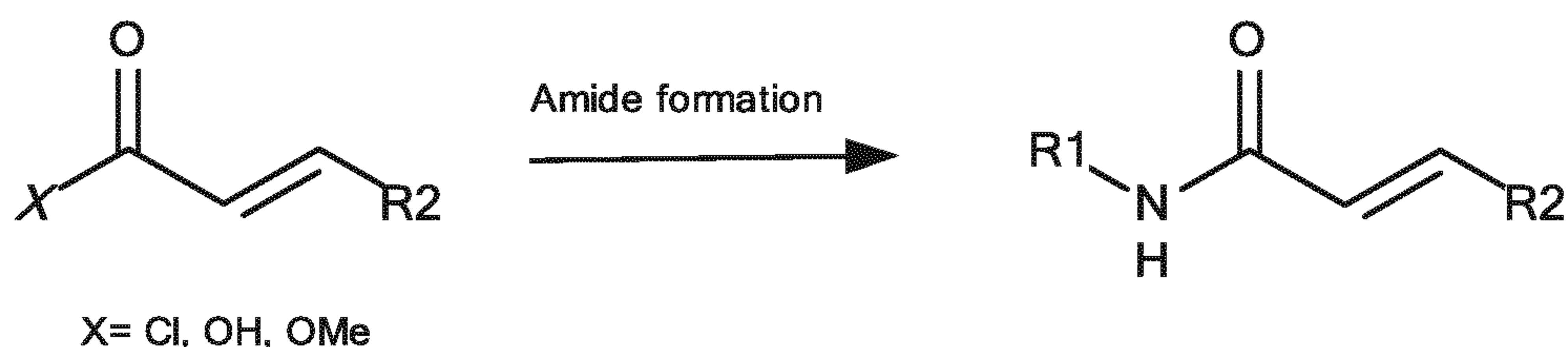
[0107] Analytical CAM-F4 chiral LC were performed on Waters LC system using Chiralpak AS-H columns (4.6 mm x 250 mm, 5 μ m; temperature: RT) and an isocratic eluent of 7/3 heptane/EtOH over 60 min, with an injection volume of 20 μ L and a flow rate of 1 mL/min. UV spectra were recorded at 254 nm using a Waters 2996 photo diode array detector. Data were integrated and reported using Waters MassLynx and OpenLynx software.

[0108] All compounds displayed a purity >95% as determined by these methods unless otherwise stated.

[0109] Compound names were generated using ChemAxon software: Instant JChem Excel IUPAC Name function.

EPOXIDE ROUTE: SYNTHESIS OF INTERMEDIATES I-1-I-26

GENERAL SCHEME 1:



Method A: Amide formation using acid chloride

(2E)-N-[(3-Chlorophenyl)methyl]but-2-enamide (I-1)

[0110] To a stirred solution of (3-chlorophenyl)methanamine (2.34 mL, 19.13 mmol) and DIPEA (10 mL, 57.41 mmol) in DCM (50 mL) at 0 °C was added (2E)-but-2-enoyl chloride (1.83 mL, 19.13 mmol) dropwise, and the resulting mixture stirred at RT, under nitrogen for 2 h. The solution was washed with saturated K₂CO₃ (20 mL) followed by 1N HCl (20 mL). The organic layer was separated, dried over sodium sulfate, filtered and concentrated *in vacuo*. The residue was suspended in Et₂O (30 mL), the precipitate was filtered and washed with Et₂O (2 x 15 mL) to afford 2 g of the title compound (50%) as an off-white solid. The filtrate was concentrated and suspended in Et₂O (20 mL) to afford, after filtration, 0.65 g of the required amide (16%). The two crops were combined to give 2.65 g of (2E)-N-[(3-chlorophenyl)methyl]but-2-enamide as an off-white solid (99% purity, 76%) which was used in the next step without further purification.

¹H NMR (250 MHz, Chloroform-d) δ 1.87 (dd, *J* = 6.9, 1.7 Hz, 3H), 4.48 (d, *J* = 5.9 Hz, 2H), 5.82 (dq, *J* = 15.2, 1.6 Hz, 2H), 6.79-7.01 (m, 1H), 7.11-7.33 (m, 4H).

LC-MS (METCR1410): 99% (UV), Rt= 1.02 min, m/z (ESI⁺)= 210.1/212.1 [M+H]⁺

N-[(3-Chlorophenyl)methyl]-3-methylbut-2-enamide (I-2)

[0111] The title compound was synthesized in a similar manner to method A, general scheme 1, as a yellow viscous oil (5.1 g, 100% purity, quantitative) which was used in the next step without further purification.

¹H NMR (500 MHz, Chloroform-d) δ 1.85 (d, *J* = 1.3 Hz, 3H), 2.18 (d, *J* = 1.2 Hz, 3H), 4.43 (d, *J* = 6.0 Hz, 2H), 5.58-5.61 (m, 1H), 5.85 (s, 1H), 7.14-7.18 (m, 1H), 7.21-7.25 (m, 2H), 7.25-7.27 (m, 1H).

LC-MS (METCR1278): 100% (UV), Rt= 1.95 min, m/z (ESI⁺)= 223.9/225.9 [M+H]⁺

(2E)-N-[(3-Chlorophenyl)methyl]-3-phenylprop-2-enamide (I-3)

[0112] The title compound was synthesized in a similar manner to method A, general scheme 1 as a yellow solid (6 g, 94% purity, quantitative) and was used in the next step without further purification.

¹H NMR (250 MHz, Chloroform-d) δ 4.55 (d, J = 5.9 Hz, 2H), 5.90-6.12 (m, 1H), 6.37-6.58 (m, 1H), 7.18-7.28 (m, 3H), 7.29-7.33 (m, 1H), 7.33-7.45 (m, 3H), 7.46-7.61 (m, 2H), 7.63-7.90 (m, 1H).

LC-MS (METCR1278): 94% (UV), R_t = 2.10 min, m/z (ESI⁺) = 271.9/273.9 [M+H]⁺

(2E)-N-(Cyclopropylmethyl)but-2-enamide (I-4)

[0113] The title compound was synthesized in a similar manner to method A, general scheme 1 as a white crystalline solid (4.86 g, 90% purity by ¹H NMR, 69%) after purification by flash column chromatography on normal phase silica (100 g SNAP HP-SIL cartridge, 10-100% EtOAc in heptane gradient).

¹H NMR (500 MHz, Chloroform-d) δ 0.15-0.26 (m, 2H), 0.41-0.54 (m, 2H), 0.88-1.04 (m, 1H), 1.82-1.88 (m, 3H), 3.16 (dd, J = 5.6, 7.1 Hz, 2H), 5.56-5.73 (m, 1H), 5.77-5.85 (m, 1H), 6.76-6.92 (m, 1H).

LC-MS (METCR1410): 89% (UV), R_t = 0.82 min, m/z (ESI⁺) = 140.1 [M+H]⁺

(2E)-N-Cyclopropylbut-2-enamide (I-5)

[0114] The title compound was synthesized in a similar manner to method A, general scheme 1 as a yellow crystalline solid (3.91 g, 93% purity by ¹H NMR, 83%) used in the next step without further purification.

¹H NMR (250 MHz, Chloroform-d) δ 0.39-0.56 (m, 2H), 0.76 (q, J = 7.0 Hz, 2H), 1.81 (dd, J = 1.5, 6.9 Hz, 3H), 2.75 (tq, J = 3.6, 7.1 Hz, 1H), 5.67-6.00 (m, 2H), 6.81 (dq, J = 6.9, 13.7 Hz, 1H).

LC-MS (METCR1410): 97% (UV), R_t = 0.59 min, m/z (ESI⁺) = 126.0 [M+H]⁺

(2E)-N-(2-methylpropyl)but-2-enamide (I-6)

[0115] The title compound was synthesized in a similar manner to method A, general scheme 1 as a colourless powder (6.08 g, 100% purity, 90%) following purification by recrystallization from hot heptane.

¹H NMR (250 MHz, Chloroform-d) δ 0.91 (d, J = 6.7 Hz, 6H), 1.80-1.72 (m, 1H), 1.84 (dd, J = 6.9, 1.7 Hz, 3H), 3.13 (t, 2H), 5.54 (s, 1H), 5.80 (dd, J = 15.2, 1.7 Hz, 1H), 6.82 (dq, J = 15.0, 6.9 Hz, 1H).

LC-MS (METCR1410): 100% (UV), R_t = 0.94 min, m/z (ESI⁺)= 141.9 [M+H]⁺

N[(3-Chlorophenyl)methyl]prop-2-enamide (I-7)

[0116] The title compound was synthesized in a similar manner to method A, general scheme 1 as an off-white solid (3.8 g, 80% purity by ¹H NMR, 81%) used in the next step without further purification.

¹H NMR (250 MHz, Chloroform-*d*) δ 4.47 (d, J = 6.0 Hz, 2H), 5.67 (dd, J = 1.6, 10.1 Hz, 1H), 6.04-6.24 (m, 2H), 6.32 (dd, J = 1.6, 17.0 Hz, 1H), 7.11-7.31 (m, 4H).

LC-MS (METCR1410): 84% (UV), R_t = 0.98 min, m/z (ESI⁺)= 196.0/198.0 [M+H]⁺

(2*E*)-*N*-(Cyclohexylmethyl)but-2-enamide (I-8)

[0117] The title compound was synthesized in a similar manner to method A, general scheme 1 as an off-white solid (1.56 g, 100% purity, 97%) after purification by flash column chromatography on normal phase silica (100 g SNAP KP-SIL cartridge, 0-100% TBME in heptane gradient).

¹H NMR (250 MHz, Chloroform-*d*) δ 0.81-1.03 (m, 2H), 1.10-1.33 (m, 3H), 1.39-1.52 (m, 1H), 1.62-1.78 (m, 5H), 1.85 (dd, J = 1.7, 6.9 Hz, 3H), 3.16 (t, J = 6.5 Hz, 2H), 5.41 (s, 1H), 5.67-5.86 (m, 1H), 6.74-6.94 (m, 1H).

LC-MS (METCR1410): 100% (UV), R_t = 1.03 min, m/z (ESI⁺)= 182.4 [M+H]⁺

(2*E*)-*N*[2-(Cyclohexyloxy)ethyl]but-2-enamide (I-9)

[0118] The title compound was synthesized in a similar manner to method A, general scheme 1 as an off-white solid (905 mg, 99% purity, 61%) after purification by flash column chromatography on normal phase silica (25 g SNAP KP-SIL cartridge, 0-100% TBME in heptane gradient).

¹H NMR (250 MHz, Chloroform-*d*) δ 1.13-1.36 (m, 6H), 1.48-1.59 (m, 1H), 1.68-1.79 (m, 1H), 1.81-1.94 (m, 5H), 3.13-3.38 (m, 1H), 3.38-3.65 (m, 4H), 5.62-6.07 (m, 2H), 6.70-6.97 (m, 1H).

LC-MS (METCR1410): 99% (UV), R_t = 1.08 min, m/z (ESI⁺)= 212.1 [M+H]⁺

Methyl 2-[(2*E*)-but-2-enamido]acetate (I-10)

[0119] The title compound was synthesized in a similar manner to method A, general scheme 1 as a yellow free-flowing oil (2.4 g, 95% purity by ¹H NMR, 76%) used in the next step without further purification.

¹H NMR (500 MHz, Chloroform-d) δ 1.86 (dd, *J* = 1.7, 6.9 Hz, 3H), 3.77 (s, 3H), 4.11 (d, *J* = 5.2 Hz, 2H), 5.87 (dq, *J* = 1.6, 15.2 Hz, 1H), 5.96 (br. s, 1H), 6.88 (dq, *J* = 6.9, 15.0 Hz, 1H).

LC-MS (METCR0990): 100% (UV), *R*_t = 1 min, *m/z* (ESI⁺) = 158.2 [M+H]⁺

(2E)-N-[2-(3-Chlorophenyl)propan-2-yl]but-2-enamide (I-11)

[0120] The title compound was synthesized in a similar manner to method A, general scheme 1 as an off-white solid (1.9 g, 97% purity, 66%) after purification by flash column chromatography on normal phase silica (100 g SNAP KP-SIL cartridge, 0-100% EtOAc in heptane gradient).

¹H NMR (500 MHz, DMSO-d₆) δ 1.55 (s, 6H), 1.78 (dd, *J* = 6.9, 1.5 Hz, 3H), 6.04 (dd, *J* = 15.3, 1.7 Hz, 1H), 6.40-6.58 (m, 1H), 7.17-7.35 (m, 4H), 8.13 (s, 1H).

LC-MS (METCR1410): 97% (UV), *R*_t = 1.13 min, *m/z* (ESI⁺) = 238.1/240.0 [M+H]⁺

(2E)-N-tert-Butylbut-2-enamide (I-12)

[0121] The title compound was synthesized in a similar manner to method A, general scheme 1 as a colourless powder (597 mg, 100% purity, 65%) after purification by recrystallization from EtOAc.

¹H NMR (250 MHz, Chloroform-d) δ 1.37 (s, 9H), 1.82 (dd, *J* = 1.5, 6.9 Hz, 3H), 5.23 (s, 1H), 5.71 (dd, *J* = 1.7, 15.1 Hz, 1H), 6.66-6.89 (m, 1H).

LC-MS (METCR1278): 100% (UV), *R*_t = 1.41 min, *m/z* (ESI⁺) = 142.0 [M+H]⁺

(2E)-N-(Propan-2-yl)but-2-enamide (I-13)

[0122] The title compound was synthesized in a similar manner to method A, general scheme 1 as an off-white solid (11 g, 98% purity by ¹H NMR, 63%) after purification by flash column chromatography on normal phase silica (100 g SNAP KP-SIL cartridge, 0-100% EtOAc in heptane gradient).

¹H NMR (500 MHz, DMSO-d₆) δ 1.06 (d, *J* = 6.6 Hz, 6H), 1.77 (dd, *J* = 6.9, 1.7 Hz, 3H), 3.93-3.80 (m, 1H), 5.86 (dq, *J* = 15.2, 1.6 Hz, 1H), 6.58 (dq, *J* = 15.2, 6.9 Hz, 1H), 7.71 (d, *J* = 6.9 Hz, 1H).

LC-MS (METCR1410): 100% (UV), *R*_t = 0.75 min, *m/z* (ESI⁺) = 128.0 [M+H]⁺

(2E)-1-(7-Chloro-1,2,3,4-tetrahydroisoquinolin-2-yl)but-2-en-1-one (I-14)

[0123] The title compound was synthesized in a similar manner to method A, general scheme 1 as a yellow oil (614 mg, 90% purity by ¹H NMR, 83%) used in the next step without further purification.

¹H NMR (250 MHz, Chloroform-d) δ 1.91 (dd, J = 1.7, 6.8 Hz, 3H), 2.85 (s, 2H), 3.77 (s, 2H), 4.72 (s, 2H), 6.32 (dq, J = 1.6, 15.0 Hz, 1H), 6.83-7.03 (m, 1H), 7.03-7.21 (m, 3H).

LC-MS (METCR1278): 89% (UV), R_t = 1.96 min, m/z (ESI⁺) = 236.0/238.0 [M+H]⁺

Method B: Amide formation using carboxylic acid

(2E)-N-(Cyclopropylmethyl)pent-2-enamide (I-15)

[0124] To a stirred solution of (2E)-pent-2-enoic acid (5.1 mL, 49.94 mmol) and DIPEA (13.1 mL, 74.91 mmol) in dry DMF (40 mL) at 0 °C was added HATU (20.9 g, 54.94 mmol). The reaction mixture was stirred under nitrogen at 0 °C for 15 min and 1-cyclopropylmethanamine (4.3 mL, 49.94 mmol) was added dropwise. The mixture was stirred at 0 °C for 15 min, then RT for 3 h. The reaction mixture was diluted with water (100 mL) and the aqueous layer extracted with EtOAc (3 x 150 mL). The organic layers were combined, washed with saturated K₂CO₃ (100 mL), 1N HCl (100 mL), dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude material was purified by flash column chromatography on normal phase silica in 2 batches (100 g SNAP Ultra cartridge, 0-80% EtOAc in heptane gradient) to give 6.48 g of (2E)-N-(cyclopropyl-methyl)pent-2-enamide as a yellow oil (90% purity by ¹HNMR, 76%).

¹H NMR (500 MHz, DMSO-d₆) δ 0.08-0.20 (m, 2H), 0.34-0.46 (m, 2H), 0.83-0.95 (m, 1H), 0.99 (t, J = 7.4 Hz, 3H), 2.09-2.18 (m, 2H), 2.95-3.02 (m, 2H), 5.89 (dt, J = 1.7, 15.4 Hz, 1H), 6.65 (dt, J = 6.4, 15.4 Hz, 1H), 7.94 (s, 1H).

LC-MS (METCR1410): 95% (UV), R_t = 0.94 min, m/z (ESI⁺) = 154.1 [M+H]⁺

(2E)-N-[(3-Chlorophenyl)methyl]pent-2-enamide (I-16)

[0125] The title compound was synthesized in a similar manner to method B, general scheme 1 as an off-white solid (5.43 g, 98% purity, 80%) after purification by recrystallization from 1:4 EtOAc/heptane.

¹H NMR (500 MHz, Chloroform-d) δ 1.06 (t, J = 7.4 Hz, 3H), 2.18-2.26 (m, 2H), 4.49 (d, J = 6.0 Hz, 2H), 5.73-5.88 (m, 2H), 6.94 (dt, J = 6.4, 15.3 Hz, 1H), 7.15-7.19 (m, 1H), 7.22-7.26 (m, 2H), 7.27-7.29 (m, 1H).

LC-MS (METCR1410): 98% (UV), R_t = 1.06 min, m/z (ESI⁺) = 224.1/226.1 [M+H]⁺

N-(Cyclopropylmethyl)-4-methylpent-2-enamide (I-17)

[0126] The title compound was synthesized in a similar manner to method B, general scheme 1 as a yellow free-flowing oil (7.27 g, 91% purity, 90%) after purification by

flash column chromatography on normal phase silica (100 g SNAP Ultra cartridge, 0-50% EtOAc in heptane gradient).

¹H NMR (250 MHz, Chloroform-d) δ 0.17-0.25 (m, 2H), 0.46-0.55 (m, 2H), 0.92-1.00 (m, 1H), 1.05 (d, J = 6.8 Hz, 6H), 2.43 (dq, J = 1.4, 6.7, 13.5 Hz, 1H), 3.18 (dd, J = 5.5, 7.1 Hz, 2H), 5.60 (s, 1H), 5.72 (dd, J = 1.4, 15.4 Hz, 1H), 6.81 (dd, J = 6.6, 15.4 Hz, 1H).

LC-MS (METCR1410): 91% (UV), R_t = 0.99 min, m/z (ESI⁺) = 168.4 [M+H]⁺

(2E)-N-(Cyclopropylmethyl)hex-2-enamide (I-18)

[0127] The title compound was synthesized in a similar manner to method B, general scheme 1 as a yellow oil (6.78 g, 90% purity by ¹H NMR, 83%) after purification by flash column chromatography on normal phase silica in 2 batches (100 g SNAP Ultra cartridge, 0-50% EtOAc in heptane gradient).

¹H NMR (500 MHz, DMSO-d₆) δ 0.09-0.20 (m, 2H), 0.33-0.46 (m, 2H), 0.82-0.95 (m, 4H), 1.41 (h, J = 7.3 Hz, 2H), 2.10 (qd, J = 1.5, 7.2 Hz, 2H), 2.93-3.02 (m, 2H), 5.89 (dt, J = 1.5, 15.4 Hz, 1H), 6.59 (dt, J = 7.0, 15.3 Hz, 1H), 7.94 (s, 1H)

LC-MS (METCR1410): 96% (UV), R_t = 1.02 min, m/z (ESI⁺) = 168.1 [M+H]⁺

(2E)-N-(Cyclohexylmethyl)pent-2-enamide (I-19)

[0128] The title compound was synthesized in a similar manner to method B, general scheme 1 as an off-white solid (6 g, 99% purity, 89%) after purification by flash column chromatography on normal phase silica (100 g SNAP KP-SIL cartridge, 0-100% EtOAc in heptane gradient).

¹H NMR (500 MHz, Chloroform-d) δ 0.89-0.98 (m, 2H), 1.05 (t, J = 7.4 Hz, 3H), 1.12-1.27 (m, 3H), 1.43-1.53 (m, 1H), 1.63-1.68 (m, 1H), 1.72 (d, J = 11.3 Hz, 4H), 2.20 (pd, J = 1.6, 7.5 Hz, 2H), 3.16 (t, J = 6.5 Hz, 2H), 5.50 (s, 1H), 5.75 (dt, J = 1.6, 15.3 Hz, 1H), 6.87 (dt, J = 6.4, 15.3 Hz, 1H).

LC-MS (METCR1410): 99% (UV), R_t = 1.08 min, m/z (ESI⁺) = 196.4 [M+H]⁺

N-[(3-Chlorophenyl)methyl]-4-methylpent-2-enamide (I-20)

[0129] The title compound was synthesized in a similar manner to method B, general scheme 1 as an off-white solid in 2 batches (1.8 g, 95% purity, 41% and 1.7 g, 98% purity, 40%) after purification by flash column chromatography on normal phase silica (25 g SNAP Ultra and 100 g SNAP KP-SIL cartridges, 10-100% EtOAc in heptane gradient).

^1H NMR (500 MHz, Chloroform-*d*) δ 1.06 (d, J = 6.8 Hz, 6H), 2.38-2.52 (m, 1H), 4.49 (d, J = 5.9 Hz, 2H), 5.68-5.81 (m, 2H), 6.88 (dd, J = 6.6, 15.4 Hz, 1H), 7.10-7.22 (m, 1H), 7.22-7.33 (m, 3H).

LC-MS (METCR1410): 95% (UV), R_t = 1.18 min, m/z (ESI⁺) = 238.4/240.4 [M+H]⁺

LC-MS (METCR1410): 98% (UV), R_t = 1.15 min, m/z (ESI⁺) = 238.4/240.4 [M+H]⁺

Method C: Amide formation using methyl ester

(2E)-N-(Cyclopropylmethyl)-5-methylhex-2-enamide (I-21)

[0130] To a stirred solution of methyl (2E)-5-methylhex-2-enoate (10.0 g, 70.33 mmol) in 2:2:1 THF/H₂O/MeOH (75 mL) was added lithium hydroxide hydrate (1:1:1) (2.95 g, 70.33 mmol) and the reaction stirred at RT for 2 h. The mixture was concentrated *in vacuo* and the resulting solid was dried in a high-vac oven for 18 h to afford 9.86 g of (2E)-5-methylhex-2-enoic acid lithium salt as an off-white solid (89% purity by ^1H NMR, 93%) used in the next step without further purification.

^1H NMR (500 MHz, DMSO-*d*₆) δ 0.86 (d, J = 6.7 Hz, 6H), 1.61 (dt, J = 6.7, 13.3 Hz, 1H), 1.87-1.94 (m, 2H), 5.57-5.64 (m, 1H), 6.26 (dt, J = 7.4, 15.1 Hz, 1H).

LC-MS (METCR1410): 98% (UV), R_t = 1.03 min, no mass ion detected

[0131] To a stirred solution of (2E)-5-methylhex-2-enoic acid lithium salt (89%, 4.5 g, 29.87 mmol) and DIPEA (10.4 mL, 59.73 mmol) in DMF (90 mL) at RT was added HATU (12.5 g, 32.85 mmol) portion wise over 20 min. The mixture was stirred at RT for 30 min, cooled to 0 °C and 1-cyclopropylmethanamine (2.9 mL, 32.85 mmol) added. The reaction was stirred at 0 °C for 20 min then at RT for 1 h. HATU (2.3 g, 5.97 mmol) was added and the reaction stirred at RT for 60 h. The mixture was diluted with DCM (100 mL) and 1M HCl (100 mL) added. The biphasic layers were separated and the aqueous phase extracted with DCM (20 mL). The organic phases were combined, washed with saturated NaHCO₃ (2 x 100 mL), dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography on normal phase silica (100 g SNAP KP-SIL cartridge, 10-80% TBME in heptane gradient) to afford 2.93 g of (2E)-N-(cyclopropyl-methyl)-5-methylhex-2-enamide as a brown oil (93% purity, 50%).

^1H NMR (500 MHz, Chloroform-*d*) δ 0.22 (q, J = 4.8 Hz, 2H), 0.49-0.54 (m, 2H), 0.89-1.03 (m, 7H), 1.75 (dt, J = 6.7, 13.3 Hz, 1H), 2.03-2.09 (m, 2H), 3.16-3.21 (m, 2H), 5.56 (s, 1H), 5.76 (d, J = 15.2 Hz, 1H), 6.82 (dt, J = 7.5, 15.1 Hz, 1H).

LC-MS (METCR1410): 93% (UV), R_t = 1.08 min, m/z (ESI⁺)= 182.1 [M+H]⁺

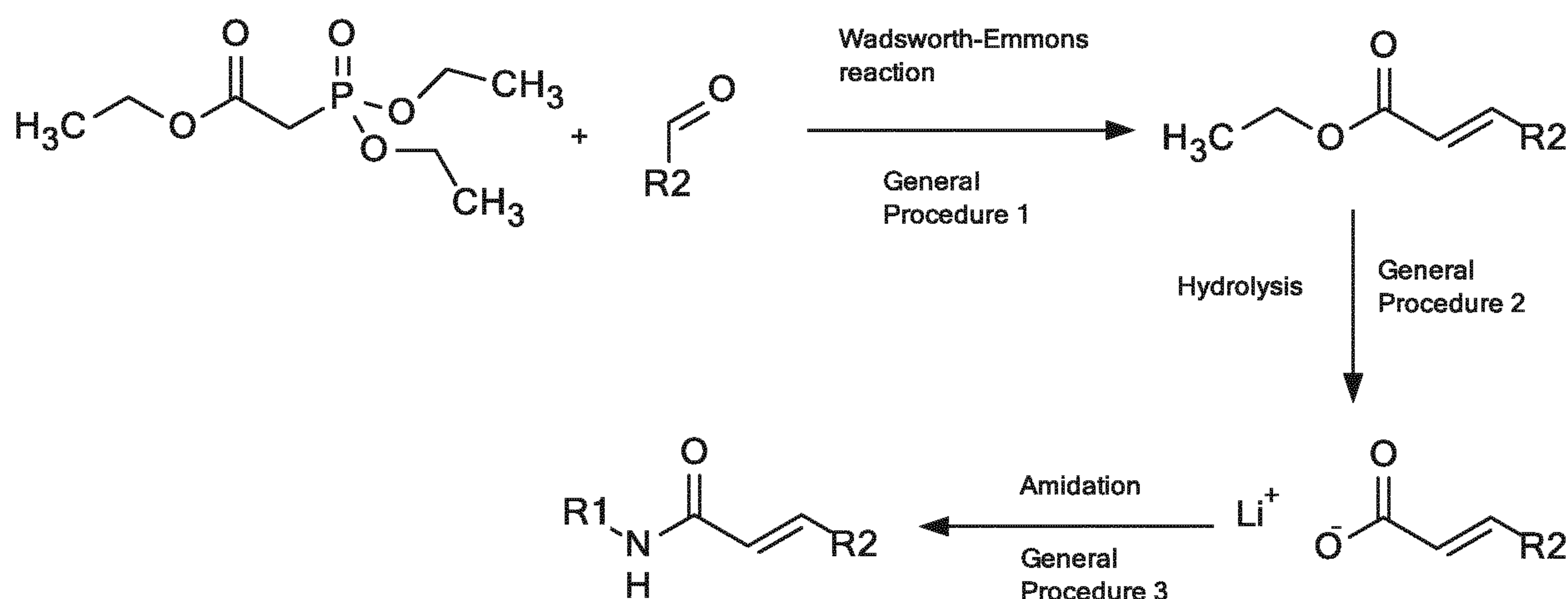
(2E)-N-[(3-Chlorophenyl)methyl]-5-methylhex-2-enamide (I-22)

[0132] The title compound was synthesized in a similar manner to method C, general scheme 1 as an off-white solid (3 g, 95% purity by ¹H NMR, 32%) after purification by flash column chromatography on normal phase silica (100 g SNAP KP-SIL cartridge, 0-100% EtOAc in heptane gradient).

¹H NMR (500 MHz, DMSO-d₆) δ 0.89 (d, J = 6.7 Hz, 6H), 1.69 (tp, J = 6.7, 13.3 Hz, 1H), 1.98-2.09 (m, 2H), 4.34 (d, J = 6.0 Hz, 2H), 5.95 (dt, J = 1.3, 15.3 Hz, 1H), 6.65 (dt, J = 7.4, 15.1 Hz, 1H), 7.22 (d, J = 7.5 Hz, 1H), 7.27-7.39 (m, 3H), 8.46 (t, J = 5.9 Hz, 1H).

LC-MS (METCR1410): 91% (UV), R_t = 1.24 min, m/z (ESI⁺)= 252.0/254.0 [M+H]⁺

GENERAL SCHEME 2:



GENERAL PROCEDURE 1 (GENERAL SCHEME 2): WADSWORTH-EMMONS REACTION

Ethyl (2E)-3-cyclopropylprop-2-enoate (I-23a)

[0133] To an ice-cold stirred solution of triethyl phosphonoacetate (9.0 mL, 45.16 mmol) in anhydrous THF (70 mL) was added NaH (60% in mineral oil, 1.90 g, 47.50 mmol) portion wise over 10 min. The reaction mixture was stirred at RT under nitrogen for 1 h. Cyclopropanecarbaldehyde (3 mL, 40.15 mmol) was added dropwise and the resulting mixture was stirred at RT for 1 h. The reaction mixture was diluted with EtOAc (50 mL) and washed with saturated NaHCO₃ (80 mL). The organic layer was separated, dried over sodium sulfate, filtered and concentrated *in vacuo* to give a pale yellow liquid which was purified by flash column chromatography on normal phase

silica (100 g SNAP KP-SIL cartridge, 0-60% EtOAc in heptane gradient) to afford 4.2 g of ethyl (2E)-3-cyclopropylprop-2-enoate as a colourless liquid (95% purity by ^1H NMR, 71%).

^1H NMR (250 MHz, Chloroform- d) δ 0.58-0.66 (m, 2H), 0.88-0.98 (m, 2H), 1.27 (t, J = 7.1 Hz, 3H), 1.48-1.64 (m, 1H), 4.16 (q, J = 7.1 Hz, 2H), 5.87 (d, J = 15.4 Hz, 1H), 6.41 (dd, J = 10.0, 15.4 Hz, 1H).

LC-MS (METCR1410): 77% (UV), R_t = 1.17 min, m/z (ESI $^+$) = 140.9 [M+H] $^+$

GENERAL PROCEDURE 2 (GENERAL SCHEME 2): Hydrolysis

(2E)-3-Cyclopropylprop-2-enoic acid lithium salt (I-23b)

[0134] To a stirred solution of ethyl (2E)-3-cyclopropylprop-2-enoate (I-23a, 95% purity by ^1H NMR, 4.2 g, 28.46 mmol) in 1:1 THF/ H_2O (60 mL) was added lithium hydroxide hydrate (1.2 g, 28.60 mmol). The mixture was stirred at 50 $^\circ\text{C}$ for 1 h and at RT for 3 days. Lithium hydroxide hydrate (200 mg, 4.77 mmol) was added and the reaction heated at 50 $^\circ\text{C}$ for 5 h. The reaction was concentrated *in vacuo* to give a yellow solid which was triturated via sonication in 9:1 heptane/EtOAc (30 mL) and filtered. The solid was dried *in vacuo* to afford 3.67 g of (2E)-3-cyclopropylprop-2-enoic acid lithium salt as a yellow solid (100% purity, quantitative).

^1H NMR (250 MHz, Deuterium Oxide) δ 0.56-0.64 (m, 2H), 0.86-0.96 (m, 2H), 1.52-1.68 (m, 1H), 5.92 (d, J = 15.5 Hz, 1H), 6.16 (dd, J = 9.7, 15.5 Hz, 1H).

LC-MS (METCR1410): 100% (UV), R_t = 0.76 min, m/z (ESI $^+$) = 113.6 [M+H] $^+$

GENERAL PROCEDURE 3 (GENERAL SCHEME 2): Amide formation

(2E)-3-Cyclopropyl-*N*-(cyclopropylmethyl)prop-2-enamide (I-23c)

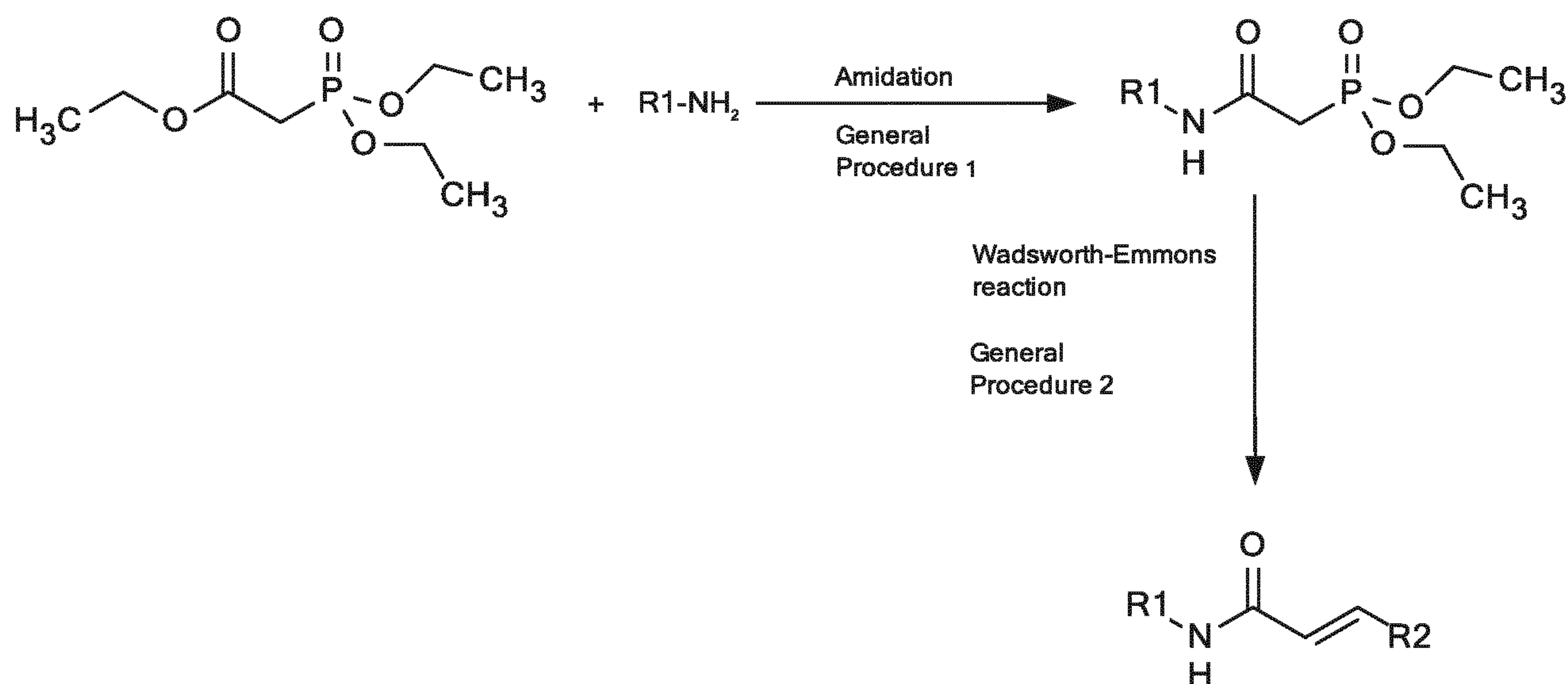
[0135] To a stirred suspension of (2E)-3-cyclopropylprop-2-enoic acid lithium salt (I-23b) (1.8 g, 15.25 mmol) and DIPEA (5.3 mL, 30.43 mmol) in dry DMF (70 mL) was added HATU (6.3 g, 16.57 mmol) portion wise and the reaction stirred at RT for 15 min. Cyclopropylmethylamine (1.7 mL, 19.60 mmol) was added and the mixture stirred at RT under nitrogen for 1 h. The reaction mixture was diluted with water (200 mL) and extracted with EtOAc (3 x 60 mL). The combined organic extracts were washed with water (2 x 100 mL) and brine (50 mL), dried over sodium sulfate and concentrated *in vacuo* to give a brown solid which was purified by flash column chromatography on normal phase silica (50 g SNAP KP-SIL cartridge, 0-50% EtOAc in heptane gradient)

to afford 1.67 g of (2E)-3-cyclopropyl-*N*-(cyclopropylmethyl)prop-2-enamide as a yellow solid (97% purity, 67%).

^1H NMR (500 MHz, Chloroform-*d*) δ 0.21 (q, $J = 4.7$ Hz, 2H), 0.47-0.53 (m, 2H), 0.57-0.63 (m, 2H), 0.84-0.91 (m, 2H), 0.92-1.02 (m, 1H), 1.46-1.58 (m, 1H), 3.17 (dd, $J = 5.6, 7.1$ Hz, 2H), 5.47 (s, 1H), 5.85 (d, $J = 15.0$ Hz, 1H), 6.32 (dd, $J = 10.0, 15.0$ Hz, 1H).

LC-MS (METCR1410): 97% (UV), $R_t = 0.88$ min, m/z (ESI $^+$) = 166.4 [M+H] $^+$

GENERAL SCHEME 3:



GENERAL PROCEDURE 1 (GENERAL SCHEME 3): Amide formation

Diethyl {[[(cyclopropylmethyl)carbamoyl]methyl}phosphonate (I-24a)

[0136] To a solution of cyclopropylmethylamine (7.5 mL, 86.47 mmol) in ethanol (40 mL) was added triethyl phosphonoacetate (6 mL, 30.11 mmol) dropwise and the mixture was stirred at 60 °C for 50 h. The reaction was stood at RT for 64 h and solvent and excess amine were removed *in vacuo* to give 8.2 g of diethyl{[(cyclopropylmethyl)carbamoyl]methyl}phosphonate as a yellow oil (90% purity, 98%). The crude material was used in the next step without further purification.

^1H NMR (500 MHz, Chloroform-*d*) δ 0.13-0.35 (m, 2H), 0.41-0.57 (m, 2H), 0.86-1.19 (m, 1H), 1.24-1.36 (m, 6H), 2.64-2.97 (m, 3H), 3.04-3.14 (m, 1H), 3.87-4.22 (m, 4H), 6.77-7.60 (m, 1H).

LC-MS (METCR1410): 90% (UV), $R_t = 0.80$ min, m/z (ESI $^+$) = 250.5 [M+H] $^+$

GENERAL PROCEDURE 2 (GENERAL SCHEME 3): Wadsworth-Emmons reaction

Method A: Preparation of aldehyde *in situ*

(2E)-N-(Cyclopropylmethyl)-5-methoxypent-2-enamide (I-24b)

[0137] To a cold stirred solution of 1,1,3-trimethoxypropane (0.72 mL, 5.05 mmol) in THF (8 mL) was added 6M HCl (0.6 mL) and the mixture stirred at RT for 1 h. The reaction mixture was dried over sodium sulfate, filtered and the filtrate (filtrate A) containing 3-methoxypropanal used in the next step. To a cold stirred solution of diethyl{[(cyclopropylmethyl)carbamoyl]methyl}phosphonate (I-24a, 91% purity, 1.0 g, 3.65 mmol) in dry THF (15 mL) was added NaH (60% in mineral oil, 315 mg, 7.88 mmol) portion wise over 5 min under nitrogen. The mixture was stirred at RT for 15 min and filtrate A added dropwise over 5 min. The mixture was stirred at RT for 1 h, NaH (60% in mineral oil, 100 mg, 2.50 mmol) added and the reaction stirred at RT for 1 h. Water (20 mL) was added and the mixture acidified to pH 5 with 2N HCl. The crude product was extracted into EtOAc (2 x 20 mL) and the combined organic layers dried over sodium sulfate, filtered and concentrated *in vacuo* to give a yellow oil which was purified by flash column chromatography on normal phase silica (10 g SNAP KP-SIL cartridge, 0-80% EtOAc in heptane gradient) to afford 158 mg of (2E)-N-(cyclopropylmethyl)-5-methoxypent-2-enamide as a colourless oil (96% purity, 23%).

¹H NMR (500 MHz, Chloroform-d) δ 0.18-0.23 (m, 2H), 0.48-0.54 (m, 2H), 0.91-1.01 (m, 1H), 2.45 (qd, J = 1.5, 6.6 Hz, 2H), 3.17 (dd, J = 5.5, 7.1 Hz, 2H), 3.34 (s, 3H), 3.49 (t, J = 6.5 Hz, 2H), 5.56 (s, 1H), 5.86 (dt, J = 1.5, 15.3 Hz, 1H), 6.81 (dt, J = 6.9, 15.3 Hz, 1H).

LC-MS (METCR1410): 96% (UV), R_t = 0.79 min, m/z (ESI⁺) = 184.4 [M+H]⁺

Method B: Use of commercially available aldehyde(2E) N-(Cyclopropylmethyl)-3-(oxan-4-yl)prop-2-enamide (I-25)

[0138] To a cold, stirred solution of diethyl{[(cyclopropylmethyl)carbamoyl]methyl}phosphonate (I-24a, 91% purity, 700 mg, 2.56 mmol) in dry THF (15 mL) under nitrogen was added NaH (60% in mineral oil, 210 mg, 5.25 mmol) over 5 min. The mixture was stirred at RT under nitrogen for 15 min and a solution of oxane-4-carbaldehyde (320 mg, 2.80 mmol) in THF (2 mL) added. The mixture was stirred at RT for 45 min, quenched with water (20 mL) and acidified to pH 5 with 2N HCl and the aqueous layer was extracted with EtOAc (2 x 20 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated *in vacuo* to give a yellow solid which was purified by flash column chromatography on normal phase silica (10 g

SNAP KP-SIL cartridge, 0-80% EtOAc in heptane gradient) to afford 238 mg of (2E) *N*-(cyclopropylmethyl)-3-(oxan-4-yl)prop-2-enamide as an off-white solid (93% purity, 41%).

¹H NMR (500 MHz, Chloroform-*d*) δ 0.18-0.24 (m, 2H), 0.49-0.55 (m, 2H), 0.90-1.02 (m, 1H), 1.49-1.57 (m, 2H), 1.62-1.70 (m, 2H), 2.31-2.41 (m, 1H), 3.18 (dd, *J* = 5.6, 7.1 Hz, 2H), 3.43 (td, *J* = 2.1, 11.7 Hz, 2H), 3.96-4.01 (m, 2H), 5.54-5.60 (m, 1H), 5.75 (dd, *J* = 1.3, 15.4 Hz, 1H), 6.80 (dd, *J* = 6.5, 15.4 Hz, 1H).

LC-MS (METCR1410): 93% (UV), *R*_t = 0.84 min, *m/z* (ESI⁺) = 210.3 [M+H]⁺

(2E)-*N*-(Cyclopropylmethyl)-5-phenylpent-2-enamide (I-26)

[0139] The title compound was synthesized in a similar manner to method B, general procedure 2 (general scheme 3) as a yellow viscous oil (974 mg, 97% purity, 57%) following purification by flash column chromatography on normal phase silica (25 g SNAP KP-SIL cartridge, 0-40% EtOAc in heptane gradient).

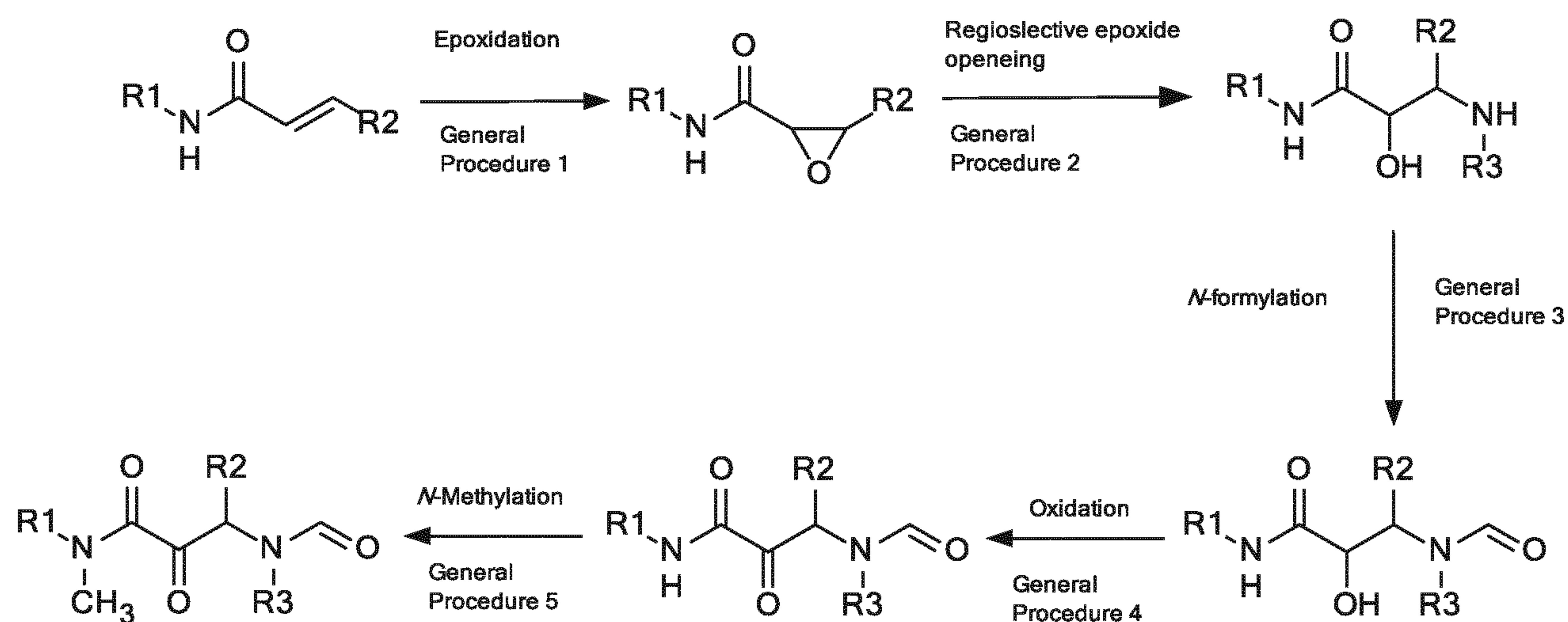
¹H NMR (500 MHz, Chloroform-*d*) δ 0.15-0.23 (m, 2H), 0.46-0.54 (m, 2H), 0.92-1.00 (m, 1H), 2.46-2.54 (m, 2H), 2.74-2.81 (m, 2H), 3.17 (dd, *J* = 5.5, 7.1 Hz, 2H), 5.53 (s, 1H), 5.75-5.82 (m, 1H), 6.88 (dt, *J* = 6.9, 15.2 Hz, 1H), 7.17-7.21 (m, 3H), 7.26-7.32 (m, 2H).

LC-MS (METCR1410): 97% (UV), *R*_t = 1.08 min, *m/z* (ESI⁺) = 230.3 [M+H]⁺

EPOXIDE ROUTE: SYNTHESIS OF FINAL COMPOUNDS (FP 1-82)

GENERAL SCHEME 4:

GENERAL PROCEDURE 1 (GENERAL SCHEME 4): Epoxidation



N[(3-Chlorophenyl)methyl]-3-methyloxirane-2-carboxamide (I-27)

[0140] To a stirred solution of (2E)-*N*[(3-chlorophenyl)methyl]but-2-enamide (I-1, 2.13 g, 9.85 mmol) in DCM (40 mL) at RT was added *m*-CPBA (70%, 12.15 g, 49.27 mmol). The resulting mixture was stirred at RT for 3 days. The solution was washed with 20% Na₂S₂O₃ (30 mL), saturated NaHCO₃ (30 mL) and water (10 mL). The organic layer was separated, dried over sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on normal phase silica (25 g SNAP KP-SIL cartridge, 0-80% EtOAc in heptane gradient) to afford a colourless solid which was suspended in EtOAc (20 mL) and washed with 1N NaOH (20 mL). The organic layer was separated, dried over sodium sulfate and concentrated *in vacuo* to afford 276 mg of *N*[(3-chlorophenyl)-methyl]-3-methyloxirane-2-carboxamide as a colourless oil (85% purity, 11%).

¹H NMR (500 MHz, Chloroform-*d*) δ 1.41 (d, *J* = 5.1 Hz, 3H), 3.05 (qd, *J* = 5.1, 2.1 Hz, 1H), 3.26 (d, *J* = 2.1 Hz, 1H), 4.39 (d, *J* = 6.2 Hz, 2H), 6.45 (s, 1H), 7.10-7.14 (m, 1H), 7.21-7.24 (m, 1H), 7.25-7.27 (m, 2H).

LC-MS (METCR1278): 85% (UV), Rt= 1.75 min, m/z (ESI⁺)= 225.9/227.9 [M+H]⁺
N[(3-Chlorophenyl)methyl]-3,3-dimethyloxirane-2-carboxamide (I-28)

[0141] The title compound was synthesized from *N*[(3-chlorophenyl)methyl]-3-methylbut-2-enamide (I-2) in a similar manner to general procedure 1 (general scheme 4) as an off-white solid (1.17 g, 90% purity by ¹H NMR, 63%) after purification by flash column chromatography on normal phase silica (25 g SNAP KP-SIL cartridge, 0-75% EtOAc in heptane gradient).

¹H NMR (500 MHz, Chloroform-*d*) δ 1.30 (s, 3H), 1.42 (s, 3H), 3.36 (s, 1H), 4.43 (d, *J* = 6.2 Hz, 2H), 6.51 (s, 1H), 7.13-7.17 (m, 1H), 7.23-7.28 (m, 3H).

LC-MS (METCR1278): 100% (UV), Rt= 1.82 min, m/z (ESI⁺)= 239.9/241.9 [M+H]⁺
N[(3-Chlorophenyl)methyl]-3-phenyloxirane-2-carboxamide (I-29)

[0142] The title compound was synthesized from (2E)-*N*[(3-chlorophenyl)methyl]-3-phenylprop-2-enamide (I-3) in a similar manner general procedure 1 (general scheme 4) as an off-white solid (1.26 g, 100% purity, 67%) after purification by recrystallization from 1:3 EtOAc/heptane.

¹H NMR (500 MHz, Chloroform-*d*) δ 3.59 (d, *J* = 2.0 Hz, 1H), 3.91 (d, *J* = 2.0 Hz, 1H), 4.43 (dd, *J* = 14.9, 6.0 Hz, 1H), 4.50 (dd, *J* = 14.9, 6.3 Hz, 1H), 6.50-6.64 (m, 1H), 7.16-7.20 (m, 1H), 7.26-7.30 (m, 5H), 7.33-7.40 (m, 3H).

LC-MS (MET-μHPLC-AB-101): 100% (UV), Rt= 3.26 min, m/z (ESI⁺)= 288.0/290.0 [M+H]⁺

N-(Cyclopropylmethyl)-3-methyloxirane-2-carboxamide (I-30)

[0143] The title compound was synthesized from (2E)-*N*-(cyclopropylmethyl)but-2-enamide (I-4) in a similar manner to general procedure 1 (general scheme 4) as a light yellow solid (8.94 g, 84% purity by ¹H NMR, 53%) after trituration in EtOAc to remove the 3-chlorobenzoic acid by-product.

¹H NMR (500 MHz, Chloroform-d) δ 0.17 (q, *J* = 4.7 Hz, 2H), 0.42-0.55 (m, 2H), 0.84-0.97 (m, 1H), 1.39 (d, *J* = 5.2 Hz, 3H), 2.99-3.14 (m, 3H), 3.18 (d, *J* = 2.1 Hz, 1H), 6.22 (s, 1H).

LC-MS (METCR1410): 63% (UV), Rt= 0.70 min, m/z (ESI⁺)= 156.5 [M+H]⁺

N-Cyclopropyl-3-methyloxirane-2-carboxamide (I-31)

[0144] The title compound was synthesized from (2E)-*N*-cyclopropylbut-2-enamide (I-5) in a similar manner to general procedure 1 (general scheme 4) as a colourless free-flowing oil (1.98 g, 89% purity by ¹H NMR, 40%) after purification by flash column chromatography on normal phase silica (25 g SNAP Ultra cartridge, 10-100% EtOAc in heptane gradient).

¹H NMR (250 MHz, Chloroform-d) δ 0.37-0.60 (m, 2H), 0.76 (qd, *J* = 1.5, 6.4 Hz, 2H), 1.36 (d, *J* = 5.1 Hz, 3H), 2.66 (tq, *J* = 3.7, 7.3 Hz, 1H), 2.96 (qd, *J* = 2.1, 5.1 Hz, 1H), 3.15 (d, *J* = 2.1 Hz, 1H), 6.02-6.39 (m, 1H).

LC-MS (METCR1410): 80% (UV), Rt= 0.42 min, m/z (ESI⁺)= 142.0 [M+H]⁺

3-Methyl-*N*-(2-methylpropyl)oxirane-2-carboxamide (I-32)

[0145] The title compound was synthesized from (2E)-*N*-(2-methylpropyl)but-2-enamide (I-6) in a similar manner to general procedure 1 (general scheme 4) as a yellow free-flowing oil (5.3 g, 100% purity by ¹H NMR, 78%) after purification by flash column chromatography on normal phase silica (100 g SNAP KP-SIL cartridge, 0-100% TBME in heptane gradient).

¹H NMR (250 MHz, Chloroform-d) δ 0.91 (d, *J* = 6.7 Hz, 6H), 1.42 (d, *J* = 5.1 Hz, 3H), 1.82-1.71 (m, 1H), 3.11-2.99 (m, 3H), 3.22 (d, *J* = 2.1 Hz, 1H), 6.20 (s, 1H).

LC-MS (METCR1278): 86% (UV), Rt= 1.19-1.28 min (two peaks), m/z (ESI⁺)= 158.0 [M+H]⁺

N-[(3-Chlorophenyl)methyl]oxirane-2-carboxamide (I-33)

[0146] The title compound was synthesized from *N*-[(3-chlorophenyl)methyl]prop-2-enamide (I-7) in a similar manner to general procedure 1 (general scheme 4) at 55 °C in 1,2-DCE and was obtained as a colourless viscous oil (1.4 g, 80% purity by ¹H NMR, 46%) after purification by flash column chromatography on normal phase silica (100 g SNAP KP-SIL cartridge, 5-100% EtOAc in heptane gradient).

¹H NMR (500 MHz, Chloroform-d) δ 2.78 (dd, *J* = 2.6, 5.5 Hz, 1H), 3.01 (dd, *J* = 4.8, 5.4 Hz, 1H), 3.50 (dd, *J* = 2.6, 4.6 Hz, 1H), 4.40 (qd, *J* = 6.2, 15.0 Hz, 2H), 6.34-6.61 (m, 1H), 7.05-7.16 (m, 1H), 7.20-7.30 (m, 3H).

LC-MS (METCR1410): 95% (UV), *R*_t = 0.96 min, *m/z* (ESI⁺) = 212.0/214.0 [M+H]⁺
N-(Cyclohexylmethyl)-3-methyloxirane-2-carboxamide (I-34)

[0147] The title compound was synthesized from (2E)-*N*-(cyclohexylmethyl)but-2-enamide (I-8) in a similar manner to general procedure 1 (general scheme 4) as a yellow viscous oil (1.23 g, 87% purity, 62%) used in the next step without further purification.

¹H NMR (250 MHz, Chloroform-d) δ 0.78-1.02 (m, 2H), 1.08-1.30 (m, 3H), 1.35-1.50 (m, 4H), 1.60-1.79 (m, 6H), 2.95-3.11 (m, 3H), 3.19 (d, *J* = 2.1 Hz, 1H).

LC-MS (METCR1410): 87% (UV), *R*_t = 0.99 min, *m/z* (ESI⁺) = 198.5 [M+H]⁺
N-[2-(Cyclohexyloxy)ethyl]-3-methyloxirane-2-carboxamide (I-35)

[0148] The title compound was synthesized from (2E)-*N*-[2-(cyclohexyloxy)ethyl]-but-2-enamide (I-9) in a similar manner to general procedure 1 (general scheme 4) as a yellow viscous oil (275 mg, 93% purity, 59%) after purification by flash column chromatography on normal phase silica (50 g SNAP KP-SIL cartridge, 0-100% EtOAc in heptane gradient).

¹H NMR (250 MHz, Chloroform-d) δ 1.10-1.34 (m, 5H), 1.40 (d, *J* = 5.13 Hz, 3H), 1.48-1.56 (m, 1H), 1.64-1.78 (m, 2H), 1.78-1.93 (m, 2H), 2.95-3.07 (m, 1H), 3.14-3.29 (m, 2H), 3.34-3.56 (m, 4H), 6.49 (s, 1H).

LC-MS (METCR1410): 93% (UV), *R*_t = 1 min, *m/z* (ESI⁺) = 228.2 [M+H]⁺
Methyl 2-[(3-methyloxiran-2-yl)formamido]acetate (I-36)

[0149] The title compound was synthesized from methyl 2-[(2E)-but-2-enamido]-acetate (I-10) in a similar manner to general procedure 1 (general scheme 4) as a colourless viscous oil (629 mg, 100% purity, 50%) after purification by flash column

chromatography on normal phase silica (100 g SNAP KP-SIL cartridge, 0-100% TBME in heptane gradient).

¹H NMR (500 MHz, Chloroform-d) δ 1.41 (d, J = 5.1 Hz, 3H), 3.11 (qd, J = 2.1, 5.1 Hz, 1H), 3.24 (d, J = 2.1 Hz, 1H), 3.76 (s, 3H), 3.96 (dd, J = 5.2, 18.3 Hz, 1H), 4.09 (dd, J = 6.1, 18.3 Hz, 1H), 6.57 (br. s, 1H).

LC-MS (METCR0990): 100% (UV), R_t = 0.90-1.10 min, m/z (ESI⁺) = 174.2 [M+H]⁺

N-[2-(3-Chlorophenyl)propan-2-yl]-3-methyloxirane-2-carboxamide (I-37)

[0150] The title compound was synthesized from (2E)-*N*-[2-(3-chlorophenyl)-propan-2-yl]but-2-enamide (I-11) in a similar manner to general procedure 1 (general scheme 4) as a yellow viscous oil (1.05 g, 94% purity, 50%) after purification by flash column chromatography on normal phase silica (100 g SNAP KP-SIL cartridge, 0-100% EtOAc in heptane gradient).

¹H NMR (500 MHz, DMSO-d₆) δ 1.29 (d, J = 5.1 Hz, 3H), 1.53-1.59 (m, 6H), 3.09 (qd, J = 2.0, 5.1 Hz, 1H), 3.19 (d, J = 2.0 Hz, 1H), 7.19-7.38 (m, 4H), 8.13 (s, 1H).

LC-MS (METCR1410): 94% (UV), R_t = 1.11 min, m/z (ESI⁺) = 254.0 [M+H]⁺

N-tert-Butyl-3-methyloxirane-2-carboxamide (I-38)

[0151] The title compound was synthesized from (2E)-*N-tert*-butylbut-2-enamide (I-12) in a similar manner to general procedure 1 (general scheme 4) as an off-white crystalline solid (659 mg, 80% purity by ¹H NMR, 79%) after purification by flash column chromatography on normal phase silica (25 g SNAP KP-SIL cartridge, 0-50% EtOAc in heptane gradient).

¹H NMR (250 MHz, Chloroform-d) δ 1.33 (s, 9H), 1.38 (d, J = 5.2 Hz, 3H), 2.97 (qd, J = 5.1, 2.1 Hz, 1H), 3.09 (d, J = 2.1 Hz, 1H), 5.94 (s, 1H).

3-Methyl-*N*-(propan-2-yl)oxirane-2-carboxamide (I-39)

[0152] The title compound was synthesized from (2E)-*N*-(propan-2-yl)but-2-enamide (I-13) in a similar manner to general procedure 1 (general scheme 4) as an off-white crystalline solid (4 g, 95% purity by ¹H NMR, 32%) after purification by flash column chromatography on normal phase silica (100 g SNAP KP-SIL cartridge, 0-80% EtOAc in heptane gradient).

¹H NMR (500 MHz, DMSO-d₆) δ 1.05 (t, J = 6.6 Hz, 6H), 1.28 (d, J = 5.1 Hz, 3H), 3.05 (qd, J = 5.1, 2.0 Hz, 1H), 3.09 (d, J = 2.0 Hz, 1H), 3.77-3.93 (m, 1H), 7.82 (d, J = 7.3 Hz, 1H).

7-Chloro-2-(3-methyloxirane-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline (I-40)

[0153] The title compound was synthesized from (2E)-1-(7-chloro-1,2,3,4-tetrahydroisoquinolin-2-yl)but-2-en-1-one (I-14) in a similar manner to general procedure 1 (general scheme 4) as a colourless crystalline solid (292 mg, 100% purity by ¹H NMR, 45%) after purification by flash column chromatography on normal phase silica (25 g SNAP KP-SIL cartridge, 0-50% EtOAc in heptane gradient).

¹H NMR (250 MHz, Chloroform-d) δ 1.44 (d, *J* = 5.2 Hz, 3H), 2.81-3.01 (m, 2H), 3.21-3.31 (m, 1H), 3.40 (d, *J* = 2.1 Hz, 1H), 3.64-3.83 (m, 1H), 3.88-4.00 (m, 1H), 4.60-4.81 (m, 2H), 7.02-7.23 (m, 3H).

N-(Cyclopropylmethyl)-3-ethyloxirane-2-carboxamide (I-41)

[0154] The title compound was synthesized from (2E)-*N*-(cyclopropylmethyl)pent-2-enamide (I-15) in a similar manner to general procedure 1 (general scheme 4) as a colourless free-flowing oil (4.02 g, 91% purity by ¹H NMR, 54%) after trituration in EtOAc to remove the 3-chlorobenzoic acid by-product.

¹H NMR (500 MHz, Chloroform-d) δ 0.17 (q, *J* = 4.8 Hz, 2H), 0.45-0.52 (m, 2H), 0.85-0.95 (m, 1H), 1.00 (t, *J* = 7.5 Hz, 3H), 1.60 (dp, *J* = 7.4, 14.5 Hz, 1H), 1.72 (dq, *J* = 4.7, 7.6, 15.0 Hz, 1H), 2.91-2.96 (m, 1H), 3.08 (tp, *J* = 6.5, 13.7 Hz, 2H), 3.23 (d, *J* = 2.0 Hz, 1H), 6.23 (s, 1H).

LC-MS (METCR1410): 48% (UV), *R*_t = 0.82 min, *m/z* (ESI⁺) = 170.4 [M+H]⁺

N-[(3-Chlorophenyl)methyl]-3-ethyloxirane-2-carboxamide (I-42)

[0155] The title compound was synthesized from (2E)-*N*-[(3-chlorophenyl)methyl]pent-2-enamide (I-16) in a similar manner to general procedure 1 (general scheme 4) as a yellow solid (4.12 g, 100% purity, 72%) after purification by flash column chromatography on normal phase silica (100 g SNAP KP-SIL cartridge, 0-80% EtOAc in heptane gradient).

¹H NMR (250 MHz, Chloroform-d) δ 1.01 (t, *J* = 7.5 Hz, 3H), 1.55-1.77 (m, 2H), 2.96 (ddd, *J* = 2.2, 4.7, 5.9 Hz, 1H), 3.30 (d, *J* = 2.1 Hz, 1H), 4.39 (d, *J* = 6.1 Hz, 2H), 6.48 (s, 1H), 7.08-7.16 (m, 1H), 7.20-7.31 (m, 3H).

LC-MS (METCR1278): 100% (UV), *R*_t = 1.82 min, *m/z* (ESI⁺) = 240.0/241.9 [M+H]⁺

N-(Cyclopropylmethyl)-3-(propan-2-yl)oxirane-2-carboxamide (I-43)

[0156] The title compound was synthesized from *N*-(cyclopropylmethyl)-4-methylpent-2-enamide (I-17) in a similar manner to general procedure 1 (general scheme 4)

in 1,2-DCE at RT then at 60 °C and was obtained as an off-white crystalline solid (6.83 g, 90% purity by ¹H NMR, 77%) after purification by flash column chromatography on normal phase silica (100 g SNAP KP-SIL cartridge, 0-100% TBME in heptane gradient).

¹H NMR (250 MHz, Chloroform-d) δ 0.12-0.23 (m, 2H), 0.44-0.55 (m, 2H), 0.87-0.94 (m, 1H), 1.01 (t, *J* = 6.3 Hz, 6H), 1.60-1.73 (m, 1H), 2.77 (dd, *J* = 2.1, 6.4 Hz, 1H), 3.00-3.18 (m, 2H), 3.27 (d, *J* = 2.1 Hz, 1H), 6.22 (s, 1H).

N-(Cyclopropylmethyl)-3-propyloxirane-2-carboxamide (I-44)

[0157] The title compound was synthesized from (2E)-*N*-(cyclopropylmethyl)hex-2-enamide (I-18) in a similar manner to general procedure 1 (general scheme 4) as a yellow crystalline solid (4.54 g, 89% purity by ¹H NMR, 57%) after trituration in EtOAc to remove the 3-chlorobenzoic acid by-product.

¹H NMR (500 MHz, Chloroform-d) δ 0.18 (q, *J* = 4.8 Hz, 2H), 0.46-0.52 (m, 2H), 0.86-0.94 (m, 1H), 0.97 (t, *J* = 7.3 Hz, 3H), 1.42-1.58 (m, 3H), 1.60-1.71 (m, 1H), 2.91-2.97 (m, 1H), 3.01-3.15 (m, 2H), 3.21 (d, *J* = 2.1 Hz, 1H), 6.22 (s, 1H).

LC-MS (METCR1410): 74% (UV), *R*_t = 0.92 min, *m/z* (ESI⁺) = 184.4 [M+H]⁺

N-(Cyclohexylmethyl)-3-ethyloxirane-2-carboxamide (I-45)

[0158] The title compound was synthesized from (2E)-*N*-(cyclohexylmethyl)pent-2-enamide (I-19) in a similar manner to general procedure 1 (general scheme 4) as an off-white viscous oil (4.6 g, 94% purity by ¹H NMR, 67%) used in the next step without further purification.

¹H NMR (500 MHz, Chloroform-d) δ 0.87-0.96 (m, 2H), 1.02 (t, *J* = 7.5 Hz, 3H), 1.11-1.27 (m, 3H), 1.44 (dddq, *J* = 3.4, 6.8, 10.3, 14.4 Hz, 1H), 1.57-1.65 (m, 1H), 1.65-1.78 (m, 6H), 2.93 (ddd, *J* = 2.2, 4.7, 6.6 Hz, 1H), 3.08 (t, *J* = 6.6 Hz, 2H), 3.25 (d, *J* = 2.1 Hz, 1H), 6.19 (s, 1H).

LC-MS (METCR1410): 53% (UV), *R*_t = 1.09 min, *m/z* (ESI⁺) = 212.0 [M+H]⁺

N-[(3-Chlorophenyl)methyl]-3-(propan-2-yl)oxirane-2-carboxamide (I-46)

[0159] The title compound was synthesized from *N*-[(3-chlorophenyl)methyl]-4-methylpent-2-enamide (I-20) in a similar manner to general procedure 1 (general scheme 4) as an off-white crystalline solid (1.4 g, 90% purity by ¹H NMR, 66%) after purification by flash column chromatography on normal phase silica (100 g SNAP KP-SIL cartridge, 5-100% EtOAc in heptane gradient).

¹H NMR (500 MHz, Chloroform-d) δ 1.01 (t, J = 7.0 Hz, 6H), 1.68 (dq, J = 6.7, 13.5 Hz, 1H), 2.78 (dd, J = 2.2, 6.3 Hz, 1H), 3.33 (d, J = 2.2 Hz, 1H), 4.39 (qd, J = 6.1, 15.0 Hz, 2H), 6.39-6.55 (m, 1H), 7.08-7.17 (m, 1H), 7.20-7.30 (m, 3H).

LC-MS (METCR1410): 81% (UV), R_t = 1.15 min, m/z (ESI⁺) = 254.1/ 256.0 [M+H]⁺

N-(Cyclopropylmethyl)-3-(2-methylpropyl)oxirane-2-carboxamide (I-47)

[0160] The title compound was synthesized from (2E)-*N*-(cyclopropylmethyl)-5-methylhex-2-enamide (I-21) in a similar manner to general procedure 1 (general scheme 4) as a yellow oil (975 mg, 100% purity by ¹H NMR, 20%) after purification by flash column chromatography on normal phase silica (100 g SNAP KP-SIL cartridge, 0-100% TBME in heptane gradient).

¹H NMR (500 MHz, Chloroform-d) δ 0.16-0.23 (m, 2H), 0.47-0.54 (m, 2H), 0.88-0.96 (m, 1H), 0.99 (dd, J = 6.7, 1.1 Hz, 6H), 1.40-1.48 (m, 1H), 1.55 (ddd, J = 14.1, 7.4, 4.8 Hz, 1H), 1.85 (dp, J = 13.4, 6.7 Hz, 1H), 2.95 (ddd, J = 6.9, 4.8, 2.2 Hz, 1H), 3.02-3.10 (m, 1H), 3.14 (ddd, J = 13.1, 7.1, 5.8 Hz, 1H), 3.19 (d, J = 2.2 Hz, 1H), 6.21 (s, 1H)

LC-MS (METCR1410): 60% (UV), R_t = 1.02-1.05 min (two peaks), m/z (ESI⁺) = 198.4 [M+H]⁺

N-[(3-Chlorophenyl)methyl]-3-(2-methylpropyl)oxirane-2-carboxamide (I-48)

[0161] The title compound was synthesized from (2E)-*N*-[(3-chlorophenyl)methyl]-5-methylhex-2-enamide (I-22) in a similar manner to general procedure 1 (general scheme 4) as an off-white viscous oil (1 g, 70% purity by ¹H NMR, 27%) after purification by flash column chromatography on normal phase silica (25 g SNAP KP-SIL cartridge, 0-80% EtOAc in heptane gradient).

¹H NMR (500 MHz, DMSO-d₆) δ 8.57 (t, J = 6.0 Hz, 1H), 7.41-7.27 (m, 3H), 7.21 (d, J = 7.5 Hz, 1H), 4.32-4.19 (m, 2H), 3.23 (d, J = 2.0 Hz, 1H), 3.04 (td, J = 5.9, 2.0 Hz, 1H), 1.79 (dp, J = 13.5, 6.7 Hz, 1H), 1.46-1.41 (m, 2H), 0.94 (d, J = 6.7 Hz, 6H).

LC-MS (METCR1673): 50% (UV), R_t = 1.21 min, m/z (ESI⁺) = 268.0/270.0 [M+H]⁺

3-Cyclopropyl-*N*-(cyclopropylmethyl)oxirane-2-carboxamide (I-49)

[0162] The title compound was synthesized from (2E)-3-cyclopropyl-*N*-(cyclopropylmethyl)prop-2-enamide (I-23c) in a similar manner to general procedure 1 (general scheme 4) as an off-white solid (587 mg, 95% purity, 37%) after purification by flash column chromatography on normal phase silica (25 g SNAP KP-SIL cartridge, 0-60% EtOAc in heptane gradient).

^1H NMR (500 MHz, Chloroform- d) δ 0.14-0.20 (m, 2H), 0.38-0.45 (m, 2H), 0.46-0.51 (m, 2H), 0.53-0.65 (m, 2H), 0.84-0.99 (m, 2H), 2.76 (dd, $J = 2.1, 5.6$ Hz, 1H), 3.01-3.14 (m, 2H), 3.28 (d, $J = 2.1$ Hz, 1H), 6.19 (s, 1H).

LC-MS (METCR1410): 95% (UV), $R_t = 0.86$ min, m/z (ESI $^+$) = 182.4 [M+H] $^+$

N-(Cyclopropylmethyl)-3-(2-methoxyethyl)oxirane-2-carboxamide (I-50)

[0163] The title compound was synthesized from (2E)-*N*-(cyclopropylmethyl)-5-methoxypent-2-enamide (I-24b) in a similar manner to general procedure 1 (general scheme 4) as a colourless viscous oil (116 mg, 97% purity, 68%) after purification by flash column chromatography on normal phase silica (10 g SNAP KP-SIL cartridge, 0-80% EtOAc in heptane gradient).

^1H NMR (500 MHz, Chloroform- d) δ 0.18 (q, $J = 4.8$ Hz, 2H), 0.45-0.52 (m, 2H), 0.84-0.95 (m, 1H), 1.68-1.76 (m, 1H), 1.97-2.06 (m, 1H), 3.01-3.16 (m, 3H), 3.26 (d, $J = 2.2$ Hz, 1H), 3.36 (s, 3H), 3.47-3.57 (m, 2H), 6.22 (s, 1H).

LC-MS (METCR1410): 97% (UV), $R_t = 1.08$ min, m/z (ESI $^+$) = 200.0 [M+H] $^+$

N-(Cyclopropylmethyl)-3-(oxan-4-yl)oxirane-2-carboxamide (I-51)

[0164] The title compound was synthesized from (2E)-*N*-(cyclopropylmethyl)-3-(oxan-4-yl)prop-2-enamide (I-25) in a similar manner to general procedure 1 (general scheme 4) as a colourless viscous oil (165 mg, 59% purity, 41%) after purification by flash column chromatography on normal phase silica (10 g SNAP KP-SIL cartridge, 0-100% EtOAc in heptane gradient).

LC-MS (METCR1410): 59% (UV), $R_t = 0.81$ min, m/z (ESI $^+$) = 226.2 [M+H] $^+$

N-(Cyclopropylmethyl)-3-(2-phenylethyl)oxirane-2-carboxamide (I-52)

[0165] The title compound was synthesized from (2E)-*N*-(cyclopropylmethyl)-5-phenylpent-2-enamide (I-26) in a similar manner to procedure 1 (general scheme 4) as a colourless free-flowing oil (435 mg, 87% purity, 37%) after purification by flash column chromatography on normal phase silica (25 g SNAP KP-SIL cartridge, 0-70% EtOAc in heptane gradient).

^1H NMR (500 MHz, Chloroform- d) δ 0.14-0.22 (m, 2H), 0.44-0.54 (m, 2H), 0.87-0.95 (m, 1H), 1.82-1.93 (m, 1H), 1.99-2.09 (m, 1H), 2.73-2.86 (m, 2H), 2.99 (ddd, $J = 2.2, 4.5, 6.6$ Hz, 1H), 3.01-3.09 (m, 1H), 3.10-3.17 (m, 1H), 3.26 (d, $J = 2.2$ Hz, 1H), 6.18 (s, 1H), 7.18-7.24 (m, 3H), 7.28-7.33 (m, 2H).

LC-MS (METCR1410): 87% (UV), $R_t = 1.07$ min, m/z (ESI $^+$) = 246.5 [M+H] $^+$

3-Methyloxirane-2-carboxamide (I-53)

[0166] The title compound was synthesized from (2E)-but-2-enamide in a similar manner to general procedure 1 (general scheme 4) as an off-white solid (316 mg, 60% purity by ¹H NMR, 16%) used in the next step without further purification.

¹H NMR (500 MHz, DMSO-d₆) δ 1.27 (d, *J* = 4.7 Hz, 3H), 2.98-3.13 (m, 2H), 7.11-7.37 (m, 2H).

GENERAL PROCEDURE 2 (GENERAL SCHEME 4): Regioselective epoxide opening

Method A: Epoxide opening in the presence of titanium(IV) isopropoxide at RT

N-[(3-chlorophenyl)methyl]-2-hydroxy-3-[(2-methoxyphenyl) amino]butanamide (I-54)

[0167] To a stirred solution of *N*-[(3-chlorophenyl)methyl]-3-methyloxirane-2-carboxamide (I-27, 200 mg, 0.89 mmol) and 2-methoxyaniline (0.8 mL, 7.09 mmol) was added at RT titanium(IV) isopropoxide (378 mg, 1.33 mmol). The mixture was stirred at RT for 16 h. The reaction was quenched with 10% tartaric acid (10 mL) and the aqueous layer extracted with EtOAc (3 x 15 mL). The organic layers were combined, washed with water (10 mL), dried over sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on normal phase silica (25 g SNAP KP-SIL cartridge, 5-100% EtOAc in heptane gradient) to afford 200 mg of *N*-[(3-chlorophenyl)methyl]-2-hydroxy-3-[(2-methoxyphenyl) amino]butanamide as a viscous yellow oil (85% purity by ¹H NMR, 55%).

130 mg of I-54 were further purified by flash column chromatography on normal phase silica (25 g SNAP-HP-SIL cartridge, 10-100% EtOAc in heptane gradient) to afford 65 mg of *N*-[(3-chlorophenyl)methyl]-2-hydroxy-3-[(2-methoxyphenyl) amino]butanamide as a viscous yellow oil (95% purity, 20%).

¹H NMR (500 MHz, Chloroform-d) δ 1.21 (d, *J* = 6.62 Hz, 3H), 3.05-3.15 (m, 1H), 3.85 (s, 3H), 3.97-4.04 (m, 1H), 4.37-4.52 (m, 3H), 6.78-6.84 (m, 2H), 6.85-6.93 (m, 2H), 7.12-7.18 (m, 1H), 7.18-7.23 (m, 1H), 7.23-7.26 (m, 3H)

LC-MS (METCR1416): 96% (UV), *R*_t = 3.88 min, *m/z* (ESI⁺) = 349.2/351.2 [M+H]⁺

N-[(3-Chlorophenyl)methyl]-3-(cyclohexylamino)-2-hydroxybutanamide (I-55)

[0168] The title compound was synthesized from *N*-[(3-chlorophenyl)methyl]-3-methyloxirane-2-carboxamide (I-27) in a similar manner to method A, general procedure 2 (general scheme 4) as an off-white solid (110 mg, 97% purity, 32%) after purification by flash column chromatography on normal phase silica (10 g SNAP KP-SIL cartridge,

0-100% EtOAc in heptane gradient followed by 0-10% MeOH in EtOAc gradient and 10% 7N methanolic ammonia solution in EtOAc flush).

¹H NMR (500 MHz, Chloroform-d) δ 1.01-1.05 (m, 1H), 1.07 (d, J = 6.5 Hz, 3H), 1.09-1.20 (m, 2H), 1.20-1.28 (m, 2H), 1.55-1.65 (m, 1H), 1.65-1.78 (m, 2H), 1.80-1.90 (m, 1H), 1.92-2.01 (m, 1H), 2.51-2.63 (m, 1H), 3.27-3.39 (m, 1H), 4.09 (d, J = 4.9 Hz, 1H), 4.37-4.49 (m, 2H), 7.14-7.18 (m, 1H), 7.21-7.26 (m, 2H), 7.27-7.28 (m, 1H), 7.68-7.78 (m, 1H)

LC-MS (METCR1410): 97% (UV), R_t = 0.99 min, m/z (ESI⁺) = 325.0/327.0 [M+H]⁺

N[(3-Chlorophenyl)methyl]-2-hydroxy-3-[(3-methoxyphenyl)-amino]butanamide (I-56)

[0169] The title compound was synthesized from *N*[(3-chlorophenyl)methyl]-3-methyloxirane-2-carboxamide (I-27) in a similar manner to method A, general procedure 2 (general scheme 4) as an off-white solid (258 mg, 100% purity, 46%) after purification by flash column chromatography on normal phase silica (50 g SNAP KP-SIL cartridge, 0-50% EtOAc in heptane gradient) followed by recrystallization from 1:1 EtOAc/heptane.

¹H NMR (500 MHz, Chloroform-d) δ 1.17 (d, J = 6.6 Hz, 3H), 3.00 (s, 1H), 3.76 (s, 3H), 3.97-4.03 (m, 1H), 4.38-4.50 (m, 3H), 6.29 (t, J = 2.2 Hz, 1H), 6.33-6.38 (m, 2H), 7.08-7.13 (m, 2H), 7.13-7.16 (m, 1H), 7.24-7.26 (m, 3H).

LC-MS (METCR1278): 100% (UV), R_t = 1.93 min, m/z (ESI⁺) = 348.9/350.9 [M+H]⁺

N[(3-Chlorophenyl)methyl]-2-hydroxy-3-[(4-methoxyphenyl)amino]butanamide (I-57)

[0170] The title compound was synthesized from *N*[(3-chlorophenyl)methyl]-3-methyloxirane-2-carboxamide (I-27) in a similar manner to method A, general procedure 2 (general scheme 4) as a brown solid (371 mg, 100% purity, 64%) after purification by flash column chromatography on normal phase silica (25 g SNAP KP-SIL cartridge, 0-50% EtOAc in heptane gradient).

¹H NMR (500 MHz, Chloroform-d) δ 1.16 (d, J = 6.6 Hz, 3H), 3.75 (s, 3H), 3.82-3.92 (m, 1H), 4.33 (d, J = 4.2 Hz, 1H), 4.39-4.50 (m, 2H), 6.69-6.74 (m, 2H), 6.77-6.82 (m, 2H), 7.13-7.17 (m, 1H), 7.21-7.26 (m, 4H).

LC-MS (METCR1278): 100% (UV), R_t = 1.59 min, m/z (ESI⁺) = 349.0/351.0 [M+H]⁺

N[(3-Chlorophenyl)methyl]-2-hydroxy-3-(phenylamino)butanamide (I-58)

[0171] The title compound was synthesized from *N*[(3-chlorophenyl)methyl]-3-methyloxirane-2-carboxamide (I-27) in a similar manner to method A, general procedure 2

(general scheme 4) as an off-white solid (500 mg, 97% purity, 85%) after purification by recrystallization from 1:1 EtOAc/heptane.

¹H NMR (500 MHz, Chloroform-d) δ 1.17 (d, *J* = 6.6 Hz, 3H), 3.97-4.05 (m, 1H), 4.37-4.50 (m, 3H), 6.77 (d, *J* = 7.9 Hz, 2H), 6.82 (t, *J* = 7.3 Hz, 1H), 7.11-7.18 (m, 2H), 7.11-7.17 (m, 2H), 7.18-7.24 (m, 3H).

LC-MS (METCR1278): 97% (UV), *R*_t = 1.86 min, *m/z* (ESI⁺) = 318.9/321.0 [M+H]⁺

3-(Benzylamino)-*N*-[(3-chlorophenyl)methyl]-2-hydroxybutanamide (I-59)

[0172] The title compound was synthesized from *N*-[(3-chlorophenyl)methyl]-3-methyloxirane-2-carboxamide (I-27) in a similar manner to method A, general procedure 2 (general scheme 4) as an off-white solid (394 mg, 90% purity by ¹H NMR, 93%) after purification by flash column chromatography on reverse phase silica (60 g SNAP KP-C18-HS cartridge, acidic pH, standard elution method).

¹H NMR (500 MHz, DMSO-d₆) δ 0.95 (d, *J* = 6.5 Hz, 3H), 3.08-3.18 (m, 1H), 3.89 (s, 2H), 4.20-4.25 (m, 1H), 4.24-4.34 (m, 2H), 7.22 (d, *J* = 7.5 Hz, 1H), 7.25-7.31 (m, 2H), 7.30-7.37 (m, 4H), 7.40 (d, *J* = 7.4 Hz, 2H), 8.16 (s, 1H), 8.54 (t, *J* = 6.0 Hz, 1H).

LC-MS (METCR1410): 97% (UV), *R*_t = 0.81 min, *m/z* (ESI⁺) = 333.4/335.0 [M+H]⁺

N-[(3-Chlorophenyl)methyl]-2-hydroxy-3-[(propan-2-yl)amino]butanamide (I-60)

[0173] The title compound was synthesized from *N*-[(3-chlorophenyl)methyl]-3-methyloxirane-2-carboxamide (I-27) in a similar manner to method A, general procedure 2 (general scheme 4) as a yellow oil (212 mg, 93% purity by ¹H NMR, 60%) after purification by flash column chromatography on reverse phase silica (30 g SNAP KP-SIL-HS cartridge, acidic pH, standard elution method).

¹H NMR (500 MHz, Chloroform-d) δ 1.19 (d, *J* = 6.6 Hz, 3H), 1.34 (d, *J* = 6.4 Hz, 3H), 1.39 (d, *J* = 6.4 Hz, 3H), 3.37 (p, *J* = 6.3 Hz, 1H), 3.72-3.85 (m, 1H), 4.29-4.50 (m, 2H), 4.69 (s, 1H), 7.10-7.17 (m, 1H), 7.20-7.26 (m, 3H), 7.76 (s, 1H), 8.38 (s, 1H).

LC-MS (METCR1410): 99% (UV), *R*_t = 0.74 min, *m/z* (ESI⁺) = 285.0/287.0 [M+H]⁺

N-[(3-chlorophenyl)methyl]-2-hydroxy-3-[(oxan-4-yl)amino]butanamide (I-61)

[0174] The title compound was synthesized from *N*-[(3-chlorophenyl)methyl]-3-methyloxirane-2-carboxamide (I-27) in a similar manner to method A, general procedure 2 (general scheme 4) as an off-white solid (180 mg, 65% purity, 27%) used in the next step without further purification.

LC-MS (METCR1410): 65% (UV), *R*_t = 0.78 min, *m/z* (ESI⁺) = 327.0/329.0 [M+H]⁺

N[(3-Chlorophenyl)methyl]-2-hydroxy-3-[(2-methoxyphenyl)amino]-3-methylbutanamide (I-62)

[0175] The title compound was synthesized from *N*[(3-chlorophenyl)methyl]-3,3-dimethyloxirane-2-carboxamide (I-28) in a similar manner to method A, general procedure 2 (general scheme 4) as a brown viscous oil (203 mg, 71% purity, 24%) after purification by flash column chromatography on normal phase silica (25 g SNAP KP-SIL cartridge, 0-50% EtOAc in heptane gradient) followed by recrystallization from heptane.

¹H NMR (500 MHz, Chloroform-d) δ 1.29-1.31 (m, 6H), 3.84 (s, 3H), 4.29-4.41 (m, 1H), 4.43-4.48 (m, 3H), 6.85-6.90 (m, 2H), 6.95-7.06 (m, 2H), 7.15-7.20 (m, 1H), 7.24-7.27 (m, 2H), 7.27-7.30 (m, 1H), 7.68-7.76 (m, 1H).

LC-MS (METCR1278): 71% (UV), Rt= 1.63 min, m/z (ESI⁺)= 363.0/365.0 [M+H]⁺

N[(3-Chlorophenyl)methyl]-2-hydroxy-3-[(2-methoxyphenyl)amino]-3-phenylpropanamide (I-63)

[0176] The title compound was synthesized from *N*[(3-chlorophenyl)methyl]-3-phenyloxirane-2-carboxamide (I-29) in a similar manner to method A, general procedure 2 (general scheme 4) as a brown solid (680 mg, 100% purity, 95%) after purification by flash column chromatography on normal phase silica (25 g SNAP KP-SIL cartridge, 0-50% EtOAc in heptane gradient) followed by recrystallization from heptane.

¹H NMR (500 MHz, Chloroform-d) δ 3.17 (s, 1H), 3.87 (s, 3H), 4.18 (dd, *J* = 15.0, 5.3 Hz, 1H), 4.38 (dd, *J* = 15.0, 6.6 Hz, 1H), 4.67 (s, 1H), 4.96 (d, *J* = 4.1 Hz, 1H), 6.57-6.63 (m, 1H), 6.63-6.67 (m, 1H), 6.71-6.83 (m, 4H), 6.97-7.00 (m, 1H), 7.15 (t, *J* = 7.8 Hz, 1H), 7.18-7.22 (m, 1H), 7.28-7.33 (m, 3H), 7.36-7.40 (m, 2H).

LC-MS (METCR1278): 100% (UV), Rt= 2.2 min, m/z (ESI⁺)= 411.0/413.0 [M+H]⁺

N[(3-Chlorophenyl)methyl]-2-hydroxy-3-[(2-methoxyphenyl)amino]-5-methylhexanamide (I-64)

[0177] The title compound was synthesized from *N*[(3-chlorophenyl)methyl]-3-(2-methylpropyl)oxirane-2-carboxamide (I-48) in a similar manner to method A, general procedure 2 (general scheme 4) as an off-white solid (250 mg, 80% purity by ¹H NMR, 46%) after purification by flash column chromatography on normal phase silica (10 g SNAP KP-SIL cartridge, 0-100% EtOAc in heptane gradient).

^1H NMR (500 MHz, DMSO- d_6) δ 0.69 (d, J = 6.5 Hz, 3H), 0.80-0.83 (m, 3H), 1.24-1.28 (m, 1H), 1.43-1.51 (m, 1H), 1.54-1.65 (m, 1H), 3.78 (s, 3H), 4.05-4.08 (m, 1H), 4.18 (dd, J = 5.6, 14.9 Hz, 1H), 4.33-4.47 (m, 2H), 5.73-5.79 (m, 1H), 6.56 (td, J = 1.3, 7.8 Hz, 1H), 6.62-6.67 (m, 1H), 6.76-6.84 (m, 2H), 7.22-7.26 (m, 1H), 7.27-7.35 (m, 3H), 8.51 (t, J = 6.4 Hz, 1H).

LC-MS (METCR1410): 85% (UV), R_t = 1.26 min, m/z (ESI $^+$) = 391.1/393.1 [M+H] $^+$

Method B: Epoxide opening in presence of titanium(IV) isopropoxide at 50-75 °C

N[(3-Chlorophenyl)methyl]-3-[(5-fluoro-2-methoxyphenyl)amino]-2-hydroxybutanamide (I-65)

[0178] To a stirred solution of *N*[(3-chlorophenyl)methyl]-3-methyloxirane-2-carboxamide (I-27, 86% purity, 340 mg, 1.30 mmol) and 5-fluoro-2-methoxyaniline (1.3 mL, 10.69 mmol) was added titanium(IV) isopropoxide (0.6 mL, 2.03 mmol) at RT. The mixture was stirred at RT for 4 h, heated at 50 °C for 18 h, cooled, diluted with EtOAc (30 mL) and washed with 10% citric acid (30 mL). The aqueous layer was extracted with EtOAc (20 mL). The combined organic extracts were washed with brine (20 mL), dried over sodium sulfate and concentrated *in vacuo* to give a brown oil which was triturated in 1:5 EtOAc/heptane (25 mL). The resulting precipitate was collected by filtration, dissolved in hot EtOAc (10 mL), diluted with heptane (25 mL) and sonicated in a cold water bath for 5 min. The resulting precipitate was collected by filtration and dried *in vacuo* to afford 207 mg of *N*[(3-chlorophenyl)methyl]-3-[(5-fluoro-2-methoxyphenyl)amino]-2-hydroxybutanamide as an off-white solid (100% purity, 44%).

^1H NMR (500 MHz, Chloroform- d) δ 1.19 (d, J = 6.6 Hz, 3H), 2.66-3.19 (m, 1H), 3.82 (s, 3H), 3.92-3.98 (m, 1H), 4.39-4.51 (m, 3H), 6.40 (td, J = 2.9, 8.5 Hz, 1H), 6.56 (dd, J = 2.8, 10.3 Hz, 1H), 6.67 (dd, J = 5.0, 8.8 Hz, 1H), 7.07-7.13 (m, 1H), 7.13-7.18 (m, 1H), 7.24-7.26 (m, 3H).

LC-MS (METCR1410): 100% (UV), R_t = 1.17 min, m/z (ESI $^+$) = 367.1/369.1 [M+H] $^+$

N[(3-Chlorophenyl)methyl]-3-[(4-fluoro-2-methoxyphenyl)amino]-2-hydroxybutanamide (I-66)

[0179] The title compound was synthesized from *N*[(3-chlorophenyl)methyl]-3-methyloxirane-2-carboxamide (I-27) in a similar manner to method B, general procedure 2 (general scheme 4) as a light brown solid (377 mg, 95% purity, 75%) after purification by flash column chromatography on normal phase silica (50 g SNAP KP-SIL silica

cartridge, 0-100% EtOAc in heptane gradient) followed by recrystallization from heptane.

¹H NMR (250 MHz, DMSO-d₆) δ 0.96 (d, *J* = 6.5 Hz, 3H), 3.67 (s, 3H), 3.74-3.87 (m, 1H), 4.08 (dd, *J* = 2.8, 5.2 Hz, 1H), 4.25-4.39 (m, 3H), 5.83 (d, *J* = 5.3 Hz, 1H), 6.59-6.68 (m, 1H), 6.70-6.82 (m, 2H), 7.18-7.38 (m, 4H), 8.50 (t, *J* = 6.2 Hz, 1H).

LC-MS (METCR1410): 95% (UV), *R*_t = 1.28 min, *m/z* (ESI⁺) = 367.0/369.0 [M+H]⁺

N[(3-Chlorophenyl)methyl]-3-[(cyclohexylmethyl)amino]-2-hydroxybutanamide (I-67)

[0180] The title compound was synthesized from *N*[(3-chlorophenyl)methyl]-3-methyloxirane-2-carboxamide (I-27) in a similar manner to method B, general procedure 2 (general scheme 4) as an off-white solid (633 mg, 99% purity, 121%) after purification by trituration in 1:1 EtOAc/heptane.

¹H NMR (500 MHz, DMSO-d₆) δ 0.81-1.28 (m, 5H), 1.32-1.43 (m, 1H), 1.57-1.68 (m, 6H), 1.69-1.76 (m, 3H), 2.42-2.47 (m, 2H), 4.09 (s, 1H), 4.28 (qd, *J* = 6.4, 15.2 Hz, 2H), 7.21-7.24 (m, 1H), 7.26-7.29 (m, 1H), 7.29-7.36 (m, 2H), 8.42-8.53 (m, 1H).

LC-MS (METCR1410): 99% (UV), *R*_t = 0.89 min, *m/z* (ESI⁺) = 339.0/341.1 [M+H]⁺

N[(3-Chlorophenyl)methyl]-3-[(2,2-dimethylpropyl)amino]-2-hydroxybutanamide (I-68)

[0181] The title compound was synthesized from *N*[(3-chlorophenyl)methyl]-3-methyloxirane-2-carboxamide (I-27) in a similar manner to method B, general procedure 2 (general scheme 4) as a yellow solid (267 mg, 98% purity, 73%) after purification by ion-exchange flash chromatography (5 g Isolute SCX-2 cartridge, 0-20% MeOH in EtOAc gradient then 0-10% 7N methanolic ammonia in EtOAc gradient).

¹H NMR (500 MHz, DMSO-d₆) δ 0.81-0.86 (m, 12H), 1.21-1.44 (m, 1H), 2.19-2.31 (m, 2H), 2.76-2.84 (m, 1H), 3.97-4.03 (m, 1H), 4.20-4.34 (m, 2H), 5.47 (d, *J* = 4.3 Hz, 1H), 7.20-7.24 (m, 1H), 7.26-7.29 (m, 1H), 7.29-7.35 (m, 2H), 8.42 (t, *J* = 6.3 Hz, 1H).

LC-MS (METCR1410): 98% (UV), *R*_t = 0.85 min, *m/z* (ESI⁺) = 313.1/315.1 [M+H]⁺

N[(3-Chlorophenyl)methyl]-2-hydroxy-3-[(oxan-4-yl)methyl]amino}butanamide (I-69)

[0182] The title compound was synthesized from *N*[(3-chlorophenyl)methyl]-3-methyloxirane-2-carboxamide (I-27) in a similar manner to method B, general procedure 2 (general scheme 4) as an off-white solid (505 mg, 100% purity, 78%) after purification by trituration in 1:2 EtOAc/heptane.

¹H NMR (500 MHz, DMSO-d₆) δ 0.83 (d, *J* = 6.5 Hz, 3H), 1.05-1.19 (m, 2H), 1.33-1.62 (m, 4H), 2.32-2.44 (m, 2H), 2.78-2.88 (m, 1H), 3.21-3.28 (m, 2H), 3.81 (dd, *J* = 3.5,

11.1 Hz, 2H), 3.96-4.04 (m, 1H), 4.27 (qd, $J = 6.4, 15.2$ Hz, 2H), 5.46 (d, $J = 4.2$ Hz, 1H), 7.20-7.25 (m, 1H), 7.25-7.29 (m, 1H), 7.30-7.35 (m, 2H), 8.41 (t, $J = 6.3$ Hz, 1H).

LC-MS (METCR1278): 100% (UV), $R_t = 1.32$ min, m/z (ESI⁺) = 341.1/343.1 [M+H]⁺

N[(3-Chlorophenyl)methyl]-2-hydroxy-3-[(2-methoxyphenyl)amino]propanamide (I-70)

[0183] The title compound was synthesized from *N*[(3-chlorophenyl)methyl]-oxirane-2-carboxamide (I-33) in a similar manner to method B, general procedure 2 (general scheme 4) as a colourless viscous oil (1.66 g, 90% purity by ¹H NMR, 67%) after purification by flash column chromatography on normal phase silica (100 g SNAP HP-SIL cartridge, 20-100% EtOAc in heptane gradient).

¹H NMR (250 MHz, Chloroform-*d*) δ 3.46 (dd, $J = 6.8, 13.6$ Hz, 2H), 3.65 (dd, $J = 4.8, 13.6$ Hz, 1H), 3.84 (s, 3H), 4.37 (dd, $J = 4.9, 6.7$ Hz, 1H), 4.45 (d, $J = 6.1$ Hz, 2H), 6.67-6.96 (m, 4H), 7.08-7.33 (m, 5H).

LC-MS (METCR1410): 88% (UV), $R_t = 1.11$ min, m/z (ESI⁺) = 335.1/337.1 [M+H]⁺

N-(Cyclohexylmethyl)-2-hydroxy-3-[(2-methoxyphenyl)amino]butanamide (I-71)

[0184] The title compound was synthesized from *N*-(cyclohexylmethyl)-3-methyloxirane-2-carboxamide (I-34) in a similar manner to method B, general procedure 2 (general scheme 4) as an off-white solid (479 mg, 100% purity, 57%) after purification by flash column chromatography on normal phase silica (100 g SNAP Ultra cartridge, 0-40% EtOAc in heptane gradient) followed by recrystallization from 1:1 EtOAc/heptane.

¹H NMR (250 MHz, Chloroform-*d*) δ 0.82-1.02 (m, 2H), 1.07-1.32 (m, 6H), 1.39-1.58 (m, 1H), 1.63-1.80 (m, 5H), 3.01 (s, 1H), 3.05-3.24 (m, 2H), 3.86 (s, 3H), 3.90-4.04 (m, 1H), 4.32 (d, $J = 3.8$ Hz, 1H), 6.71-6.95 (m, 5H).

LC-MS (METCR1410): 100% (UV), $R_t = 1.16$ min, m/z (ESI⁺) = 321.1 [M+H]⁺

N-[2-(3-Chlorophenyl)propan-2-yl]-2-hydroxy-3-[(2-methoxyphenyl)amino]butanamide (I-72)

[0185] The title compound was synthesized from *N*-[2-(3-chlorophenyl)propan-2-yl]-3-methyloxirane-2-carboxamide (I-37) in a similar manner to method B, general procedure 2 (general scheme 4) as a brown viscous oil (360 mg, 88% purity, 76%) after purification by flash column chromatography on normal phase silica (10 g SNAP KP-SIL cartridge, 0-100% EtOAc in heptane gradient).

¹H NMR (500 MHz, DMSO-d₆) δ 0.99 (d, *J* = 6.5 Hz, 3H), 1.59 (d, *J* = 5.7 Hz, 6H), 3.78 (s, 3H), 3.99-4.03 (m, 1H), 4.57 (d, *J* = 10.1 Hz, 1H), 5.79 (d, *J* = 5.8 Hz, 1H), 6.53-6.60 (m, 2H), 6.74-6.80 (m, 1H), 6.80-6.85 (m, 1H), 7.24 (dt, *J* = 2.0, 6.8 Hz, 1H), 7.27-7.32 (m, 2H), 7.35-7.37 (m, 1H), 7.77 (s, 1H).

LC-MS (METCR1410): 88% (UV), *R*_t = 1.19 min, *m/z* (ESI⁺) = 377.1/379.1 [M+H]⁺

N-[2-(3-Chlorophenyl)propan-2-yl]-2-hydroxy-3-[(propan-2-yl)amino]butanamide (I-73)

[0186] The title compound was synthesized from *N*-[2-(3-chlorophenyl)propan-2-yl]-3-methyloxirane-2-carboxamide (I-37) in a similar manner to method B, general procedure 2 (general scheme 4) as a colourless crystalline solid (110 mg, 95% purity, 45%) after purification by ion-exchange flash chromatography (5 g Isolute SCX-2 cartridge, 0-10% 7N methanolic ammonia in EtOAc gradient).

¹H NMR (500 MHz, DMSO-d₆) δ 0.88 (d, *J* = 6.5 Hz, 3H), 0.95-1.03 (m, 6H), 1.58 (s, 6H), 2.98 (d, *J* = 39.7 Hz, 2H), 3.91 (s, 1H), 7.23-7.27 (m, 1H), 7.31-7.33 (m, 2H), 7.35-7.37 (m, 1H), 7.87 (s, 1H).

LC-MS (METCR1410): 100% (UV), *R*_t = 0.79 min, *m/z* (ESI⁺) = 313.4/315.0 [M+H]⁺

N-[2-(3-Chlorophenyl)propan-2-yl]-3-(cyclohexylamino)-2-hydroxybutanamide (I-74)

[0187] The title compound was synthesized from *N*-[2-(3-chlorophenyl)propan-2-yl]-3-methyloxirane-2-carboxamide (I-37) in a similar manner to method B, general procedure 2 (general scheme 4) as an off-white crystalline solid (160 mg, 80% purity by ¹H NMR, 39%) after purification by flash column chromatography on normal phase silica (25 g SNAP KP-SIL cartridge, 0-70% EtOAc in heptane gradient).

¹H NMR (500 MHz, DMSO-d₆) δ 1.09 (d, *J* = 6.7 Hz, 3H), 1.17-1.21 (m, 1H), 1.21-1.41 (m, 4H), 1.55 (s, 1H), 1.57-1.62 (m, 6H), 1.70-1.79 (m, 2H), 1.95-2.12 (m, 2H), 3.04-3.17 (m, 1H), 3.52-3.69 (m, 1H), 4.37 (s, 1H), 6.47 (s, 1H), 7.24-7.27 (m, 1H), 7.30-7.34 (m, 2H), 7.38 (s, 1H), 8.05 (s, 1H).

LC-MS (METCR1410): 72% (UV), *R*_t = 0.94 min, *m/z* (ESI⁺) = 353.6/355.2 [M+H]⁺

N-*tert*-butyl-2-hydroxy-3-[(2-methoxyphenyl)amino]butanamide (I-75)

[0188] The title compound was synthesized from *N*-*tert*-butyl-3-methyloxirane-2-carboxamide (I-38) in a similar manner to method B, general procedure 2 (general scheme 4) as an orange crystalline solid (186 mg, 90% purity by ¹H NMR, 57%) after purification by flash column chromatography on normal phase silica (25 g SNAP KP-SIL cartridge, 0-50% EtOAc in heptane gradient).

¹H NMR (250 MHz, Chloroform-d) δ 1.17 (d, J = 6.6 Hz, 3H), 1.36 (s, 9H), 2.88 (d, J = 3.3 Hz, 1H), 3.85 (s, 3H), 3.89-3.98 (m, 1H), 4.20 (t, J = 3.3 Hz, 1H), 6.62 (s, 1H), 6.68-6.91 (m, 4H).

2-Hydroxy-3-[(2-methoxyphenyl)amino]-*N*-(propan-2-yl)butanamide (I-76)

[0189] The title compound was synthesized from 3-methyl-*N*-(propan-2-yl)oxirane-2-carboxamide (I-39) in a similar manner to method B, general procedure 2 (general scheme 4) as an off-white solid (214 mg, 100% purity, 29%) after purification by flash column chromatography on normal phase silica (25 g SNAP KP-SIL cartridge, 0-50% EtOAc in heptane gradient) followed by recrystallization from 1:1 EtOAc/heptane.

¹H NMR (500 MHz, Chloroform-d) δ 1.13 (d, J = 6.6 Hz, 3H), 1.15-1.19 (m, 6H), 2.95 (s, 1H), 3.85 (s, 3H), 3.96 (qd, J = 3.9, 6.6 Hz, 1H), 4.10 (dt, J = 6.6, 8.0 Hz, 1H), 4.29 (d, J = 3.5 Hz, 1H), 6.60 (d, J = 7.5 Hz, 1H), 6.74 (td, J = 1.5, 7.7 Hz, 1H), 6.78-6.82 (m, 2H), 6.88 (td, J = 1.4, 7.8 Hz, 1H)

LC-MS (METCR1278): 100% (UV), R_t = 1.45 min, m/z (ESI⁺) = 267.0 [M+H]⁺

3-[(2,2-Dimethylpropyl)amino]-2-hydroxy-*N*-(propan-2-yl)butanamide (I-77)

[0190] The title compound was synthesized from 3-methyl-*N*-(propan-2-yl)oxirane-2-carboxamide (I-39) in a similar manner to method B, general procedure 2 (general scheme 4) as a yellow solid (196 mg, 85% purity by ¹H NMR, 26%) after purification by ion exchange flash chromatography (10 g Isolute SCX-2 cartridge, 0-20% MeOH in EtOAc gradient then 0-10% 7N methanolic ammonia in EtOAc gradient).

¹H NMR (500 MHz, Chloroform-d) δ 0.90-0.93 (m, 9H), 1.02 (d, J = 6.5 Hz, 3H), 1.14-1.18 (m, 6H), 2.29 (d, J = 11.3 Hz, 1H), 2.51 (d, J = 11.3 Hz, 1H), 3.00-3.07 (m, 1H), 3.96 (d, J = 5.1 Hz, 1H), 4.06-4.16 (m, 1H), 6.96-7.18 (m, 1H).

LC-MS (METCR1410): 74% (UV), R_t = 0.76 min, m/z (ESI⁺) = 231.1 [M+H]⁺

1-(7-Chloro-1,2,3,4-tetrahydroisoquinolin-2-yl)-2-hydroxy-3-[(2-methoxyphenyl)amino]-butan-1-one (I-78)

[0191] The title compound was synthesized from 7-chloro-2-(3-methyloxirane-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline (I-40) in a similar manner to method B, general procedure 2 (general scheme 4) at 50 °C then 75 °C and was obtained as a yellow viscous oil (85 mg, 60% purity by ¹H NMR, 25%) after purification by flash column chromatography on normal phase silica (25 g SNAP KP-SIL cartridge, 0-50% EtOAc in heptane gradient).

¹H NMR (250 MHz, Chloroform-d) δ 1.08-1.22 (m, 3H), 2.76-2.96 (m, 1H), 3.53-3.96 (m, 7H), 4.39-4.91 (m, 4H), 6.54-6.72 (m, 2H), 6.75-7.20 (m, 5H).

N[(3-Chlorophenyl)methyl]-2-hydroxy-3-[(2-methoxyphenyl)amino]pentanamide (I-79)

[0192] The title compound was synthesized from *N*[(3-chlorophenyl)methyl]-3-ethyloxirane-2-carboxamide (I-42) in a similar manner to method B, general procedure 2 (general scheme 4) as a brown solid (427 mg, 100% purity, 63%) after purification by flash column chromatography on normal phase silica (25 g SNAP KP-SIL cartridge, 0-60% EtOAc in heptane gradient) then recrystallization from 1:1 EtOAc/heptane.

¹H NMR (500 MHz, Chloroform-d) δ 0.98 (t, *J* = 7.4 Hz, 3H), 1.53-1.62 (m, 1H), 1.65-1.72 (m, 1H), 3.04 (s, 1H), 3.74 (dt, *J* = 4.0, 8.7 Hz, 1H), 3.85 (s, 3H), 4.30-4.34 (m, 1H), 4.42 (qd, *J* = 6.0, 14.9 Hz, 2H), 6.74 (td, *J* = 1.5, 7.7 Hz, 1H), 6.79 (ddd, *J* = 1.3, 8.0, 9.4 Hz, 2H), 6.87 (td, *J* = 1.4, 7.7 Hz, 1H), 7.09-7.14 (m, 1H), 7.14-7.19 (m, 1H), 7.19-7.22 (m, 1H), 7.22-7.26 (m, 2H).

LC-MS (METCR1410): 100% (UV), *R*_t = 1.17 min, *m/z* (ESI⁺) = 363.0/365.0 [M+H]⁺

N-(Cyclopropylmethyl)-2-hydroxy-4-methyl-3-[(2-methylpropyl)amino]pentanamide (I-80)

[0193] The title compound was synthesized from *N*-(cyclopropylmethyl)-3-(propan-2-yl)oxirane-2-carboxamide (I-43) in a similar manner to method B, general procedure 2 (general scheme 4) as a yellow solid (135 mg, 100% purity by ¹H NMR, 32%) after purification by recrystallization from hot heptane.

¹H NMR (500 MHz, Chloroform-d) δ 0.16-0.25 (m, 2H), 0.44-0.54 (m, 2H), 0.86-1.00 (m, 13H), 1.67-1.76 (m, 1H), 2.06-2.17 (m, 1H), 2.38-2.55 (m, 2H), 2.66-2.72 (m, 1H), 3.06-3.23 (m, 2H), 4.00 (d, *J* = 6.6 Hz, 1H), 7.52 (s, 1H).

N-(Cyclopropylmethyl)-3-[(2,2-dimethylpropyl)amino]-2-hydroxy-4-methylpentanamide (I-81)

[0194] The title compound was synthesized from *N*-(cyclopropylmethyl)-3-(propan-2-yl)oxirane-2-carboxamide (I-43) in a similar manner to method B, general procedure 2 (general scheme 4) as a colourless powder (183 mg, 85% purity by ¹H NMR, 35%) after purification by recrystallization from heptane followed by trituration in cooled heptane.

¹H NMR (250 MHz, Chloroform-d) δ 0.21 (q, J = 4.8 Hz, 2H), 0.44-0.56 (m, 2H), 0.92-1.02 (m, 16H), 2.07-2.19 (m, 1H), 2.33-2.51 (m, 2H), 2.69 (dd, J = 3.9, 6.3 Hz, 1H), 3.03-3.29 (m, 2H), 4.04 (d, J = 6.3 Hz, 1H), 7.41-7.50 (m, 1H).

N[(3-Chlorophenyl)methyl]-2-hydroxy-3-[(2-methoxyphenyl)amino]-4-methylpentanamide (I-82)

[0195] The title compound was synthesized from *N*[(3-chlorophenyl)methyl]-3-(propan-2-yl)oxirane-2-carboxamide (I-46) in a similar manner to method B, general procedure 2 (general scheme 4) as a brown-beige solid (468 mg, 90% purity by ¹H NMR, 56%) after purification by flash column chromatography on normal phase silica (50 g SNAP Ultra cartridge, 7-60% EtOAc in heptane gradient).

¹H NMR (500 MHz, Chloroform-d) δ 0.84 (d, J = 6.9 Hz, 3H), 0.92-0.98 (m, 3H), 2.18-2.30 (m, 1H), 3.42-3.50 (m, 1H), 3.64 (s, 1H), 3.79 (s, 3H), 4.08-4.14 (m, 1H), 4.16 (dd, J = 5.4, 14.8 Hz, 1H), 4.33-4.40 (m, 1H), 6.64-6.81 (m, 4H), 6.94 (d, J = 7.3 Hz, 1H), 7.03 (s, 1H), 7.04-7.10 (m, 1H), 7.09-7.18 (m, 2H).

LC-MS (METCR1410): 94% (UV), R_t = 1.22 min, m/z (ESI⁺) = 377.1/379.1 [M+H]⁺

2-Hydroxy-3-[(2-methoxyphenyl)amino]butanamide (I-83)

[0196] The title compound was synthesized from 3-methyloxirane-2-carboxamide (I-53) in a similar manner to method B, general procedure 2 (general scheme 4) as a brown oil (56 mg, 90% purity, 10%) after purification by flash column chromatography on normal phase silica (10 g SNAP KP-SIL cartridge, 0-80% EtOAc in heptane gradient).

LC-MS (METCR1410): 90% (UV), R_t = 0.63 min, m/z (ESI⁺) = 225.2 [M+H]⁺

Method C: Epoxide opening without titanium(IV) isopropoxide

3-(Cyclohexylamino)-2-hydroxy-*N*-(propan-2-yl)butanamide (I-84)

[0197] To a stirred solution of 3-methyl-*N*-(propan-2-yl)oxirane-2-carboxamide (I-39) (400 mg, 2.79 mmol) in EtOH (10 mL) was added cyclohexylamine (2.5 mL, 21.9 mmol) at RT. The reaction mixture was stirred at RT for 18 h, heated and stirred at 50 °C for 24 h then concentrated *in vacuo*. The solid residue was dissolved in hot EtOAc (25 mL), the solution diluted with heptane (25 mL) and cooled by sonication in a cold water bath for 10 min. The precipitate was collected by filtration and dried *in vacuo* to afford 320 mg of 3-(cyclohexylamino)-2-hydroxy-*N*-(propan-2-yl)butanamide as an off-white solid (100% purity, 47%).

¹H NMR (500 MHz, Chloroform-d) δ 1.01 (d, J = 6.5 Hz, 3H), 1.02-1.10 (m, 2H), 1.10-1.19 (m, 7H), 1.19-1.32 (m, 2H), 1.62 (dt, J = 3.5, 12.6 Hz, 1H), 1.67-1.79 (m, 2H), 1.83 – 1.92 (m, 1H), 1.92-2.01 (m, 1H), 2.44-2.58 (m, 1H), 3.26 (p, J = 6.4 Hz, 1H), 3.91 (d, J = 5.1 Hz, 1H), 4.01-4.18 (m, 1H), 6.99-7.17 (m, 1H).

LC-MS (METCR1410): 100% (UV), R_t = 0.70 min, m/z (ESI⁺) = 243.2 [M+H]⁺

N-(Cyclopropylmethyl)-2-hydroxy-4-methyl-3-([(oxan-4-yl)methyl]amino}pentanamide (I-85)

[0198] The title compound was synthesized from *N*-(cyclopropylmethyl)-3-(propan-2-yl)oxirane-2-carboxamide (I-43) in a similar manner to method C, general procedure 2 (general scheme 4) at 70 °C and was obtained as an off-white solid (203 mg, 92% purity, 42%) after purification by recrystallization from 1:1 EtOAc/heptane followed by ion-exchange flash chromatography (10 g Isolute SCX cartridge, 0-10% 7N methanolic ammonia in EtOAc gradient).

¹H NMR (500 MHz, Chloroform-d) δ 0.16-0.26 (m, 2H), 0.46-0.54 (m, 2H), 0.91-1.02 (m, 7H), 1.24-1.38 (m, 3H), 1.59-1.70 (m, 4H), 2.06-2.14 (m, 1H), 2.50 (dd, J = 6.7, 11.7 Hz, 1H), 2.59-2.63 (m, 1H), 2.72 (dd, J = 3.6, 6.2 Hz, 1H), 3.05-3.14 (m, 1H), 3.17-3.24 (m, 1H), 3.35-3.43 (m, 2H), 3.96-4.00 (m, 2H), 4.04 (d, J = 6.2 Hz, 1H), 7.32-7.40 (m, 1H).

LC-MS (METCR0990): 92% (UV), R_t = 1.48 min, m/z (ESI⁺) = 299.3 [M+H]⁺

3-(Benzylamino)-*N*-(cyclopropylmethyl)-2-hydroxybutanamide (I-86)

[0199] The title compound was synthesized from *N*-(cyclopropylmethyl)-3-methyloxirane-2-carboxamide (I-30) in a similar manner to method C, general procedure 2 (general scheme 4) as an off-white solid (365.5 mg, 96% purity, 61%) after purification by recrystallization from 1:2 EtOAc/heptane.

¹H NMR (500 MHz, Chloroform-d) δ 0.01 (q, J = 4.7 Hz, 2H), 0.26-0.32 (m, 2H), 0.74 (dt, J = 4.8, 7.5, 15.2 Hz, 1H), 0.85 (d, J = 6.5 Hz, 3H), 2.86-2.97 (m, 2H), 2.98-3.05 (m, 1H), 3.57-3.65 (m, 2H), 3.87 (d, J = 4.7 Hz, 1H), 7.00-7.15 (m, 6H).

LC-MS (METCR1410): 96% (UV), R_t = 0.75 min, m/z (ESI⁺) = 263.1 [M+H]⁺

3-[(Cyclohexylmethyl)amino]-*N*-(cyclopropylmethyl)-2-hydroxybutanamide (I-87)

[0200] The title compound was synthesized from *N*-(cyclopropylmethyl)-3-methyloxirane-2-carboxamide (I-30) in a similar manner to method C, general procedure 2

(general scheme 4) as an off-white solid (282 mg, 100% purity, 47%) after purification by recrystallization from EtOAc/heptane.

¹H NMR (500 MHz, Chloroform-d) δ 0.21 (q, *J* = 4.8 Hz, 2H), 0.47-0.54 (m, 2H), 0.94 (tt, *J* = 4.1, 8.3, 9.2, 17.0 Hz, 3H), 1.00 (d, *J* = 6.5 Hz, 3H), 1.10-1.29 (m, 3H), 1.40 (dt, *J* = 3.4, 7.1, 14.5 Hz, 1H), 1.63-1.83 (m, 5H), 2.39 (dd, *J* = 7.1, 11.6 Hz, 1H), 2.56 (dd, *J* = 6.1, 11.6 Hz, 1H), 3.00-3.08 (m, 1H), 3.08-3.22 (m, 2H), 3.98 (d, *J* = 5.1 Hz, 1H), 7.35 (s, 1H).

LC-MS (METCR1410): 100% (UV), *R*_t = 0.82 min, *m/z* (ESI⁺) = 269.1 [M+H]⁺

tert-Butyl 4-[(1-[(cyclopropylmethyl)carbamoyl]-1-hydroxypropan-2-yl)amino)methyl]-piperidine-1-carboxylate (I-88)

[0201] The title compound was synthesized from *N*-(cyclopropylmethyl)-3-methyloxirane-2-carboxamide (I-30) in a similar manner to method C, general procedure 2 (general scheme 4) as a yellow solid (959 mg, 90% purity by ¹H NMR, 48%) after purification by trituration in 95:5 heptane/EtOAc then in 90:10 heptane/EtOAc.

¹H NMR (500 MHz, Chloroform-d) δ 0.21 (q, *J* = 4.7 Hz, 2H), 0.47-0.54 (m, 2H), 0.90-0.99 (m, 1H), 1.03 (d, *J* = 6.5 Hz, 3H), 1.07-1.21 (m, 2H), 1.45 (s, 9H), 1.54-1.63 (m, 1H), 1.63-1.78 (m, 2H), 1.82-2.38 (m, 2H), 2.47 (dd, *J* = 7.2, 11.9 Hz, 1H), 2.62-2.75 (m, 3H), 3.08-3.21 (m, 3H), 4.05 (d, *J* = 4.7 Hz, 1H), 4.11 (s, 2H), 7.15-7.25 (m, 1H).

LC-MS (METCR0990): 77% (UV), *R*_t = 1.6 min, *m/z* (ESI⁺) = 370.3 [M+H]⁺

3-(Cyclohexylamino)-*N*-(cyclopropylmethyl)-2-hydroxybutanamide (I-89)

[0202] The title compound was synthesized from *N*-(cyclopropylmethyl)-3-methyloxirane-2-carboxamide (I-30) in a similar manner to method C, general procedure 2 (general scheme 4) at 60 °C and was obtained as an off-white solid (435 mg, 95% purity by ¹H NMR, 73%) after purification by trituration in Et₂O and heptane.

¹H NMR (500 MHz, Chloroform-d) δ 0.14-0.28 (m, 2H), 0.45-0.58 (m, 2H), 0.90-1.01 (m, 1H), 1.09 (d, *J* = 6.5 Hz, 3H), 1.11-1.36 (m, 5H), 1.57-2.06 (m, 7H), 2.62 (t, *J* = 9.4 Hz, 1H), 3.14 (h, *J* = 6.8 Hz, 2H), 3.33 (p, *J* = 6.0 Hz, 1H), 3.99-4.09 (m, 1H), 7.34-7.45 (m, 1H).

LC-MS (METCR1410): 88% (UV), *R*_t = 0.76 min, *m/z* (ESI⁺) = 255.6 [M+H]⁺

N-(Cyclopropylmethyl)-3-[(2,2-dimethylpropyl)amino]-2-hydroxybutanamide (I-90)

[0203] The title compound was synthesized from *N*-(cyclopropylmethyl)-3-methyloxirane-2-carboxamide (I-30) in a similar manner to method C, general procedure 2

(general scheme 4) at 60 °C and was obtained as an off-white solid (418 mg, 95% purity, 74%) after purification by trituration in Et₂O and heptane.

¹H NMR (500 MHz, Chloroform-d) δ 0.14-0.26 (m, 2H), 0.43-0.57 (m, 2H), 0.87-1.01 (m, 11H), 1.10 (d, *J* = 6.4 Hz, 3H), 1.84 (br.s, 1H), 2.34 (d, *J* = 11.4 Hz, 1H), 2.58 (d, *J* = 11.4 Hz, 1H), 3.02-3.23 (m, 3H), 4.09 (d, *J* = 4.0 Hz, 1H), 7.39 (s, 1H).

LC-MS (METCR1410): 100% (UV), *R*_t = 0.74 min, *m/z* (ESI⁺) = 243.2 [M+H]⁺

3-(Cyclohexylamino)-*N*-cyclopropyl-2-hydroxybutanamide (I-91)

[0204] The title compound was synthesized from *N*-cyclopropyl-3-methyloxirane-2-carboxamide (I-31) in a similar manner to method C, general procedure 2 (general scheme 4) at 60 °C and was obtained as an off-white solid (355 mg, 100% purity by ¹H NMR, 78%) after purification by recrystallization from 1:2.5 EtOAc/heptane.

¹H NMR (500 MHz, Chloroform-d) δ 0.47-0.55 (m, 2H), 0.74-0.82 (m, 2H), 1.02 (d, *J* = 6.5 Hz, 3H), 1.04-1.32 (m, 5H), 1.58-1.65 (m, 1H), 1.69-1.76 (m, 2H), 1.84-1.90 (m, 1H), 1.94-2.00 (m, 1H), 2.49-2.57 (m, 1H), 2.69-2.79 (m, 1H), 3.22-3.28 (m, 1H), 3.92 (d, *J* = 5.3 Hz, 1H), 7.35 (s, 1H).

LC-MS (METCR1410): No UV integration, *R*_t = 0.59 min, *m/z* (ESI⁺) = 241.1 [M+H]⁺

3-[(Cyclohexylmethyl)amino]-*N*-cyclopropyl-2-hydroxybutanamide (I-92)

[0205] The title compound was synthesized from *N*-cyclopropyl-3-methyloxirane-2-carboxamide (I-31) in a similar manner to method C, general procedure 2 (general scheme 4) at 60 °C and was obtained as a white solid (344 mg, 100% purity, 72%) after purification by recrystallization from 1:2.5 EtOAc/heptane.

¹H NMR (500 MHz, Chloroform-d) δ 0.44-0.56 (m, 2H), 0.74-0.81 (m, 2H), 0.87-0.97 (m, 2H), 1.00 (d, *J* = 6.5 Hz, 3H), 1.13-1.29 (m, 3H), 1.35-1.44 (m, 1H), 1.65-1.80 (m, 5H), 2.37 (dd, *J* = 7.1, 11.7 Hz, 1H), 2.53-2.59 (m, 1H), 2.71-2.77 (m, 1H), 3.00-3.06 (m, 1H), 3.95 (d, *J* = 5.3 Hz, 1H), 7.33 (s, 1H).

LC-MS (METCR1410): 100% (UV), *R*_t = 0.72 min, *m/z* (ESI⁺) = 255.1 [M+H]⁺

3-(Benzylamino)-*N*-cyclopropyl-2-hydroxybutanamide (I-93)

[0206] The title compound was synthesized from *N*-cyclopropyl-3-methyloxirane-2-carboxamide (I-31) in a similar manner to method C, general procedure 2 (general scheme 4) at 60 °C and was obtained as an off-white solid (360 mg, 96% purity, 63%) after purification by trituration in 1:4 EtOAc/heptane.

^1H NMR (500 MHz, Chloroform- d) δ 0.43-0.54 (m, 2H), 0.72-0.82 (m, 2H), 1.04 (d, J = 6.5 Hz, 3H), 2.70-2.78 (m, 1H), 3.17-3.24 (m, 1H), 3.75-3.86 (m, 2H), 4.03 (d, J = 4.8 Hz, 1H), 7.22 (s, 1H), 7.27-7.36 (m, 5H).

LC-MS (METCR0990): 96% (UV), R_t = 1.36 min, m/z (ESI $^+$) = 249.3 $[\text{M}+\text{H}]^+$

3-(Cyclohexylamino)-2-hydroxy-*N*-(2-methylpropyl)butanamide (I-94)

[0207] The title compound was synthesized from 3-methyl-*N*-(2-methylpropyl)-oxirane-2-carboxamide (I-32) in a similar manner to method C, general procedure 2 (general scheme 4) as a white solid (310 mg, 90% purity by ^1H NMR, 43%) after purification by recrystallization from 1:1 EtOAc/heptane.

^1H NMR (500 MHz, Chloroform- d) δ 0.95 (d, J = 6.7 Hz, 6H), 1.15 (d, J = 6.6 Hz, 3H), 1.18-1.35 (m, 5H), 1.61-1.68 (m, 1H), 1.74-1.88 (m, 3H), 1.94-2.02 (m, 1H), 2.05-2.13 (m, 1H), 2.66-2.77 (m, 1H), 3.02-3.09 (m, 1H), 3.15-3.23 (m, 1H), 3.40-3.49 (m, 1H), 4.20 (d, J = 4.7 Hz, 1H), 7.31 (m, 1H).

LC-MS (METCR1410): 73% (UV), R_t = 0.81 min, m/z (ESI $^+$) = 257.2 $[\text{M}+\text{H}]^+$

3-[(Cyclopropylmethyl)amino]-2-hydroxy-*N*-(2-methylpropyl)butanamide (I-95)

[0208] The title compound was synthesized from 3-methyl-*N*-(2-methylpropyl)-oxirane-2-carboxamide (I-32) in a similar manner to method C, general procedure 2 (general scheme 4) as an off-white solid (320 mg, 80% purity by ^1H NMR, 44%) after purification by recrystallization from 1:1 EtOAc/heptane followed by recrystallization from EtOAc and trituration in heptane.

^1H NMR (500 MHz, Chloroform- d) δ -0.06-0.05 (m, 2H), 0.30-0.42 (m, 2H), 0.81 (d, J = 6.7 Hz, 6H), 0.90 (d, J = 6.5 Hz, 3H), 1.11 (dd, J = 26.2, 6.4 Hz, 1H), 1.59-1.75 (m, 1H), 2.29 (dd, J = 12.1, 7.4 Hz, 1H), 2.45 (dd, J = 12.1, 6.4 Hz, 1H), 2.90-3.12 (m, 3H), 3.87 (d, J = 5.0 Hz, 1H), 7.24 (s, 1H).

3-[(2,2-Dimethylpropyl)amino]-2-hydroxy-*N*-(2-methylpropyl)butanamide (I-96)

[0209] The title compound was synthesized from 3-methyl-*N*-(2-methylpropyl)-oxirane-2-carboxamide (I-32) in a similar manner to method C, general procedure 2 (general scheme 4) as an off-white solid (242 mg, 100% purity, 28%) after purification by recrystallization from 1:1 EtOAc/heptane.

^1H NMR (250 MHz, Chloroform- d) δ 0.87-1.01 (m, 15H), 1.11 (d, J = 6.5 Hz, 3H), 1.81 (dt, J = 13.4, 6.7 Hz, 1H), 2.36 (d, J = 11.4 Hz, 1H), 2.60 (d, J = 11.4 Hz, 1H), 2.96-3.26 (m, 4H), 4.12 (d, J = 5.3 Hz, 1H), 7.35 (s, 1H).

LC-MS (METCR1410): 100% (UV), Rt= 0.76 min, m/z (ESI⁺)= 245.6 [M+H]⁺

2-Hydroxy-N-(2-methylpropyl)-3-[(2,2,2-trifluoroethyl)amino]butanamide (I-97)

[0210] The title compound was synthesized from 3-methyl-N-(2-methylpropyl)-oxirane-2-carboxamide (I-32) in a similar manner to method C, general procedure 2 (general scheme 4) at 70 °C and was obtained as a white solid (382 mg, 100% purity, 68%) after purification by recrystallization from 1:3 EtOAc/heptane.

¹H NMR (500 MHz, Chloroform-d) δ 0.92 (d, *J* = 6.7 Hz, 6H), 1.08 (d, *J* = 6.5 Hz, 3H), 1.79 (dp, *J* = 6.7, 13.5 Hz, 1H), 3.01-3.09 (m, 1H), 3.10-3.23 (m, 3H), 3.36 (dq, *J* = 9.0, 14.4 Hz, 1H), 3.43-3.58 (m, 1H), 4.00 (d, *J* = 4.7 Hz, 1H), 6.98-7.12 (m, 1H).

LC-MS (METCR1410): 100% (UV), Rt= 0.71 min, m/z (ESI⁺)= 257.1 [M+H]⁺

3-(Benzylamino)-2-hydroxy-N-(2-methylpropyl)butanamide (I-98)

[0211] The title compound was synthesized from 3-methyl-N-(2-methylpropyl)-oxirane-2-carboxamide (I-32) in a similar manner to method C, general procedure 2 (general scheme 4) at 60 °C and was obtained as an off-white solid (301 mg, 98% purity, 50%) after purification by trituration in 1:4 EtOAc/heptane.

¹H NMR (500 MHz, Chloroform-d) δ 0.92 (d, *J* = 6.7 Hz, 6H), 1.05 (d, *J* = 6.5 Hz, 3H), 1.73-1.83 (m, 1H), 2.99-3.07 (m, 1H), 3.14-3.20 (m, 1H), 3.20-3.27 (m, 1H), 3.78-3.86 (m, 2H), 4.09 (d, *J* = 4.7 Hz, 1H), 7.12-7.22 (m, 1H), 7.26-7.37 (m, 5H).

LC-MS (METCR1410): 98% (UV), Rt= 0.75 min, m/z (ESI⁺)= 265.5 [M+H]⁺

N-(Cyclohexylmethyl)-2-hydroxy-3-[(propan-2-yl)amino]butanamide (I-99)

[0212] The title compound was synthesized from N-(cyclohexylmethyl)-3-methyl-oxirane-2-carboxamide (I-34) in a similar manner to method C, general procedure 2 (general scheme 4) as an off-white solid (420 mg, 100% purity, 95%) after purification by recrystallization from EtOAc.

¹H NMR (250 MHz, DMSO-*d*₆) δ 0.81 (d, *J* = 6.5 Hz, 3H), 0.87 (s, 1H), 0.92-0.98 (m, 6H), 1.06-1.22 (m, 3H), 1.29-1.55 (m, 2H), 1.64 (d, *J* = 10.8 Hz, 5H), 2.79-3.06 (m, 4H), 3.90 (s, 1H), 5.34 (s, 1H), 7.69 (t, *J* = 5.9 Hz, 1H).

LC-MS (METCR1410): 100% (UV), Rt= 0.79 min, m/z (ESI⁺)= 257.1 [M+H]⁺

N-(Cyclohexylmethyl)-2-hydroxy-3-([(oxan-4-yl)methyl]amino)butanamide (I-100)

[0213] The title compound was synthesized from N-(cyclohexylmethyl)-3-methyl-oxirane-2-carboxamide (I-34) in a similar manner to method C, general procedure 2

(general scheme 4) at 60 °C as an off-white solid (500 mg, 88% purity by ¹H NMR, 81%) after purification by recrystallization from 1:1 EtOAc/heptane.

¹H NMR (500 MHz, Chloroform-d) δ 0.89-0.98 (m, 2H), 1.03 (d, *J* = 6.5 Hz, 3H), 1.10-1.37 (m, 7H), 1.42-1.52 (m, 1H), 1.69-1.76 (m, 7H), 2.47 (dd, *J* = 7.0, 11.9 Hz, 1H), 2.67 (dd, *J* = 5.9, 11.9 Hz, 1H), 3.05-3.20 (m, 2H), 3.33-3.43 (m, 2H), 3.94-4.01 (m, 2H), 4.04 (d, *J* = 4.9 Hz, 1H), 7.12-7.23 (m, 1H).

LC-MS (METCR1416): 100% (UV), *R*_t = 2.66 min, *m/z* (ESI⁺) = 313.5 [M+H]⁺

N-(Cyclohexylmethyl)-2-hydroxy-3-[(2,2,2-trifluoroethyl)amino]butanamide (I-101)

[0214] The title compound was synthesized from *N*-(cyclohexylmethyl)-3-methyloxirane-2-carboxamide (I-34) in a similar manner to method C, general procedure 2 (general scheme 4) at 60 °C and was obtained as an off-white powder (300 mg, 10% purity, 8%) used in the next step without further purification.

N-(Cyclohexylmethyl)-3-[(cyclopropylmethyl)amino]-2-hydroxybutanamide (I-102)

[0215] The title compound was synthesized from *N*-(cyclohexylmethyl)-3-methyloxirane-2-carboxamide (I-34) in a similar manner to method C, general procedure 2 (general scheme 4) at 60 °C and was obtained as an off-white solid (337 mg, 100% purity, 71%) after purification by recrystallization from 1:2 EtOAc/heptane.

¹H NMR (500 MHz, Chloroform-d) δ 0.07-0.19 (m, 2H), 0.45-0.54 (m, 2H), 0.85-0.99 (m, 3H), 1.01 (d, *J* = 6.5 Hz, 3H), 1.10-1.28 (m, 3H), 1.41-1.52 (m, 1H), 1.62-1.69 (m, 1H), 1.69-1.76 (m, 4H), 2.41 (dd, *J* = 7.4, 12.1 Hz, 1H), 2.56 (dd, *J* = 6.4, 12.1 Hz, 1H), 3.04-3.12 (m, 2H), 3.12-3.20 (m, 1H), 3.99 (d, *J* = 5.0 Hz, 1H), 7.33 (s, 1H).

LC-MS (METCR1410): 100% (UV), *R*_t = 0.81 min, *m/z* (ESI⁺) = 269.2 [M+H]⁺

3-(Cyclohexylamino)-*N*-(cyclohexylmethyl)-2-hydroxybutanamide (I-103)

[0216] The title compound was synthesized from *N*-(cyclohexylmethyl)-3-methyloxirane-2-carboxamide (I-34) in a similar manner to method C, general procedure 2 (general scheme 4) as an off-white powder (441 mg, 100% purity, 69%) after purification by recrystallization from 1:2 EtOAc/heptane.

¹H NMR (500 MHz, Chloroform-d) δ 0.90-1.05 (m, 7H), 1.10-1.30 (m, 6H), 1.41-1.52 (m, 1H), 1.59-1.67 (m, 2H), 1.68-1.76 (m, 6H), 1.81-1.89 (m, 1H), 1.91-1.99 (m, 1H), 2.49 (tt, *J* = 3.7, 10.5 Hz, 1H), 3.03-3.10 (m, 1H), 3.14-3.21 (m, 1H), 3.21-3.27 (m, 1H), 3.91 (d, *J* = 5.2 Hz, 1H), 7.27-7.35 (m, 1H).

LC-MS (METCR1410): 100% (UV), *R*_t = 0.87 min, *m/z* (ESI⁺) = 297.2 [M+H]⁺

tert-Butyl 4-[(1-[(cyclohexylmethyl)carbamoyl]-1-hydroxypropan-2-yl)amino)methyl]-piperidine-1-carboxylate (I-104)

[0217] The title compound was synthesized from *N*-(cyclohexylmethyl)-3-methyloxirane-2-carboxamide (I-34) in a similar manner to method C, general procedure 2 (general scheme 4) at 60 °C and was obtained as an off-white solid (410 mg, 85% purity by ¹H NMR, 66%) after purification by recrystallization from heptane.

¹H NMR (500 MHz, Chloroform-*d*) δ 0.84-1.00 (m, 2H), 1.08 (d, *J* = 6.5 Hz, 3H), 1.10-1.28 (m, 6H), 1.39-1.51 (m, 11H), 1.59-1.79 (m, 6H), 2.50 (dd, *J* = 7.0, 11.9 Hz, 1H), 2.65-2.77 (m, 3H), 3.04-3.19 (m, 3H), 3.98-4.23 (m, 3H), 7.10-7.21 (m, 1H).

tert-Butyl *N*-[(1*s*,4*s*)-4-[(1-[(cyclohexylmethyl)carbamoyl]-1-hydroxypropan-2-yl)amino)cyclohexyl]carbamate (I-105)

[0218] The title compound was synthesized from *N*-(cyclohexylmethyl)-3-methyloxirane-2-carboxamide (I-34) in a similar manner to method C, general procedure 2 (general scheme 4) at 60 °C then 70 °C and was obtained as an off-white powder (552 mg, 93% purity by ¹H NMR, 82%) after purification by flash column chromatography on normal phase silica (50 g SNAP KP-SIL cartridge, 0-100% TBME in heptane gradient then 0-20% MeOH in TBME gradient).

¹H NMR (250 MHz, Chloroform-*d*) δ 0.83-1.07 (m, 5H), 1.07-1.41 (m, 7H), 1.41-1.50 (m, 10H), 1.53-1.82 (m, 9H), 2.59-2.76 (m, 1H), 2.97-3.31 (m, 3H), 3.55-3.71 (m, 1H), 3.95 (d, *J* = 4.7 Hz, 1H), 4.40-4.70 (m, 1H), 7.12 (t, *J* = 5.7 Hz, 1H).

LC-MS (METCR1410): 100% (UV), *R*_t = 0.93 min, *m/z* (ESI⁺) = 412.6 [M+H]⁺

3-(Cyclohexylamino)-*N*-[2-(cyclohexyloxy)ethyl]-2-hydroxybutanamide (I-106)

[0219] The title compound was synthesized from *N*-[2-(cyclohexyloxy)ethyl]-3-methyloxirane-2-carboxamide (I-35) in a similar manner to method C, general procedure 2 (general scheme 4) at 50-70°C and was obtained as an off-white powder (247 mg, 100% purity, 63%) after purification by triturated in Et₂O.

¹H NMR (250 MHz, Chloroform-*d*) δ 0.91-1.02 (m, 4H), 1.03-1.38 (m, 10H), 1.41-2.03 (m, 9H), 2.40-2.59 (m, 1H), 3.16-3.34 (m, 2H), 3.34-3.59 (m, 4H), 3.94 (d, *J* = 5.1 Hz, 1H), 7.54 (s, 1H).

LC-MS (METCR1410): 100% (UV), *R*_t = 0.89 min, *m/z* (ESI⁺) = 327.6 [M+H]⁺

Methyl 2-[3-(benzylamino)-2-hydroxybutanamido]acetate (I-107)

[0220] The title compound was synthesized from methyl 2-[(3-methyloxiran-2-yl)formamido]acetate (I-36) in a similar manner to method C, general procedure 2 (general scheme 4) at 70 °C and was obtained as a yellow viscous oil (594 mg, 77% purity, 63%) after 2 purifications by flash column chromatography on normal phase silica (10 g SNAP KP-SIL cartridge, 0-20% MeOH in DCM gradient then 10 g SNAP KP-SIL cartridge, 2-12% MeOH in DCM gradient).

LC-MS (METCR0990): 77% (UV), Rt= 1.32 min, m/z (ESI⁺)= 281.2 [M+H]⁺

3-(Benzylamino)-2-hydroxy-N-(propan-2-yl)butanamide (I-108)

[0221] The title compound was synthesized from 3-methyl-N-(propan-2-yl)oxirane-2-carboxamide (I-39) in a similar manner to method C, general procedure 2 (general scheme 4) at 50-60 °C and was obtained as an off-white solid (148 mg, 96% purity, 33%) after purification by trituration in 1:5 EtOAc/heptane.

¹H NMR (500 MHz, Chloroform-d) δ 1.03 (d, *J* = 6.5 Hz, 3H), 1.13-1.19 (m, 6H), 3.18-3.25 (m, 1H), 3.76-3.86 (m, 2H), 4.04 (d, *J* = 4.7 Hz, 1H), 4.06-4.15 (m, 1H), 6.89-7.00 (m, 1H), 7.26-7.37 (m, 5H).

LC-MS (METCR1410): 96% (UV), Rt= 0.65 min, m/z (ESI⁺)= 251.1 [M+H]⁺

N-(Cyclopropylmethyl)-2-hydroxy-3-[(oxan-4-yl)methyl]amino}hexanamide (I-109)

[0222] The title compound was synthesized from N-(cyclopropylmethyl)-3-propyloxirane-2-carboxamide (I-44) in a similar manner to method C, general procedure 2 (general scheme 4) at 60 °C and was obtained as an off-white solid (360 mg, 90% purity by ¹H NMR, 57%) after purification by trituration in 1:5 EtOAc/heptane.

¹H NMR (500 MHz, Chloroform-d) δ 0.16-0.27 (m, 2H), 0.45-0.56 (m, 2H), 0.87-1.00 (m, 4H), 1.22-1.55 (m, 6H), 1.56-1.76 (m, 3H), 2.48-2.55 (m, 1H), 2.64 (dd, *J* = 5.9, 12.1 Hz, 1H), 2.93-3.01 (m, 1H), 3.04-3.23 (m, 2H), 3.34-3.42 (m, 2H), 3.93-4.02 (m, 2H), 4.11 (d, *J* = 4.7 Hz, 1H), 7.11-7.25 (m, 1H).

LC-MS (METCR1410): 52% (UV), Rt= 0.72 min, m/z (ESI⁺)= 299.1 [M+H]⁺

tert-Butyl 4-[(1-[(cyclohexylmethyl)carbamoyl]-1-hydroxybutan-2-yl)amino)methyl]-piperidine-1-carboxylate (I-110)

[0223] The title compound was synthesized from N-(cyclohexylmethyl)-3-ethyloxirane-2-carboxamide (I-45) in a similar manner to method C, general procedure 2 (general scheme 4) at 70 °C and was obtained as an off-white crystalline solid (600

mg, 96% purity, 61%) after purification by flash column chromatography on normal phase silica (25 g SNAP Ultra cartridge, 0-100% EtOAc in heptane gradient).

¹H NMR (500 MHz, Chloroform-d) δ 0.87-0.99 (m, 5H), 1.05-1.28 (m, 5H), 1.30-1.40 (m, 1H), 1.44 (s, 9H), 1.46-1.61 (m, 4H), 1.61-1.67 (m, 2H), 1.67-1.76 (m, 4H), 2.44 (dd, *J* = 7.2, 11.9 Hz, 1H), 2.60 (dd, *J* = 6.0, 11.8 Hz, 1H), 2.63-2.75 (m, 2H), 2.79-2.85 (m, 1H), 3.04-3.16 (m, 2H), 4.01 (d, *J* = 5.1 Hz, 1H), 4.03-4.19 (m, 2H), 7.23 (t, *J* = 5.6 Hz, 1H).

LC-MS (METCR1410): 96% (UV), *R*_t = 0.9 min, *m/z* (ESI⁺) = 426.8 [M+H]⁺

3-(Cyclohexylamino)-*N*-(cyclohexylmethyl)-2-hydroxypentanamide (I-111)

[0224] The title compound was synthesized from *N*-(cyclohexylmethyl)-3-ethyl-oxirane-2-carboxamide (I-45) in a similar manner to method C, general procedure 2 (general scheme 4) at 70 °C and was obtained as an off-white powder (400 mg, 76% purity by ¹H NMR, 72%) after purification by flash column chromatography on normal phase silica (10 g SNAP Ultra cartridge, 0-100% EtOAc in heptane gradient).

¹H NMR (500 MHz, Chloroform-d) δ 0.88-0.96 (m, 3H), 0.96-1.09 (m, 3H), 1.09-1.36 (m, 7H), 1.42-1.52 (m, 2H), 1.54-1.76 (m, 8H), 1.78-1.88 (m, 2H), 1.93-1.99 (m, 1H), 2.47 (tt, *J* = 3.7, 10.4 Hz, 1H), 3.00-3.18 (m, 3H), 3.97 (d, *J* = 5.2 Hz, 1H), 7.21-7.31 (m, 1H).

LC-MS (METCR1410): 51% (UV), *R*_t = 0.85 min, *m/z* (ESI⁺) = 311.7 [M+H]⁺

tert-Butyl 3-[(1-[(cyclohexylmethyl)carbamoyl]-1-hydroxybutan-2-yl)amino)methyl]-azetidine-1-carboxylate (I-112)

[0225] The title compound was synthesized from *N*-(cyclohexylmethyl)-3-ethyl-oxirane-2-carboxamide (I-45) in a similar manner to method C, general procedure 2 (general scheme 4) at 60 °C then 70 °C and was obtained as a colourless gum (630 mg, 85% purity by ¹H NMR, 50%) after purification by flash column chromatography on normal phase silica (50 g SNAP KP-SIL cartridge, 0-20% MeOH in heptane gradient).

¹H NMR (250 MHz, Chloroform-d) δ 0.71-1.02 (m, 6H), 1.09-1.21 (m, 2H), 1.29-1.55 (m, 11H), 1.57-1.81 (m, 6H), 2.46-3.22 (m, 5H), 3.46-3.79 (m, 3H), 3.90-4.06 (m, 2H), 4.25-4.41 (m, 1H), 6.53-7.21 (m, 1H).

LC-MS (METCR1410): 47% (UV), *R*_t = 0.88 min, *m/z* (ESI⁺) = 398.8 [M+H]⁺

N-(Cyclopropylmethyl)-3-[(cyclopropylmethyl)amino]-2-hydroxy-5-methylhexanamide (I-113)

[0226] The title compound was synthesized from *N*-(cyclopropylmethyl)-3-(2-methylpropyl)oxirane-2-carboxamide (I-47) in a similar manner to method C, general procedure 2 (general scheme 4) at 60 °C and was obtained as an off-white powder (240 mg, 98% purity by ¹H NMR, 58%) after purification by recrystallization from 1:1 EtOAc/heptane.

[0227] ¹H NMR (500 MHz, Chloroform-d) δ 0.11-0.28 (m, 4H), 0.46-0.58 (m, 4H), 0.86-1.04 (m, 8H), 1.20-1.39 (m, 2H), 1.59-1.71 (m, 1H), 2.47 (dd, *J* = 7.4, 12.3 Hz, 1H), 2.67 (dd, *J* = 6.6, 12.3 Hz, 1H), 3.07-3.22 (m, 3H), 4.17 (d, *J* = 4.1 Hz, 1H), 7.07-7.19 (m, 1H).

LC-MS (METCR1410): 100% (UV), *R*_t = 0.81 min, *m/z* (ESI⁺) = 269.2 [M+H]⁺

N-(Cyclopropylmethyl)-2-hydroxy-5-methyl-3-([(oxan-4-yl)methyl]amino) hexanamide (I-114)

[0228] The title compound was synthesized from *N*-(cyclopropylmethyl)-3-(2-methylpropyl)oxirane-2-carboxamide (I-47) in a similar manner to method C, general procedure 2 (general scheme 4) as an off-white solid (400 mg, 55% purity by ¹H NMR, 53%) after concentration of the filtrate obtained from trituration in EtOAc/heptane.

¹H NMR (500 MHz, Chloroform-d) δ 0.16-0.27 (m, 2H), 0.44-0.57 (m, 2H), 0.88 (d, *J* = 6.5 Hz, 3H), 0.92 (d, *J* = 6.6 Hz, 3H), 0.93-1.00 (m, 1H), 1.12-1.39 (m, 3H), 1.49-1.72 (m, 4H), 2.46-2.52 (m, 1H), 2.56-2.63 (m, 3H), 2.97-3.04 (m, 1H), 3.08-3.22 (m, 2H), 3.31-3.43 (m, 2H), 3.93-4.04 (m, 2H), 4.10 (d, *J* = 4.3 Hz, 1H), 6.95-7.05 (m, 1H).

LC-MS (METCR1410): 77% (UV), *R*_t = 0.82 min, *m/z* (ESI⁺) = 313.3 [M+H]⁺

N-(Cyclopropylmethyl)-2-hydroxy-5-methyl-3-([(3*S*)-oxolan-3-yl]methyl) amino)hexanamide (I-115)

[0229] The title compound was synthesized from *N*-(cyclopropylmethyl)-3-(2-methylpropyl)oxirane-2-carboxamide (I-47) in a similar manner to method C, general procedure 2 (general scheme 4) at 60 °C then 70 °C and was obtained as an off-white powder (333 mg, 85% purity by ¹H NMR, 79%) after purification by flash column chromatography on normal phase silica (25 g SNAP KP-SIL cartridge, 0-100% TBME in heptane gradient then 0-30% MeOH in TBME gradient).

¹H NMR (250 MHz, Chloroform-d) δ 0.04-0.33 (m, 2H), 0.40-0.62 (m, 2H), 0.84-0.98 (m, 7H), 1.12-1.26 (m, 2H), 1.48-1.71 (m, 3H), 1.92-2.18 (m, 1H), 2.22-2.47 (m, 1H),

2.57-2.79 (m, 2H), 2.95-3.08 (m, 1H), 3.10-3.23 (m, 2H), 3.42-3.59 (m, 1H), 3.66-3.85 (m, 2H), 3.85-3.96 (m, 2H), 4.11 (d, $J = 4.2$ Hz, 1H), 6.98 (s, 1H).

LC-MS (METCR1278): 78% (UV), $R_t = 1.44$ min, m/z (ESI⁺) = 299.1 [M+H]⁺

N-(Cyclopropylmethyl)-2-hydroxy-5-methyl-3-({[(3R)-oxolan-3-yl]methyl}amino)hexanamide (I-116)

[0230] The title compound was synthesized from *N*-(cyclopropylmethyl)-3-(2-methylpropyl)oxirane-2-carboxamide (I-47) in a similar manner to method C, general procedure 2 (general scheme 4) at 60 °C then 70 °C and was obtained as an off-white powder (304 mg, 93% purity, 79%) after purification by flash column chromatography on normal phase silica (25 g SNAP KP-SIL cartridge, 0-100% TBME in heptane gradient then 0-30% MeOH in TBME gradient).

¹H NMR (250 MHz, Chloroform-*d*) δ 0.16-0.26 (m, 2H), 0.44-0.60 (m, 2H), 0.82-0.98 (m, 8H), 1.10-1.27 (m, 2H), 1.51-1.68 (m, 3H), 1.96-2.13 (m, 1H), 2.26-2.45 (m, 1H), 2.58-2.78 (m, 2H), 2.93-3.06 (m, 1H), 3.11-3.21 (m, 2H), 3.42-3.59 (m, 1H), 3.65-3.82 (m, 1H), 3.82-3.96 (m, 2H), 4.11 (d, $J = 4.2$ Hz, 1H), 6.98 (s, 1H).

LC-MS (METCR1278): 93% (UV), $R_t = 1.44$ min, m/z (ESI⁺) = 299.1 [M+H]⁺

N-(Cyclopropylmethyl)-2-hydroxy-3-[(3-methoxypropyl)amino]-5-methylhexanamide (I-117)

[0231] The title compound was synthesized from *N*-(cyclopropylmethyl)-3-(2-methylpropyl)oxirane-2-carboxamide (I-47) in a similar manner to method C, general procedure 2 (general scheme 4) at 70 °C and was obtained as an off-white powder (225 mg, 100% purity by ¹H NMR, 54%) after purification by trituration in heptane.

¹H NMR (500 MHz, Chloroform-*d*) δ 0.19-0.24 (m, 2H), 0.48-0.53 (m, 2H), 0.87-0.94 (m, 7H), 0.94-1.03 (m, 1H), 1.19 (ddd, $J = 3.5, 9.7, 13.9$ Hz, 1H), 1.32 (ddd, $J = 4.8, 9.8, 14.4$ Hz, 1H), 1.53-1.65 (m, 1H), 1.71-1.94 (m, 3H), 2.66-2.80 (m, 1H), 2.88-2.97 (m, 1H), 3.08-3.21 (m, 3H), 3.31-3.36 (m, 3H), 3.39-3.57 (m, 2H), 4.20 (d, $J = 3.8$ Hz, 1H), 7.08 (br. m, 1H).

LC-MS (METCR1410): 87% (UV), $R_t = 0.80$ min, m/z (ESI⁺) = 287.3 [M+H]⁺

N-(Cyclopropylmethyl)-2-hydroxy-5-methyl-3-({[(oxolan-3-yl)methyl]amino}hexanamide (I-118)

[0232] The title compound was synthesized from *N*-(cyclopropylmethyl)-3-(2-methylpropyl)oxirane-2-carboxamide (I-47) in a similar manner to method C, general

procedure 2 (general scheme 4) at 70 °C and was obtained as an off-white powder (219 mg, 97% purity, 59%) after purification twice by ion exchange flash chromatography (5 g Isolute SCX-2 cartridge, 1-5% 7N methanolic ammonia in DCM gradient) followed by trituration in heptane.

¹H NMR (500 MHz, Chloroform-d) δ 0.17-0.27 (m, 2H), 0.45-0.56 (m, 2H), 0.89 (d, *J* = 6.6 Hz, 3H), 0.92 (d, *J* = 6.6 Hz, 3H), 0.94-1.01 (m, 1H), 1.14-1.29 (m, 3H), 1.52-1.64 (m, 3H), 2.01-2.11 (m, 1H), 2.30-2.43 (m, 1H), 2.59-2.66 (m, 1H), 2.68-2.75 (m, 1H), 2.99-3.06 (m, 1H), 3.08-3.23 (m, 2H), 3.44-3.53 (m, 1H), 3.74 (q, *J* = 7.5 Hz, 1H), 3.82-3.92 (m, 2H), 4.11 (d, *J* = 4.1 Hz, 1H), 6.90-7.06 (m, 1H).

LC-MS (METCR0990): 97% (UV), *R*_t = 1.48 min, *m/z* (ESI⁺) = 299.3 [M+H]⁺

N-(Cyclopropylmethyl)-2-hydroxy-5-methyl-3-([(oxolan-2-yl)methyl]amino)hexanamide (I-119)

[0233] The title compound was synthesized from *N*-(cyclopropylmethyl)-3-(2-methylpropyl)oxirane-2-carboxamide (I-47) in a similar manner to method C, general procedure 2 (general scheme 4) at 70 °C and was obtained as a yellow powder (175 mg, 98% purity, 48%) after purification by ion exchange flash chromatography (5 g Isolute SCX-2 cartridge, 1-5% 7N methanolic ammonia in DCM gradient) followed by trituration in heptane.

¹H NMR (500 MHz, Chloroform-d) δ 0.15-0.28 (m, 2H), 0.44-0.56 (m, 2H), 0.75-1.02 (m, 8H), 1.13-1.23 (m, 1H), 1.27-1.31 (m, 1H), 1.46-1.67 (m, 3H), 1.85-2.05 (m, 3H), 2.57-2.69 (m, 1H), 2.71-2.87 (m, 1H), 2.98-3.23 (m, 3H), 3.71-3.80 (m, 1H), 3.82-3.89 (m, 1H), 3.92-4.03 (m, 1H), 4.11 (t, *J* = 3.9 Hz, 1H), 6.99-7.18 (m, 1H).

LC-MS (METCR0990): 98% (UV), *R*_t = 1.54 min, *m/z* (ESI⁺) = 299.3 [M+H]⁺

3-Cyclopropyl-*N*-(cyclopropylmethyl)-2-hydroxy-3-([(oxan-4-yl)methyl]amino)propanamide (I-120)

[0234] The title compound was synthesized from 3-cyclopropyl-*N*-(cyclopropylmethyl)oxirane-2-carboxamide (I-49) in a similar manner to method C, general procedure 2 (general scheme 4) as an off-white solid (390 mg, 100% purity, 88%) after purification by trituration in heptane.

¹H NMR (500 MHz, Chloroform-d) δ 0.05-0.12 (m, 1H), 0.22 (q, *J* = 5.0 Hz, 2H), 0.40-0.48 (m, 3H), 0.49-0.55 (m, 2H), 0.79-0.86 (m, 1H), 0.92-1.02 (m, 1H), 1.27-1.34 (m, 2H), 1.56-1.62 (m, 1H), 1.63-1.72 (m, 2H), 2.20 (dd, *J* = 3.7, 9.8 Hz, 1H), 2.45 (dd, *J* =

7.2, 12.0 Hz, 1H), 2.59 (dd, $J = 5.6, 12.0$ Hz, 1H), 3.07-3.14 (m, 1H), 3.18-3.24 (m, 1H), 3.35-3.42 (m, 2H), 3.98 (dt, $J = 2.2, 11.4$ Hz, 2H), 4.13 (d, $J = 3.7$ Hz, 1H), 6.93-7.02 (m, 1H).

LC-MS (METCR1410): 100% (UV), $R_t = 0.71$ min, m/z (ESI⁺) = 297.1 [M+H]⁺

3-(Benzylamino)-3-cyclopropyl-*N*-(cyclopropylmethyl)-2-hydroxypropanamide (I-121)

[0235] The title compound was synthesized from 3-cyclopropyl-*N*-(cyclopropylmethyl)oxirane-2-carboxamide (I-49) in a similar manner to method C, general procedure 2 (general scheme 4) as an off-white solid (278 mg, 97% purity, 63%) after purification by trituration in heptane.

¹H NMR (500 MHz, Chloroform-*d*) δ 0.00-0.09 (m, 1H), 0.22 (q, $J = 5.0$ Hz, 2H), 0.37-0.47 (m, 3H), 0.47-0.53 (m, 2H), 0.83-0.92 (m, 1H), 0.93-1.03 (m, 1H), 2.31 (dd, $J = 3.6, 9.8$ Hz, 1H), 3.06-3.15 (m, 1H), 3.17-3.25 (m, 1H), 3.72-3.86 (m, 2H), 4.21 (d, $J = 3.6$ Hz, 1H), 6.95-7.04 (m, 1H), 7.26-7.37 (m, 5H).

LC-MS (METCR1410): 97% (UV), $R_t = 0.8$ min, m/z (ESI⁺) = 289.5 [M+H]⁺

3-(Benzylamino)-*N*-(cyclopropylmethyl)-2-hydroxy-5-methoxypentanamide (I-122)

[0236] The title compound was synthesized from *N*-(cyclopropylmethyl)-3-(2-methoxyethyl)oxirane-2-carboxamide (I-50) in a similar manner to method C, general procedure 2 (general scheme 4) as a yellow viscous oil (155 mg, 90% purity, 81%). The crude material was suspended in heptane and used in the next step without further purification.

¹H NMR (500 MHz, Chloroform-*d*) δ 0.16-0.24 (m, 2H), 0.45-0.53 (m, 2H), 0.90-0.98 (m, 1H), 1.67-1.72 (m, 2H), 3.02-3.19 (m, 3H), 3.28-3.38 (m, 3H), 3.41-3.56 (m, 2H), 3.78-3.88 (m, 2H), 4.12 (d, $J = 5.2$ Hz, 1H), 7.28-7.36 (m, 6H).

LC-MS (METCR1410): 90% (UV), $R_t = 0.75$ -0.90 min (two peaks), m/z (ESI⁺) = 307.5 [M+H]⁺

3-(Benzylamino)-*N*-(cyclopropylmethyl)-2-hydroxy-3-(oxan-4-yl)propanamide (I-123)

[0237] The title compound was synthesized from *N*-(cyclopropylmethyl)-3-(oxan-4-yl)oxirane-2-carboxamide (I-51) in a similar manner to method C, general procedure 2 (general scheme 4) at 70 °C and was obtained as a yellow viscous oil (134 mg, 56% purity, 52%). The crude material was suspended in heptane and used in the next step without further purification.

LC-MS (METCR1410): 56% (UV), $R_t = 0.8$ min, m/z (ESI⁺) = 333.3 [M+H]⁺

N-(Cyclopropylmethyl)-2-hydroxy-3-[[oxan-4-yl)methyl]amino]-5-phenylpentanamide (I-124)

[0238] The title compound was synthesized from *N*-(cyclopropylmethyl)-3-(2-phenylethyl)oxirane-2-carboxamide (I-52) in a similar manner to method C, general procedure 2 (general scheme 4) at 70 °C and was obtained as an off-white solid (590 mg, 90% purity, 97%) after purification by trituration in heptane.

¹H NMR (500 MHz, Chloroform-d) δ 0.17-0.23 (m, 2H), 0.45-0.51 (m, 2H), 0.89-0.98 (m, 1H), 1.20-1.30 (m, 2H), 1.47-1.63 (m, 3H), 1.63-1.71 (m, 1H), 1.77-1.90 (m, 1H), 2.38-2.46 (m, 1H), 2.48-2.55 (m, 1H), 2.62-2.75 (m, 2H), 2.92-2.99 (m, 1H), 3.09-3.21 (m, 2H), 3.35 (tdd, *J* = 2.2, 4.7, 11.8 Hz, 2H), 3.92-3.97 (m, 2H), 4.07 (d, *J* = 5.0 Hz, 1H), 7.16-7.21 (m, 4H), 7.26-7.30 (m, 2H).

LC-MS (METCR1410): 90% (UV), *R*_t = 0.89 min, *m/z* (ESI⁺) = 361.6 [M+H]⁺

Method D: Epoxide opening with methylamine in methanol

N[(3-Chlorophenyl)methyl]-2-hydroxy-3-(methylamino)butanamide (I-125)

[0239] A solution of *N*[(3-chlorophenyl)methyl]-3-methyloxirane-2-carboxamide (I-27) (86% purity, 300 mg, 1.14 mmol) in 33% methylamine in ethanol (3 mL, 24.1 mmol) was stirred in a sealed tube at RT for 42 h. 33% methylamine in ethanol (1 mL) was added and the reaction mixture stood at RT for 24 h. The reaction mixture was concentrated *in vacuo* to give a solid which was dissolved in hot EtOAc (5 mL). The solution was diluted with heptane (15 mL) and cooled in a sonic bath over 5 min. The resulting precipitate was collected via filtration and dried *in vacuo* at 40 °C for 1 h to afford 265 mg of *N*[(3-chlorophenyl)methyl]-2-hydroxy-3-(methylamino)-butanamide as an off-white solid (100% purity, 81%).

¹H NMR (500 MHz, Chloroform-d) δ 1.01 (d, *J* = 6.5 Hz, 3H), 2.43 (s, 3H), 2.95-3.06 (m, 1H), 4.10 (d, *J* = 4.9 Hz, 1H), 4.40-4.51 (m, 2H), 7.15-7.19 (m, 1H), 7.22-7.26 (m, 2H), 7.27-7.29 (m, 1H), 7.55-7.65 (m, 1H).

LC-MS (METCR1410): 100% (UV), *R*_t = 0.72 min, *m/z* (ESI⁺) = 257.0/259.0 [M+H]⁺

GENERAL PROCEDURE 3 (GENERAL SCHEME 4): *N*-Formylation

Method A: Direct addition of acetic anhydride

N[(3-Chlorophenyl)methyl]-2-hydroxy-3-[*N*-(2-methoxyphenyl)formamido]butanamide (I-126)

[0240] To a stirred suspension of *N*-[(3-chlorophenyl)methyl]-2-hydroxy-3-[(2-methoxyphenyl)amino]butanamide (I-54, 85% purity, 120 mg, 0.29 mmol) and formic acid (75 μ L, 1.91 mmol) was added dropwise acetic anhydride (0.5 mL). The reaction was stirred at RT in a sealed vial for 1 h. The reaction mixture was quenched with ice/water (1 mL) and the solution partitioned between saturated NaHCO₃ (5 mL) and EtOAc (2 x 5 mL). The organic layers were combined, dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude material was purified twice by preparative LC (acidic pH, standard elution method) to afford 8 mg of *N*-[(3-chlorophenyl)methyl]-2-hydroxy-3-[[*N*-(2-methoxyphenyl)formamido]butanamide as a brown oil (100% purity, 7%).

¹H NMR (500 MHz, Chloroform-*d*) δ 1.34 (d, *J* = 7.2 Hz, 3H), 3.88 (s, 3H), 4.11-4.21 (m, 1H), 4.40 (dd, *J* = 6.1, 15.1 Hz, 1H), 4.48 (dd, *J* = 6.3, 15.1 Hz, 1H), 4.73 (s, 1H), 6.30-6.42 (m, 1H), 6.93-7.02 (m, 2H), 7.12-7.19 (m, 2H), 7.21-7.29 (m, 3H), 7.32-7.39 (m, 1H), 7.41-7.53 (m, 1H), 8.08 (s, 1H).

LC-MS (METCR1416): 100% (UV), Rt= 3.88 min, m/z (ESI⁺)= 377.1/379.1 [M+H]⁺

N-[(3-Chlorophenyl)methyl]-2-hydroxy-3-[[*N*-(3-methoxyphenyl)formamido]butanamide (I-127)

[0241] The title compound was synthesized from *N*-[(3-chlorophenyl)methyl]-2-hydroxy-3-[(3-methoxyphenyl)amino]butanamide (I-56) in a similar manner to method A, general procedure 3 (general scheme 4) as a yellow viscous oil (273 mg, 91% purity, 94%) used in the next step without further purification.

¹H NMR (500 MHz, Chloroform-*d*) δ 1.36 (d, *J* = 7.2 Hz, 3H), 3.83 (s, 3H), 4.42-4.51 (m, 3H), 4.62 (s, 1H), 6.16 (s, 1H), 6.76 (t, *J* = 2.2 Hz, 1H), 6.79-6.84 (m, 1H), 6.86-6.91 (m, 1H), 7.14-7.20 (m, 1H), 7.22-7.28 (m, 3H), 7.32 (t, *J* = 8.1 Hz, 1H), 7.39-7.47 (m, 1H), 8.28 (s, 1H).

LC-MS (METCR1278): 91% (UV), Rt= 1.93 min, m/z (ESI⁺)= 377.0/379.0 [M+H]⁺

N-[(3-Chlorophenyl)methyl]-2-hydroxy-3-[[*N*-(4-methoxyphenyl)formamido]butanamide (I-128)

[0242] The title compound was synthesized from *N*-[(3-chlorophenyl)methyl]-2-hydroxy-3-[(4-methoxyphenyl)amino]butanamide (I-57) in a similar manner to method A, general procedure 3 (general scheme 4) as a brown solid (273 mg, 90% purity by ¹H NMR, 89%) used in the next step without further purification.

¹H NMR (500 MHz, Chloroform-d) δ 1.33 (d, J = 7.2 Hz, 3H), 3.82 (s, 3H), 4.33-4.39 (m, 1H), 4.40-4.50 (m, 2H), 4.59-4.64 (m, 1H), 6.18 (s, 1H), 6.89-6.93 (m, 2H), 7.13-7.17 (m, 3H), 7.23-7.26 (m, 2H), 7.26-7.28 (m, 1H), 7.39-7.46 (m, 1H), 8.20 (s, 1H).

N[(3-Chlorophenyl)methyl]-2-hydroxy-3-(*N*-phenylformamido)butanamide (I-129)

[0243] The title compound was synthesized from *N*[(3-chlorophenyl)methyl]-2-hydroxy-3-(phenylamino)butanamide (I-58) in a similar manner to method A, general procedure 3 (general scheme 4) as a brown solid (273 mg, 81% purity, 84%) used in the next step without further purification.

¹H NMR (500 MHz, Chloroform-d) δ 1.36 (d, J = 7.2 Hz, 3H), 4.43-4.50 (m, 3H), 4.64 (s, 1H), 6.18 (s, 1H), 7.14-7.19 (m, 2H), 7.22-7.25 (m, 3H), 7.26-7.28 (m, 1H), 7.30-7.37 (m, 2H), 7.41-7.45 (m, 2H), 8.28 (s, 1H).

LC-MS (METCR1278): 81% (UV), R_t = 1.9 min, m/z (ESI⁺) = 346.9/348.9 [M+H]⁺

N[(3-Chlorophenyl)methyl]-3-[*N*-(5-fluoro-2-methoxyphenyl)formamido]-2-hydroxybutanamide (I-130)

[0244] The title compound was synthesized from *N*[(3-chlorophenyl)methyl]-3-[(5-fluoro-2-methoxyphenyl)amino]-2-hydroxybutanamide (I-65) in a similar manner to method A, general procedure 3 (general scheme 4) as a brown viscous oil (217 mg, 98% purity, 96%) used in the next step without further purification.

¹H NMR (500 MHz, Chloroform-d) δ 1.33 (d, J = 7.2 Hz, 3H), 3.86 (s, 3H), 4.15-4.21 (m, 1H), 4.37-4.51 (m, 2H), 4.70 (s, 1H), 6.16 (s, 1H), 6.91-6.95 (m, 2H), 7.05-7.09 (m, 1H), 7.14-7.18 (m, 1H), 7.24-7.26 (m, 2H), 7.26-7.28 (m, 1H), 7.39-7.46 (m, 1H), 8.08 (s, 1H).

LC-MS (METCR1278): 98% (UV), R_t = 2.05 min, m/z (ESI⁺) = 394.9/396.9 [M+H]⁺

N[(3-Chlorophenyl)methyl]-3-[*N*-(4-fluoro-2-methoxyphenyl)formamido]-2-hydroxybutanamide (I-131)

[0245] The title compound was synthesized from *N*[(3-chlorophenyl)methyl]-3-[(4-fluoro-2-methoxyphenyl)amino]-2-hydroxybutanamide (I-66) in a similar manner to method A, general procedure 3 (general scheme 4) as a yellow viscous oil (340 mg, 96% purity, 85%) after purification by flash column chromatography on normal phase silica (25 g SNAP KP-SIL cartridge, 0-100% EtOAc in heptane gradient).

¹H NMR (500 MHz, DMSO-d₆) δ 0.86-1.22 (m, 3H), 3.76-3.82 (m, 3H), 3.97-4.12 (m, 1H), 4.24-4.72 (m, 3H), 6.00-6.24 (m, 1H), 6.76-6.84 (m, 1H), 6.89-6.99 (m, 1H), 7.18-7.58 (m, 5H), 8.00-8.39 (m, 1H), 8.45-8.66 (m, 1H).

LC-MS (METCR1410): 96% (UV), Rt= 1.04-1.20 min (two peaks), m/z (ESI⁺)= 395.1/397.1 [M+H]⁺

N[(3-Chlorophenyl)methyl]-2-hydroxy-3-[*N*-(2-methoxyphenyl)formamido]-3-methylbutanamide (I-132)

[0246] The title compound was synthesized from *N*[(3-chlorophenyl)methyl]-2-hydroxy-3-[(2-methoxyphenyl)amino]-3-methylbutanamide (I-62) in a similar manner to method A, general procedure 3 (general scheme 4) as a brown free-flowing oil (242 mg, 96% purity, quantitative) used in the next step without further purification.

LC-MS (METCR1410): 98% (UV), Rt= 1.20-1.30 min (multiple peaks), m/z (ESI⁺)= 391.0/393.0 [M+H]⁺

N[(3-Chlorophenyl)methyl]-2-hydroxy-3-[*N*-(2-methoxyphenyl)formamido]-3-phenylpropanamide (I-133)

[0247] The title compound was synthesized from *N*[(3-chlorophenyl)methyl]-2-hydroxy-3-[(2-methoxyphenyl)amino]-3-phenylpropanamide (I-63) in a similar manner to method A, general procedure 3 (general scheme 4) as a brown viscous oil (255 mg, 100% purity, quantitative) used in the next step without further purification.

¹H NMR (500 MHz, Chloroform-d) δ 3.86 (s, 3H), 4.21 (dd, *J* = 15.1, 5.5 Hz, 1H), 4.50 (dd, *J* = 15.1, 7.0 Hz, 1H), 5.01-5.05 (m, 1H), 5.29 (s, 1H), 6.61-6.67 (m, 1H), 6.83 (td, *J* = 7.6, 1.1 Hz, 1H), 6.91-6.95 (m, 2H), 6.97 (dd, *J* = 8.3, 0.9 Hz, 1H), 7.09-7.11 (m, 1H), 7.14-7.21 (m, 3H), 7.21-7.26 (m, 4H), 7.26-7.32 (m, 2H), 8.26 (s, 1H).

LC-MS (METCR1278): 100% (UV), Rt= 2.13 min, m/z (ESI⁺)= 439.0/441.0 [M+H]⁺

N[2-(3-Chlorophenyl)propan-2-yl]-2-hydroxy-3-[*N*-(2-methoxyphenyl)formamido]-butanamide (I-134)

[0248] The title compound was synthesized from *N*[2-(3-chlorophenyl)propan-2-yl]-2-hydroxy-3-[(2-methoxyphenyl)amino]butanamide (I-72) in a similar manner to method A, general procedure 3 (general scheme 4) as a yellow viscous oil (250 mg, 83% purity, 62%) after purification by flash column chromatography on normal phase silica (25 g SNAP KP-SIL cartridge, 0-100% EtOAc in heptane gradient).

LC-MS (METCR1410): 83% (UV), Rt= 1.07-1.30 min (multiple peaks), m/z (ESI⁺)= 405.1/407.0 [M+H]⁺

N[(3-Chlorophenyl)methyl]-2-hydroxy-3-[*N*-(2-methoxyphenyl)formamido]pentanamide (I-135)

[0249] The title compound was synthesized from *N*[(3-chlorophenyl)methyl]-2-hydroxy-3-[(2-methoxyphenyl)amino]pentanamide (I-79) in a similar manner to method A, general procedure 3 (general scheme 4) as a yellow viscous oil (150 mg, 85% purity by ¹H NMR, 62%) after purification by flash column chromatography on normal phase silica (10 g SNAP KP-SIL cartridge, 0-100% EtOAc in heptane gradient).

¹H NMR (250 MHz, DMSO-d₆) δ 0.67-1.08 (m, 4H), 1.38-1.58 (m, 1H), 3.58-3.73 (m, 1H), 3.74-3.81 (m, 3H), 4.15-4.45 (m, 3H), 5.81-6.34 (m, 1H), 6.89-7.04 (m, 1H), 7.08-7.52 (m, 7H), 7.98-8.36 (m, 1H), 8.41-8.69 (m, 1H).

LC-MS (METCR1410): 99% (UV), Rt= 1.05-1.25 min (multiple peaks), m/z (ESI⁺)= 391.0/393.0 [M+H]⁺

N[(3-Chlorophenyl)methyl]-2-hydroxy-3-[*N*-(2-methoxyphenyl)formamido]-5-methylhexanamide (I-136)

[0250] The title compound was synthesized from *N*[(3-chlorophenyl)methyl]-2-hydroxy-3-[(2-methoxyphenyl)amino]-5-methylhexanamide (I-64) in a similar manner to method A, general procedure 3 (general scheme 4) as a yellow viscous oil (140 mg, 87% purity, 48%) used in the next step without further purification.

LC-MS (METCR1410): 87% (UV), Rt= 1.08-1.30 min (multiple peaks), m/z (ESI⁺)= 419.1/421.1 [M+H]⁺

2-Hydroxy-3-[*N*-(2-methoxyphenyl)formamido]butanamide (I-137)

[0251] The title compound was synthesized from 2-hydroxy-3-[(2-methoxyphenyl)amino]butanamide (I-83) in a similar manner to method A, general procedure 3 (general scheme 4) as an orange oil (18 mg, 91% purity, 26%) after purification by flash column chromatography on normal phase silica (10 g SNAP KP-SIL cartridge, 0-100% EtOAc in heptane gradient).

¹H NMR (500 MHz, Chloroform-d) δ 1.37 (d, *J* = 7.2 Hz, 3H), 3.87 (s, 3H), 4.14 (q, *J* = 7.0 Hz, 1H), 4.69 (s, 1H), 5.45-5.63 (m, 1H), 6.95-7.05 (m, 3H), 7.14-7.18 (m, 1H), 7.32-7.38 (m, 1H), 8.08 (s, 1H).

LC-MS (METCR1410): 91% (UV), Rt= 0.60-0.85 min (broad peak), m/z (ESI⁺)= 253.0 [M+H]⁺

Method B: Direct addition of acetic anhydride followed by hydrolysis

3-(*N*-Cyclohexylformamido)-2-hydroxy-*N*-(2-methylpropyl)butanamide (I-138)

[0252] To a stirred suspension of 3-(cyclohexylamino)-2-hydroxy-*N*-(2-methylpropyl)-butanamide (I-94, 287 μ L, 1.09 mmol) in formic acid (292 μ L, 7.58 mmol) was added acetic anhydride (3 mL) dropwise and the reaction stirred at RT for 18 h. The mixture was quenched with saturated NaHCO₃ (4 mL) and the aqueous layer extracted with EtOAc (2 x 5 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated *in vacuo* to give a crude material which was purified by flash column chromatography on normal phase silica (10 g SNAP KP-SIL cartridge, 0-100% EtOAc in heptane gradient). The yellow oil obtained was dissolved in 1:1 MeOH/THF (4 mL) and 2M NaOH (2 mL) added. The reaction was stirred at RT for 2 h, THF and MeOH were removed *in vacuo* and the aqueous layer was extracted with EtOAc (3 x 5 mL). The combined organics were dried over sodium sulfate, filtered and concentrated *in vacuo* to afford 332 mg of 3-(*N*-cyclohexylformamido)-2-hydroxy-*N*-(2-methylpropyl)-butanamide as a clear oil (89% purity, 95%).

¹H NMR (500 MHz, Chloroform-*d*) δ 0.90-0.95 (m, 6H), 1.21-1.28 (m, 3H), 1.28-1.36 (m, 5H), 1.61-1.69 (m, 1H), 1.72-1.92 (m, 3H), 2.07-2.30 (m, 2H), 3.01-3.20 (m, 2H), 3.30-3.40 (m, 1H), 4.02 (q, *J* = 7.2 Hz, 1H), 4.22 (s, 1H), 6.56 (s, 1H), 7.05-7.17 (m, 1H), 8.08 (s, 1H).

LC-MS (METCR1410): 89% (UV), Rt= 0.95-1.15 (two peaks), m/z (ESI⁺)= 285.2 [M+H]⁺

3-[*N*-(Cyclopropylmethyl)formamido]-2-hydroxy-*N*-(2-methylpropyl)butanamide (I-139)

[0253] The title compound was synthesized from 3-[(cyclopropylmethyl)amino]-2-hydroxy-*N*-(2-methylpropyl)butanamide (I-95) in a similar manner to method B, general procedure 3 (general scheme 4) as a clear oil (300 mg, 80% purity by ¹H NMR, 74%) used in the next step without further purification.

¹H NMR (500 MHz, Chloroform-*d*) δ 0.23-0.32 (m, 2H), 0.60-0.70 (m, 2H), 0.93 (d, *J* = 6.7 Hz, 6H), 1.04-1.14 (m, 1H), 1.29 (d, *J* = 7.2 Hz, 3H), 1.75-1.86 (m, 1H), 3.03-3.09 (m, 1H), 3.11-3.21 (m, 3H), 3.97-4.06 (m, 1H), 4.38 (s, 1H), 7.12 (s, 1H), 8.00 (s, 1H).

LC-MS (METCR1410): 96% (UV), Rt= 0.90-1.01 min, m/z (ESI⁺)= 257.2 [M+H]⁺

N[(3-Chlorophenyl)methyl]-3-(*N*-cyclohexylformamido)-2-hydroxybutanamide (I-140)

[0254] The title compound was synthesized from *N*[(3-chlorophenyl)methyl]-3-(cyclohexylamino)-2-hydroxybutanamide (I-55) in a similar manner to method B, general procedure 3 (general scheme 4) as a colourless solid (97 mg, 75% purity, 63%) used in the next step without further purification.

LC-MS (METCR1410): 75% (UV), *R*_t= 1.14-1.36 min (multiple peaks), *m/z* (ESI⁺)= 353.0/355.0 [M+H]⁺

N[(3-Chlorophenyl)methyl]-3-[*N*-(cyclohexylmethyl)formamido]-2-hydroxybutanamide (I-141)

[0255] To ice cooled acetic anhydride (0.18 mL, 1.91 mmol) in a sealed tube was added at 0 °C formic acid (0.1 mL, 2.54 mmol). The reaction was stirred at 50 °C for 1 h and dry THF (2.5 mL) added at RT. The mixture was cooled in an ice bath and a solution of *N*[(3-chlorophenyl)methyl]-3-[(cyclohexylmethyl)amino]-2-hydroxybutanamide (I-67, 250 mg, 0.73 mmol) in dry THF (2.5 mL) added. The reaction was stirred at RT for 2 h, heated at 35 °C for 4 h and stirred at RT for 18 h. The mixture was partitioned between saturated NaHCO₃ (15 mL) and EtOAc (2 x 10 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated *in vacuo* to afford a colourless oil which was dissolved in 1:1 MeOH/THF (6 mL). 2N NaOH (2 mL) was added and the reaction was stirred at RT for 1 h. The mixture was partitioned between EtOAc (15 mL) and water (15 mL). The aqueous layer was extracted with EtOAc (2 x 10 mL) and the combined organic layers were dried over sodium sulfate, filtered and concentrated *in vacuo* to afford *N*[(3-chlorophenyl)methyl]-3-[*N*-(cyclohexylmethyl)formamido]-2-hydroxybutanamide as a colourless oil (133 mg, 80% purity by ¹H NMR, 40%).

¹H NMR (500 MHz, Chloroform-*d*) δ 0.80-1.01 (m, 2H), 1.10-1.34 (m, 6H), 1.63-1.80 (m, 6H), 3.01-3.18 (m, 2H), 3.86 (q, *J* = 7.0 Hz, 1H), 4.36 (s, 1H), 4.38-4.51 (m, 2H), 6.57 (s, 1H), 7.14-7.19 (m, 1H), 7.22-7.28 (m, 3H), 7.40-7.48 (m, 1H), 7.87-8.25 (m, 1H).

LC-MS (METCR1278): 95% (UV), *R*_t= 1.90-2.25 min (multiple peaks), *m/z* (ESI⁺)= 367.4/369.4 [M+H]⁺

N[(3-Chlorophenyl)methyl]-2-hydroxy-3-[*N*-(2-methoxyphenyl)formamido]propanamide (I-142)

[0256] The title compound was synthesized from *N*-[(3-chlorophenyl)methyl]-2-hydroxy-3-[(2-methoxyphenyl)amino]propanamide (I-70) in a similar manner to method B, general procedure 3 (general scheme 4) as a light yellow oil (239 mg, 80% purity by ¹H NMR, 57%) used in the next step without further purification.

¹H NMR (500 MHz, Chloroform-d) δ 3.78 (s, 3H), 3.95 (dd, *J* = 2.4, 14.6 Hz, 1H), 4.09 (dd, *J* = 7.9, 14.6 Hz, 1H), 4.28-4.32 (m, 1H), 4.32-4.37 (m, 2H), 4.37-4.41 (m, 1H), 5.29 (d, *J* = 3.6 Hz, 1H), 6.88-6.94 (m, 2H), 7.04-7.07 (m, 1H), 7.07-7.11 (m, 1H), 7.15-7.23 (m, 2H), 7.25-7.31 (m, 1H), 7.34-7.43 (m, 1H), 8.06-8.22 (m, 1H).

LC-MS (METCR1410): 80% (UV), *R*_t = 1.03 min, *m/z* (ESI⁺) = 363.0/365.0 [M+H]⁺

Method C: Pre-formation of mixed anhydride

3-(*N*-Benzylformamido)-*N*-[(3-chlorophenyl)methyl]-2-hydroxybutanamide (I-143)

[0257] To ice-cold acetic anhydride (129 μL, 1.37 mmol) was added dropwise at 0 °C formic acid (67 μL, 1.69 mmol). The mixture was heated at 50-60 °C for 2 h and cooled to RT. The solution was diluted with dry THF (4 mL) and cooled to 0 °C. A solution of 3-(benzylamino)-*N*-[(3-chlorophenyl)methyl]-2-hydroxybutanamide (I-59, 90% purity, 195 mg, 0.53 mmol) in dry THF (4 mL) was added and the reaction stirred at RT for 18 h. The mixture was concentrated *in vacuo* to afford 205 mg of 3-(*N*-benzylformamido)-*N*-[(3-chlorophenyl)methyl]-2-hydroxybutanamide as a yellow viscous oil (83% purity, 89%) used in the next step without further purification.

¹H NMR (500 MHz, Chloroform-d) δ 1.09 (d, *J* = 7.1 Hz, 3H), 3.93 (q, *J* = 7.1 Hz, 1H), 4.30 (s, 1H), 4.33-4.43 (m, 2H), 4.42-4.51 (m, 2H), 6.32 (s, 1H), 7.09-7.14 (m, 1H), 7.20-7.25 (m, 3H), 7.27-7.32 (m, 2H), 7.32-7.42 (m, 4H), 8.27 (s, 1H)

LC-MS (MET-μHPLC-AB-101): 83% (UV), *R*_t = 2.87 min, *m/z* (ESI⁺) = 361.1/363.1 [M+H]⁺

N-[(3-Chlorophenyl)methyl]-2-hydroxy-3-[*N*-(propan-2-yl)formamido]butanamide (I-144)

[0258] The title compound was synthesized from *N*-[(3-chlorophenyl)methyl]-2-hydroxy-3-[(propan-2-yl)amino]butanamide (I-60) in a similar manner to method C, general procedure 3 (general scheme 4) as a pink viscous oil (213 mg, 80% purity by ¹H NMR, 87%) used in the next step without further purification.

¹H NMR (500 MHz, Chloroform-d) δ 1.26 (d, *J* = 7.1 Hz, 3H), 1.30 (d, *J* = 6.8 Hz, 3H), 1.35 (d, *J* = 6.8 Hz, 3H), 3.87 (hept, *J* = 6.7 Hz, 1H), 4.03 (q, *J* = 7.1 Hz, 1H), 4.29 (s,

¹H), 4.39-4.50 (m, 2H), 6.60 (s, 1H), 7.14-7.18 (m, 1H), 7.23-7.28 (m, 3H), 7.39-7.51 (m, 1H), 8.08-8.11 (m, 1H).

LC-MS (METCR1410): 92% (UV), Rt= 0.95-1.10 min (multiple peaks), m/z (ESI⁺)= 313.0/315.0 [M+H]⁺

N[(3-Chlorophenyl)methyl]-2-hydroxy-3-[*N*-(oxan-4-yl)formamido]butanamide (I-145)

[0259] The title compound was synthesized from *N*[(3-chlorophenyl)methyl]-2-hydroxy-3-[(oxan-4-yl)amino]butanamide (I-61) in a similar manner to method C, general procedure 3 (general scheme 4) as a yellow viscous oil (180 mg, 62% purity, 88%) used in the next step without further purification.

LC-MS (METCR1410): 62% (UV), Rt= 1.03 min, m/z (ESI⁺)= 355.0/357.0 [M+H]⁺

N[(3-Chlorophenyl)methyl]-3-[*N*-(2,2-dimethylpropyl)formamido]-2-hydroxybutanamide (I-146)

[0260] The title compound was synthesized from *N*[(3-chlorophenyl)methyl]-3-[(2,2-dimethylpropyl)amino]-2-hydroxybutanamide (I-68) in a similar manner to method C, general procedure 3 (general scheme 4) as a yellow solid (220 mg, 85% purity by ¹H NMR, 67%) used in the next step without further purification.

¹H NMR (500 MHz, DMSO-d₆) δ 0.82-0.90 (m, 9H), 1.12-1.27 (m, 3H), 2.53-2.57 (m, 1H), 3.48-3.57 (m, 1H), 3.64 (qd, *J* = 3.0, 7.2 Hz, 1H), 4.03-4.12 (m, 1H), 4.21-4.36 (m, 2H), 6.17-6.29 (m, 1H), 7.20-7.24 (m, 1H), 7.27-7.37 (m, 3H), 7.88-8.33 (m, 1H), 8.46-8.67 (m, 1H).

LC-MS (METCR1410): 98% (UV), Rt= 1.04-1.02 min (multiple peaks), m/z (ESI⁺)= 341.0/343.0 [M+H]⁺

N[(3-Chlorophenyl)methyl]-2-hydroxy-3-{*N*[(oxan-4-yl)methyl]formamido}butanamide (I-147)

[0261] The title compound was synthesized from *N*[(3-chlorophenyl)methyl]-2-hydroxy-3-{[(oxan-4-yl)methyl]amino}butanamide (I-69) in a similar manner to method C, general procedure 3 (general scheme 4) as a colourless viscous oil (188 mg, 90% purity by ¹H NMR, 88%) used in the next step without further purification.

¹H NMR (500 MHz, Chloroform-d) δ 1.22-1.28 (m, 4H), 1.51-1.70 (m, 3H), 1.93 (dq, *J* = 3.7, 11.3 Hz, 1H), 3.16 (qd, *J* = 7.2, 14.2 Hz, 2H), 3.40 (td, *J* = 2.1, 11.9 Hz, 2H), 3.89 (q, *J* = 7.1 Hz, 1H), 4.00 (dd, *J* = 3.2, 11.5 Hz, 2H), 4.35 (s, 1H), 4.38-4.51 (m, 2H),

6.40-6.68 (m, 1H), 7.12-7.18 (m, 1H), 7.23-7.30 (m, 3H), 7.36-7.53 (m, 1H), 7.92-8.12 (m, 1H).

LC-MS (METCR1410): 98% (UV), Rt= 0.92-1.00 min (two peaks), m/z (ESI+)= 369.0/371.0 [M+H]⁺

N-(Cyclohexylmethyl)-2-hydroxy-3-[*N*-(2-methoxyphenyl)formamido]butanamide (I-148)

[0262] The title compound was synthesized from *N*-(cyclohexylmethyl)-2-hydroxy-3-[(2-methoxyphenyl)amino]butanamide (I-71) in a similar manner to method C, general procedure 3 (general scheme 4) as a colourless viscous oil (325 mg, 99% purity, 62%) used in the next step without further purification.

¹H NMR (250 MHz, Chloroform-d) δ 0.83-1.03 (m, 2H), 1.14-1.29 (m, 4H), 1.32 (d, *J* = 7.2 Hz, 3H), 1.38-1.54 (m, 1H), 1.55-1.63 (m, 2H), 1.74 (s, 2H), 3.12 (dh, *J* = 6.4, 19.6 Hz, 2H), 3.84-3.94 (m, 3H), 4.04-4.24 (m, 1H), 4.63-4.70 (m, 1H), 6.28 (s, 1H), 6.94-7.02 (m, 2H), 7.08-7.20 (m, 2H), 7.29-7.41 (m, 1H), 8.07 (s, 1H).

LC-MS (METCR1410): 99% (UV), Rt= 1.04-1.20 min (multiple peaks), m/z (ESI+)= 349.1 [M+H]⁺

N-[2-(3-Chlorophenyl)propan-2-yl]-2-hydroxy-3-[*N*-(propan-2-yl)formamido]butanamide (I-149)

[0263] The title compound was synthesized from *N*-[2-(3-chlorophenyl)propan-2-yl]-2-hydroxy-3-[(propan-2-yl)amino]butanamide (I-73) in a similar manner to method C, general procedure 3 (general scheme 4) as a colourless viscous oil (110 mg, 85% purity by ¹H NMR, 78%) used in the next step without further purification.

¹H NMR (500 MHz, Chloroform-d) δ 1.22-1.31 (m, 9H), 1.66-1.73 (m, 6H), 3.78-3.88 (m, 1H), 3.93 (q, *J* = 7.1 Hz, 1H), 4.15-4.16 (m, 1H), 6.53-6.74 (m, 1H), 7.18-7.22 (m, 1H), 7.23-7.27 (m, 2H), 7.30-7.36 (m, 1H), 7.39-7.47 (m, 1H), 8.06-8.20 (m, 1H).

LC-MS (METCR1410): 89% (UV), Rt= 1.04-1.20 min (multiple peaks), m/z (ESI+)= 341.0/343.0 [M+H]⁺

N-[2-(3-Chlorophenyl)propan-2-yl]-3-(*N*-cyclohexylformamido)-2-hydroxybutanamide (I-150)

[0264] The title compound was synthesized from *N*-[2-(3-chlorophenyl)propan-2-yl]-3-(cyclohexylamino)-2-hydroxybutanamide (I-74) in a similar manner to method C,

general procedure 3 (general scheme 4) as a colourless viscous oil (150 mg, 70% purity by ^1H NMR, 61%) used in the next step without further purification.

^1H NMR (500 MHz, Chloroform- d) δ 1.23-1.28 (m, 3H), 1.58-1.64 (m, 2H), 1.65-1.74 (m, 10H), 1.74-1.88 (m, 5H), 3.33 (tt, $J = 4.0, 11.9$ Hz, 1H), 3.93-3.98 (m, 1H), 4.14-4.16 (m, 1H), 6.74 (s, 1H), 7.16-7.21 (m, 1H), 7.23-7.25 (m, 1H), 7.33-7.37 (m, 1H), 7.41-7.47 (m, 1H), 8.06-8.24 (m, 1H).

LC-MS (METCR1410): 71% (UV), $R_t = 0.94$ min (broad peak), m/z (ESI $^+$) = 381.2/383.2 [M+H] $^+$

N-tert-Butyl-2-hydroxy-3-[*N*-(2-methoxyphenyl)formamido]butanamide (I-151)

[0265] The title compound was synthesized from *N*-tert-butyl-2-hydroxy-3-[(2-methoxyphenyl)amino]butanamide (I-75) in a similar manner to method C, general procedure 3 (general scheme 4) as a beige crystalline solid (117 mg, 98% purity by ^1H NMR, 58%) after purification by flash column chromatography on normal phase silica (10 g SNAP KP-SIL cartridge, 0-50% EtOAc in heptane gradient).

^1H NMR (250 MHz, Chloroform- d) δ 1.32 (d, $J = 7.2$ Hz, 3H), 1.36 (s, 9H), 3.84-3.93 (m, 3H), 4.04-4.19 (m, 1H), 4.48-4.61 (m, 1H), 6.21-6.36 (m, 1H), 6.89-7.01 (m, 3H), 7.13-7.20 (m, 1H), 7.28-7.38 (m, 1H), 8.03-8.46 (m, 1H).

2-Hydroxy-3-[*N*-(2-methoxyphenyl)formamido]-*N*-(propan-2-yl)butanamide (I-152)

[0266] The title compound was synthesized from 2-hydroxy-3-[(2-methoxyphenyl)amino]-*N*-(propan-2-yl)butanamide (I-76) in a similar manner to method C, general procedure 3 (general scheme 4) as a colourless viscous oil (217 mg, 88% purity, 82%) used in the next step without further purification.

^1H NMR (500 MHz, Chloroform- d) δ 1.12-1.21 (m, 6H), 1.31 (d, $J = 7.2$ Hz, 3H), 3.86-3.90 (m, 3H), 4.01-4.10 (m, 1H), 4.10-4.15 (m, 1H), 4.62 (s, 1H), 6.26 (s, 1H), 6.86-6.94 (m, 1H), 6.94-7.00 (m, 2H), 7.15 (dd, $J = 1.6, 7.6$ Hz, 1H), 7.31-7.38 (m, 1H), 8.03-9.12 (m, 1H).

LC-MS (METCR1278): 88% (UV), $R_t = 1.40$ -1.75 min (multiple peaks), m/z (ESI $^+$) = 295.0 [M+H] $^+$

3-[*N*-(2,2-Dimethylpropyl)formamido]-2-hydroxy-*N*-(propan-2-yl)butanamide (I-153)

[0267] The title compound was synthesized from 3-[(2,2-dimethylpropyl)amino]-2-hydroxy-*N*-(propan-2-yl)butanamide (I-77) in a similar manner to method C, general

procedure 3 (general scheme 4) as an off-white solid (217 mg, 79% purity, 93%) used in the next step without further purification.

¹H NMR (500 MHz, Chloroform-d) δ 0.89-1.01 (m, 9H), 1.15-1.18 (m, 6H), 1.19-1.29 (m, 3H), 2.98 (d, *J* = 14.5 Hz, 1H), 3.20 (d, *J* = 14.6 Hz, 1H), 3.89 (m, 1H), 4.02-4.11 (m, 1H), 4.21-4.39 (m, 1H), 6.59 (s, 1H), 6.79-6.94 (m, 1H), 7.92-8.34 (m, 1H).

LC-MS (METCR1278): 79% (UV), Rt= 1.50-1.80 min (multiple peaks), m/z (ESI⁺)= 259.1 [M+H]⁺

N[4-(7-Chloro-1,2,3,4-tetrahydroisoquinolin-2-yl)-3-hydroxy-4-oxobutan-2-yl]-*N*-(2-methoxyphenyl)formamide (I-154)

[0268] The title compound was synthesized from 1-(7-chloro-1,2,3,4-tetrahydroisoquinolin-2-yl)-2-hydroxy-3-[(2-methoxyphenyl)amino]butan-1-one (I-78) in a similar manner to method C, general procedure 3 (general scheme 4) as a red viscous oil (50 mg, 70% purity by ¹H NMR, 38%) after purification by flash column chromatography on normal phase silica (10 g SNAP KP-SIL cartridge, 0-50% EtOAc in heptane gradient).

¹H NMR (250 MHz, Chloroform-d) δ 0.80-0.88 (m, 3H), 2.81-2.96 (m, 1H), 3.01 (q, *J* = 5.5 Hz, 1H), 3.81 (d, *J* = 2.9 Hz, 3H), 3.83-4.33 (m, 4H), 4.75 (d, *J* = 4.4 Hz, 1H), 4.89-5.32 (m, 2H), 6.88-7.02 (m, 2H), 7.05-7.23 (m, 3H), 7.30-7.39 (m, 1H), 7.60 (d, *J* = 7.6 Hz, 1H), 8.01-8.13 (m, 1H).

LC-MS (METCR1278): 92% (UV), Rt= 1.90-2.10 min (multiple peaks), m/z (ESI⁺)= 403.0/405.0 [M+H]⁺

N-(Cyclopropylmethyl)-2-hydroxy-4-methyl-3-[*N*-(2-methylpropyl)-formamido]pentanamide (I-155)

[0269] The title compound was synthesized from *N*-(cyclopropylmethyl)-2-hydroxy-4-methyl-3-[(2-methylpropyl)amino]pentanamide (I-80) in a similar manner to method C, general procedure 3 (general scheme 4) as a colourless glass (95 mg, 80% purity by ¹H NMR, 42%) after purification by flash column chromatography on normal phase silica (10 g SNAP KP-SIL cartridge, 0-100% TBME in heptane gradient).

¹H NMR (500 MHz, Chloroform-d) δ 0.15-0.24 (m, 2H), 0.44-0.53 (m, 2H), 0.84-0.98 (m, 13H), 1.94-2.15 (m, 1H), 2.25-2.63 (m, 1H), 3.02-3.30 (m, 4H), 3.57 (d, *J* = 10.9 Hz, 1H), 4.21-4.25 (m, 1H), 6.02-6.27 (m, 1H), 6.59-7.13 (m, 1H), 7.96-8.35 (m, 1H).

LC-MS (METCR1410): 88% (UV), Rt= 1.18 min, m/z (ESI⁺)= 285.1 [M+H]⁺

N-(Cyclopropylmethyl)-3-[*N*-(2,2-dimethylpropyl)formamido]-2-hydroxy-4-methylpentanamide (I-156)

[0270] The title compound was synthesized from *N*-(cyclopropylmethyl)-3-[(2,2-dimethylpropyl)amino]-2-hydroxy-4-methylpentanamide (I-81) in a similar manner to method C, general procedure 3 (general scheme 4) as a colourless viscous oil (95 mg, 75% purity by ¹H NMR, 42%) after purification by flash column chromatography on normal phase silica (10 g SNAP KP-SIL cartridge, 0-100% TBME in heptane gradient). ¹H NMR (500 MHz, Chloroform-d) δ 0.17-0.20 (m, 2H), 0.46-0.50 (m, 2H), 0.86-0.94 (m, 6H), 0.97-0.98 (m, 10H), 2.46-2.55 (m, 1H), 2.94 (d, *J* = 14.5 Hz, 1H), 3.01-3.08 (m, 1H), 3.13-3.20 (m, 1H), 3.30-3.34 (m, 1H), 3.63-3.67 (m, 1H), 4.42-4.46 (m, 1H), 6.41 (s, 1H), 7.04-7.17 (m, 1H), 8.00-8.42 (m, 1H).

LC-MS (METCR1410): 88% (UV), *R*_t = 1.24 min, *m/z* (ESI⁺) = 299.0 [M+H]⁺

N-(Cyclopropylmethyl)-2-hydroxy-4-methyl-3-{*N*[(oxan-4-yl)methyl]formamido}pentanamide (I-157)

[0271] The title compound was synthesized from *N*-(cyclopropylmethyl)-2-hydroxy-4-methyl-3-{[(oxan-4-yl)methyl]amino}pentanamide (I-85) in a similar manner to method C, general procedure 3 (general scheme 4) as a colourless viscous oil (108 mg, 81% purity by ¹H NMR, 38%) after purification by flash column chromatography on normal phase silica (10 g SNAP KP-SIL cartridge, 0-100% TBME in heptane gradient).

¹H NMR (500 MHz, Chloroform-d) δ 0.15-0.25 (m, 2H), 0.43-0.55 (m, 2H), 0.84-0.98 (m, 7H), 1.13-1.42 (m, 2H), 1.51-1.69 (m, 1H), 1.81-2.09 (m, 2H), 2.22-2.62 (m, 1H), 3.00-3.27 (m, 3H), 3.28-3.45 (m, 3H), 3.56 (t, *J* = 10.5 Hz, 1H), 3.88-4.01 (m, 2H), 4.15-4.21 (m, 1H), 5.94-6.44 (m, 1H), 7.02-7.27 (m, 1H), 7.95-8.31 (m, 1H).

LC-MS (METCR1410): 26% (UV), *R*_t = 1.00 min, *m/z* (ESI⁺) = 327.1 [M+H]⁺

N[(3-Chlorophenyl)methyl]-2-hydroxy-3-[*N*-(2-methoxyphenyl)formamido]-4-methylpentanamide (I-158)

[0272] The title compound was synthesized from *N*[(3-chlorophenyl)methyl]-2-hydroxy-3-[(2-methoxyphenyl)amino]-4-methylpentanamide (I-82) in a similar manner to method C, general procedure 3 (general scheme 4) as a brown free-flowing oil (276 mg, 90% purity by ¹H NMR, 53%) after purification by flash column chromatography on normal phase silica (50 g SNAP Ultra cartridge, 10-73% EtOAc in heptane gradient).

¹H NMR (500 MHz, Chloroform-d) δ 0.84 (d, J = 6.7 Hz, 3H), 0.98 (d, J = 6.7 Hz, 3H), 2.64-2.76 (m, 1H), 3.86 (s, 3H), 3.97 (d, J = 10.5 Hz, 1H), 4.37-4.50 (m, 2H), 4.84 (s, 1H), 5.95 (s, 1H), 6.94-7.02 (m, 2H), 7.15-7.21 (m, 1H), 7.21-7.33 (m, 5H), 7.38 (t, J = 4.8 Hz, 1H), 8.20 (s, 1H).

LC-MS (METCR1410): 99% (UV), R_t = 1.08-1.28 min (multiple peaks), m/z (ESI⁺) = 405.1/407.1 [M+H]⁺

3-(*N*-Cyclohexylformamido)-2-hydroxy-*N*-(propan-2-yl)butanamide (I-159)

[0273] The title compound was synthesized from 3-(cyclohexylamino)-2-hydroxy-*N*-(propan-2-yl)butanamide (I-84) in a similar manner to method C, general procedure 3 (general scheme 4) as a brown free-flowing oil (303 mg, 85% purity by ¹H NMR, 73%) used in the next step without further purification.

¹H NMR (500 MHz, Chloroform-d) δ 1.16-1.19 (m, 6H), 1.22 (d, J = 7.2 Hz, 3H), 1.27-1.36 (m, 2H), 1.50-1.63 (m, 2H), 1.63-1.69 (m, 1H), 1.70-1.78 (m, 2H), 1.79-1.89 (m, 3H), 3.31-3.40 (m, 1H), 3.97-4.08 (m, 2H), 4.15-4.19 (m, 1H), 6.55 (s, 1H), 6.80-6.91 (m, 1H), 8.08 (s, 1H).

LC-MS (METCR1278): 100% (UV), R_t = 1.55-1.80 min (multiple peaks), m/z (ESI⁺) = 271.1 [M+H]⁺

3-(*N*-Benzylformamido)-*N*-(cyclopropylmethyl)-2-hydroxybutanamide (I-160)

[0274] The title compound was synthesized from 3-(benzylamino)-*N*-(cyclopropylmethyl)-2-hydroxybutanamide (I-86) in a similar manner to method C, general procedure 3 (general scheme 4) as an off-white solid (355 mg, 88% purity, 77%) used in the next step without further purification.

¹H NMR (500 MHz, Chloroform-d) δ 0.13-0.24 (m, 2H), 0.43-0.55 (m, 2H), 0.88-0.97 (m, 1H), 1.08 (d, J = 7.1 Hz, 3H), 3.02-3.15 (m, 2H), 3.90 (q, J = 7.1 Hz, 1H), 4.25 (s, 1H), 4.40-4.52 (m, 2H), 6.25 (s, 1H), 7.01-7.14 (m, 1H), 7.27-7.41 (m, 5H), 8.27 (s, 1H).

LC-MS (METCR1410): 88% (UV), R_t = 0.88-1.00 min (two peaks), m/z (ESI⁺) = 291.1 [M+H]⁺

3-[*N*-(Cyclohexylmethyl)formamido]-*N*-(cyclopropylmethyl)-2-hydroxybutanamide (I-161)

[0275] The title compound was synthesized from 3-[(cyclohexylmethyl)amino]-*N*-(cyclopropylmethyl)-2-hydroxybutanamide (I-87) in a similar manner to method C,

general procedure 3 (general scheme 4) as an off-white solid (298 mg, 92% purity, 88%) used in the next step without further purification.

¹H NMR (500 MHz, Chloroform-d) δ 0.15-0.28 (m, 2H), 0.45-0.58 (m, 2H), 0.80-0.92 (m, 2H), 0.92-1.01 (m, 1H), 1.10-1.32 (m, 6H), 1.60-1.78 (m, 6H), 3.01-3.20 (m, 4H), 3.84 (q, *J* = 7.1 Hz, 1H), 4.30 (s, 1H), 6.51 (s, 1H), 7.07-7.22 (m, 1H), 7.92 (s, 1H). LC-MS (METCR1410): 92% (UV), Rt= 0.96-1.12 min (multiple peaks), m/z (ESI⁺) = 297.1 [M+H]⁺

tert-Butyl 4-[(*N*{1-[(cyclopropylmethyl)carbamoyl]-1-hydroxypropan-2-yl}formamido)-methyl]piperidine-1-carboxylate (I-162)

[0276] The title compound was synthesized from *tert*-butyl 4-[(1-[(cyclopropylmethyl)carbamoyl]-1-hydroxypropan-2-yl]amino)methyl]piperidine-1-carboxylate (I-88) in a similar manner to method C, general procedure 3 (general scheme 4) as a yellow viscous oil (1.02 g, 86% purity, 95%) used in the next step without further purification. ¹H NMR (500 MHz, Chloroform-d) δ 0.15-0.24 (m, 2H), 0.47-0.55 (m, 2H), 0.88-1.00 (m, 1H), 1.01-1.16 (m, 2H), 1.22-1.25 (m, 3H), 1.41-1.47 (m, 9H), 1.54-1.73 (m, 2H), 1.79-1.89 (m, 1H), 2.61-2.76 (m, 2H), 3.06-3.21 (m, 4H), 3.86 (q, *J* = 7.1 Hz, 1H), 4.00-4.21 (m, 2H), 4.28 (s, 1H), 6.24-6.41 (m, 1H), 6.98-7.20 (m, 1H), 7.90-7.95 (m, 1H). LC-MS (METCR1410): 86% (UV), Rt= 0.98-1.08 min (multiple peaks), m/z (ESI⁺) = 420.2 [M+Na]⁺

3-(*N*-Cyclohexylformamido)-*N*-(cyclopropylmethyl)-2-hydroxybutanamide (I-163)

[0277] The title compound was synthesized from 3-(cyclohexylamino)-*N*-(cyclopropylmethyl)-2-hydroxybutanamide (I-89) in a similar manner to method C, general procedure 3 (general scheme 4) as a brown free-flowing oil (262 mg, 80% purity by ¹H NMR, 99%) used in the next step without further purification.

¹H NMR (500 MHz, Chloroform-d) δ 0.15-0.27 (m, 2H), 0.44-0.58 (m, 2H), 0.88-1.03 (m, 1H), 1.08-1.45 (m, 6H), 1.49-1.92 (m, 6H), 3.05-3.42 (m, 3H), 3.71-3.87 (m, 1H), 3.97-4.17 (m, 1H), 4.19-4.71 (m, 1H), 6.25-6.71 (m, 1H), 7.01-7.24 (m, 1H), 8.00-8.15 (m, 1H).

LC-MS (METCR1410): 96% (UV), Rt= 0.96-1.08 min (multiple peaks), m/z (ESI⁺) = 283.2 [M+H]⁺

N-(Cyclopropylmethyl)-3-[*N*-(2,2-dimethylpropyl)formamido]-2-hydroxybutanamide (I-164)

[0278] The title compound was synthesized from *N*-(cyclopropylmethyl)-3-[(2,2-dimethylpropyl)amino]-2-hydroxybutanamide (I-90) in a similar manner to method C, general procedure 3 (general scheme 4) as a brown free-flowing oil (203 mg, 95% purity by ¹H NMR, 91%) used in the next step without further purification.

¹H NMR (500 MHz, Chloroform-d) δ 0.14-0.28 (m, 2H), 0.43-0.59 (m, 2H), 0.89-1.05 (m, 10H), 1.23 (d, *J* = 7.1 Hz, 3H), 2.99 (d, *J* = 14.5 Hz, 1H), 3.11-3.16 (m, 2H), 3.20 (d, *J* = 14.6 Hz, 1H), 3.91 (q, *J* = 7.1 Hz, 1H), 4.42 (s, 1H), 6.47-6.70 (m, 1H), 7.07-7.22 (m, 1H), 7.96 (s, 1H).

LC-MS (METCR1410): 92% (UV), *R*_t = 0.92-1.08 min (two peaks), *m/z* (ESI⁺) = 271.2 [M+H]⁺

3-(*N*-Cyclohexylformamido)-*N*-cyclopropyl-2-hydroxybutanamide (I-165)

[0279] The title compound was synthesized from 3-(cyclohexylamino)-*N*-cyclopropyl-2-hydroxybutanamide (I-91) in a similar manner to method C, general procedure 3 (general scheme 4) as a colourless viscous oil (178 mg, 85% purity by ¹H NMR, 81%) used in the next step without further purification.

¹H NMR (500 MHz, Chloroform-d) δ 0.48-0.58 (m, 2H), 0.74-0.83 (m, 2H), 1.11-1.19 (m, 1H), 1.21 (d, *J* = 7.1 Hz, 3H), 1.28-1.36 (m, 2H), 1.51-1.57 (m, 1H), 1.63-1.70 (m, 1H), 1.72-1.78 (m, 2H), 1.79-1.89 (m, 3H), 2.69-2.77 (m, 1H), 3.30-3.40 (m, 1H), 4.02 (q, *J* = 7.3 Hz, 1H), 4.18 (s, 1H), 6.50 (s, 1H), 7.03 (br. s, 1H), 8.07 (s, 1H).

LC-MS (METCR1410): 81% (UV), *R*_t = 0.84-1.00 min (two peaks), *m/z* (ESI⁺) = 269.1 [M+H]⁺

3-[*N*-(Cyclohexylmethyl)formamido]-*N*-cyclopropyl-2-hydroxybutanamide (I-166)

[0280] The title compound was synthesized from 3-[(cyclohexylmethyl)amino]-*N*-cyclopropyl-2-hydroxybutanamide (I-92) in a similar manner to method C, general procedure 3 (general scheme 4) as a colourless viscous oil (195 mg, 90% purity by ¹H NMR, 89%) used in the next step without further purification.

¹H NMR (500 MHz, Chloroform-d) δ 0.48-0.57 (m, 2H), 0.76-0.81 (m, 2H), 0.83-0.93 (m, 2H), 1.13-1.31 (m, 7H), 1.63-1.78 (m, 5H), 2.70-2.77 (m, 1H), 3.01-3.07 (m, 1H), 3.09-3.14 (m, 1H), 3.83 (q, *J* = 7.1 Hz, 1H), 4.26 (s, 1H), 6.46 (s, 1H), 7.04 (br. s, 1H), 7.91 (s, 1H).

LC-MS (METCR1410): 60% (UV), *R*_t = 0.92-1.04 min (two peaks), *m/z* (ESI⁺) = 283.1 [M+H]⁺

3-(*N*-Benzylformamido)-*N*-cyclopropyl-2-hydroxybutanamide (I-167)

[0281] The title compound was synthesized from 3-(benzylamino)-*N*-cyclopropyl-2-hydroxybutanamide (I-93) in a similar manner to method C, general procedure 3 (general scheme 4) as a colourless viscous oil (192 mg, 93% purity, 93%) used in the next step without further purification.

¹H NMR (500 MHz, Chloroform-*d*) δ 0.40-0.56 (m, 2H), 0.68-0.81 (m, 2H), 0.99-1.47 (m, 4H), 2.61-2.74 (m, 1H), 3.84-4.51 (m, 4H), 6.78-7.07 (m, 1H), 7.21-7.41 (m, 5H), 8.23-8.39 (m, 1H).

LC-MS (METCR1410): 93% (UV), *R*_t= 0.80-0.96 min (multiple peaks), *m/z* (ESI⁺)= 277.1 [M+H]⁺

3-[*N*-(2,2-Dimethylpropyl)formamido]-2-hydroxy-*N*-(2-methylpropyl) butanamide (I-168)

[0282] The title compound was synthesized from 3-[(2,2-dimethylpropyl)amino]-2-hydroxy-*N*-(2-methylpropyl)butanamide (I-96) in a similar manner to method C, general procedure 3 (general scheme 4) as a yellow oil (242 mg, 35% purity by ¹H NMR, 43%) used in the next step without further purification.

¹H NMR (500 MHz, Chloroform-*d*) δ 0.87-0.93 (m, 6H), 0.99 (s, 9H), 1.22 (d, *J* = 7.1 Hz, 3H), 1.72-1.83 (m, 1H), 2.95-3.24 (m, 4H), 3.90 (q, *J* = 7.1 Hz, 1H), 4.43 (s, 1H), 6.57 (s, 1H), 7.12-7.21 (m, 1H), 7.96 (s, 1H).

2-Hydroxy-*N*-(2-methylpropyl)-3-[*N*-(2,2,2-trifluoroethyl)formamido]butanamide (I-169)

[0283] The title compound was synthesized from 2-hydroxy-*N*-(2-methylpropyl)-3-[(2,2,2-trifluoroethyl)amino]butanamide (I-97) in a similar manner to method C, general procedure 3 (general scheme 4) as a colourless solid (197 mg, 100% purity, 99%) used in the next step without further purification.

¹H NMR (500 MHz, Chloroform-*d*) δ 0.89-0.96 (m, 6H), 1.28-1.37 (m, 3H), 1.74-1.84 (m, 1H), 3.03-3.11 (m, 1H), 3.12-3.22 (m, 1H), 3.72-3.94 (m, 2H), 4.00-4.09 (m, 1H), 4.35 (s, 1H), 5.62 (d, *J* = 1.1 Hz, 1H), 6.80-7.07 (m, 1H), 8.08-8.46 (m, 1H).

LC-MS (METCR1410): 100% (UV), *R*_t= 0.93 min, *m/z* (ESI⁺)= 285.0 [M+H]⁺

3-(*N*-Benzylformamido)-2-hydroxy-*N*-(2-methylpropyl)butanamide (I-170)

[0284] The title compound was synthesized from 3-(benzylamino)-2-hydroxy-*N*-(2-methylpropyl)butanamide (I-98) in a similar manner to method C, general procedure 3 (general scheme 4) as a colourless viscous oil (159 mg, 90% purity by ¹H NMR, 98%) used in the next step without further purification.

¹H NMR (500 MHz, Chloroform-d) δ 0.85-0.93 (m, 6H), 1.05-1.22 (m, 3H), 1.69-1.79 (m, 1H), 2.94-3.03 (m, 1H), 3.07-3.17 (m, 1H), 3.86-4.52 (m, 4H), 5.83-6.39 (m, 1H), 6.80-7.11 (m, 1H), 7.27-7.30 (m, 2H), 7.31-7.41 (m, 3H), 8.24-8.42 (m, 1H).

LC-MS (METCR1410): 100% (UV), Rt= 0.92-1.04 min (multiple peaks), m/z (ESI⁺)= 293.5 [M+H]⁺

N-(Cyclohexylmethyl)-2-hydroxy-3-[*N*-(propan-2-yl)formamido]butanamide (I-171)

[0285] The title compound was synthesized from *N*-(cyclohexylmethyl)-2-hydroxy-3-[(propan-2-yl)amino]butanamide (I-99) in a similar manner to method C, general procedure 3 (general scheme 4) as a colourless viscous oil (400 mg, 50% purity by ¹H NMR, 43%) used in the next step without further purification.

¹H NMR (250 MHz, Chloroform-d) δ 0.79-1.02 (m, 2H), 1.03-1.57 (m, 14H), 1.58-1.79 (m, 4H), 2.92-3.23 (m, 3H), 3.64-4.05 (m, 2H), 4.21 (s, 1H), 6.92-7.23 (m, 1H), 8.04-8.13 (m, 1H).

LC-MS (METCR1410): 100% (UV), Rt= 0.96-1.12 min (multiple peaks), m/z (ESI⁺)= 285.2 [M+H]⁺

N-(Cyclohexylmethyl)-2-hydroxy-3-{*N*-[(oxan-4-yl)methyl]formamido}butanamide (I-172)

[0286] The title compound was synthesized from *N*-(cyclohexylmethyl)-2-hydroxy-3-[[[(oxan-4-yl)methyl]amino]butanamide (I-100) in a similar manner to method C, general procedure 3 (general scheme 4) as a colourless viscous oil (400 mg, 87% purity, 64%) used in the next step without further purification.

¹H NMR (500 MHz, Chloroform-d) δ 0.79-1.03 (m, 2H), 1.07-1.35 (m, 9H), 1.37-1.54 (m, 1H), 1.55-1.78 (m, 7H), 1.86-2.01 (m, 1H), 3.03-3.24 (m, 4H), 3.39 (td, *J* = 2.0, 11.8 Hz, 2H), 3.87 (q, *J* = 7.1 Hz, 1H), 3.99 (dd, *J* = 4.2, 11.5 Hz, 2H), 4.28 (s, 1H), 6.98-7.16 (m, 1H), 7.80-8.01 (m, 1H).

LC-MS (METCR1410): 87% (UV), Rt= 0.96-1.08 min (multiple peaks), m/z (ESI⁺)= 341.2 [M+H]⁺

N-(Cyclohexylmethyl)-2-hydroxy-3-[*N*-(2,2,2-trifluoroethyl)formamido]butanamide (I-173)

[0287] The title compound was synthesized from *N*-(cyclohexylmethyl)-2-hydroxy-3-[(2,2,2-trifluoroethyl)amino]butanamide (I-101) in a similar manner to method C,

general procedure 3 (general scheme 4) as a colourless viscous oil (250 mg, 67% purity, 68%) used in the next step without further purification.

LC-MS (METCR1410): 67% (UV), Rt= 1.02 min, m/z (ESI⁺)= 325.4 [M+H]⁺

N-(Cyclohexylmethyl)-3-[*N*-(cyclopropylmethyl)formamido]-2-hydroxybutanamide (I-174)

[0288] The title compound was synthesized from *N*-(cyclohexylmethyl)-3-[(cyclopropylmethyl)amino]-2-hydroxybutanamide (I-102) in a similar manner to method C, general procedure 3 (general scheme 4) as a colourless viscous oil (194 mg, 100% purity, 98%) used in the next step without further purification.

¹H NMR (250 MHz, Chloroform-d) δ 0.20-0.35 (m, 2H), 0.57-0.72 (m, 2H), 0.84-1.02 (m, 2H), 1.02-1.23 (m, 4H), 1.28 (d, *J* = 7.2 Hz, 3H), 1.38-1.55 (m, 1H), 1.65-1.79 (m, 5H), 3.04-3.23 (m, 4H), 4.01 (q, *J* = 7.2 Hz, 1H), 4.37 (s, 1H), 6.43 (s, 1H), 7.01-7.18 (m, 1H), 8.00 (s, 1H).

LC-MS (METCR1410): 100% (UV), Rt= 1.00-1.12 min (multiple peaks), m/z (ESI⁺)= 297.1 [M+H]⁺

3-(*N*-Cyclohexylformamido)-*N*-(cyclohexylmethyl)-2-hydroxybutanamide (I-175)

[0289] The title compound was synthesized from 3-(cyclohexylamino)-*N*-(cyclohexylmethyl)-2-hydroxybutanamide (I-103) in a similar manner to method C, general procedure 3 (general scheme 4) as a colourless viscous oil (194 mg, 82% purity by ¹H NMR, 82%) used in the next step without further purification.

¹H NMR (250 MHz, Chloroform-d) δ 0.81-1.03 (m, 2H), 1.08-1.43 (m, 9H), 1.44-1.95 (m, 13H), 2.98-3.23 (m, 2H), 3.27-3.43 (m, 1H), 4.02 (q, *J* = 7.1 Hz, 1H), 4.21 (s, 1H), 6.55(s, 1H), 6.95-7.18 (m, 1H), 8.04-8.25 (m, 1H).

LC-MS (METCR1410): 100% (UV), Rt= 1.04-1.24 min (multiple peaks), m/z (ESI⁺)= 325.2 [M+H]⁺

tert-Butyl 4-[(*N*-(1-[(cyclohexylmethyl)carbamoyl]-1-hydroxypropan-2-yl)formamido)-methyl]piperidine-1-carboxylate (I-176)

[0290] The title compound was synthesized from *tert*-butyl 4-[(1-[(cyclohexylmethyl)carbamoyl]-1-hydroxypropan-2-yl)amino)methyl]piperidine-1-carboxylate (I-104) in a similar manner to method C, general procedure 3 (general scheme 4) as a colourless viscous oil (250 mg, 90% purity by ¹H NMR, 35%) used in the next step without further purification.

¹H NMR (500 MHz, Chloroform-d) δ 0.79-0.92 (m, 2H), 0.95-1.11 (m, 3H), 1.12-1.20 (m, 5H), 1.34-1.44 (m, 11H), 1.56-1.68 (m, 7H), 1.73-1.82 (m, 1H), 2.62 (q, J = 11.6, 12.2 Hz, 2H), 2.96-3.16 (m, 4H), 4.00-4.12 (m, 3H), 7.00-7.05 (m, 1H), 7.84-7.88 (m, 1H).

LC-MS (METCR1410): 84% (UV), R_t = 1.10-1.24 min, m/z (ESI⁺) = 384.6 [M+H-^{*t*}Bu]⁺
tert-Butyl *N*-[(1*S*,4*S*)-4-(*N*-{1-[(cyclohexylmethyl)carbamoyl]-1-hydroxypropan-2-yl}formamido)cyclohexyl]carbamate (I-177)

[0291] The title compound was synthesized from *tert*-butyl *N*-[(1*S*,4*S*)-4-({1-[(cyclohexylmethyl)carbamoyl]-1-hydroxypropan-2-yl}amino)cyclohexyl]carbamate (I-105) in a similar manner to method C, general procedure 3 (general scheme 4) as an orange oil (593 mg, 79% purity by ¹H NMR, 80%) used in the next step without further purification.

¹H NMR (250 MHz, Chloroform-d) δ 0.85-1.02 (m, 2H), 1.14-1.29 (m, 5H), 1.45 (s, 9H), 1.56-1.80 (m, 11H), 1.83-2.01 (m, 5H), 3.06-3.18 (m, 2H), 3.29-3.46 (m, 1H), 3.73-3.93 (m, 1H), 3.93-4.07 (m, 1H), 4.21 (s, 1H), 4.93-5.12 (m, 1H), 6.53 (s, 1H), 7.06-7.22 (m, 1H).

LC-MS (METCR1410): 95% (UV), R_t = 1.14-1.28 min (multiple peaks), m/z (ESI⁺) = 384.3 [M+H-^{*t*}Bu]⁺

3-(*N*-Cyclohexylformamido)-*N*-[2-(cyclohexyloxy)ethyl]-2-hydroxybutanamide (I-178)

[0292] The title compound was synthesized from 3-(cyclohexylamino)-*N*-[2-(cyclohexyloxy)ethyl]-2-hydroxybutanamide (I-106) in a similar manner to method C, general procedure 3 (general scheme 4) as a colourless gum (240 mg, 90% purity by ¹H NMR, 81%) used in the next step without further purification.

¹H NMR (250 MHz, Chloroform-d) δ 0.99-1.47 (m, 12H), 1.50-1.94 (m, 13H), 3.14-3.32 (m, 1H), 3.32-3.60 (m, 5H), 3.93-4.18 (m, 1H), 7.32-7.42 (m, 1H), 8.02-8.30 (m, 1H).

LC-MS (METCR0990): 98% (UV), R_t = 1.56-1.80 min (multiple peaks), m/z (ESI⁺) = 355.3 [M+H]⁺

Methyl 2-[3-(*N*-benzylformamido)-2-hydroxybutanamido]acetate (I-179)

[0293] The title compound was synthesized from methyl 2-[3-(benzylamino)-2-hydroxybutanamido]acetate (I-107) in a similar manner to method C, general procedure 3 (general scheme 4) as a colourless viscous oil (417 mg, 77% purity, 85%) used in the next step without further purification.

LC-MS (METCR1410): 77% (UV), Rt= 0.85-0.89 min, m/z (ESI⁺)= 309.1 [M+H]⁺

3-(*N*-Benzylformamido)-2-hydroxy-*N*-(propan-2-yl)butanamide (I-180)

[0294] The title compound was synthesized from 3-(benzylamino)-2-hydroxy-*N*-(propan-2-yl)butanamide (I-108) in a similar manner to method C, general procedure 3 (general scheme 4) as an off-white solid (125 mg, 99% purity, 81%) used in the next step without further purification.

¹H NMR (250 MHz, Chloroform-*d*) δ 1.06 (d, *J* = 7.1 Hz, 3H), 1.09-1.17 (m, 6H), 3.83-4.09 (m, 2H), 4.20 (s, 1H), 4.36-4.54 (m, 2H), 6.23 (s, 1H), 6.72-6.88 (m, 1H), 7.27-7.43 (m, 5H), 8.24-8.43 (m, 1H).

LC-MS (METCR1410): 99% (UV), Rt= 0.88-1.00 min (multiple peaks), m/z (ESI⁺)= 279.1 [M+H]⁺

N-(Cyclopropylmethyl)-2-hydroxy-3-{*N*-[(oxan-4-yl)methyl]formamido}hexanamide (I-181)

[0295] The title compound was synthesized from *N*-(cyclopropylmethyl)-2-hydroxy-3-{[(oxan-4-yl)methyl]amino}hexanamide (I-109) in a similar manner to method C, general procedure 3 (general scheme 4) as a colourless viscous oil (400 mg, 87% purity by ¹H NMR, 92%) used in the next step without further purification.

¹H NMR (500 MHz, Chloroform-*d*) δ 0.18-0.26 (m, 2H), 0.48-0.55 (m, 2H), 0.88-1.00 (m, 4H), 1.16-1.39 (m, 4H), 1.41-1.65 (m, 4H), 1.74-1.90 (m, 1H), 1.91-2.01 (m, 1H), 2.84-3.24 (m, 4H), 3.28-3.51 (m, 3H), 3.69-3.82 (m, 1H), 3.92-4.01 (m, 2H), 7.13 (s, 1H), 7.93-8.26 (m, 1H).

LC-MS (METCR1410): 86% (UV), Rt= 0.84-1.00 min (multiple peaks), m/z (ESI⁺)= 327.2 [M+H]⁺

tert-Butyl 4-[(*N*-{1-[(cyclohexylmethyl)carbamoyl]-1-hydroxybutan-2-yl}formamido)-methyl]piperidine-1-carboxylate (I-182)

[0296] The title compound was synthesized from *tert*-butyl 4-[(1-[(cyclohexylmethyl)carbamoyl]-1-hydroxybutan-2-yl)amino)methyl]piperidine-1-carboxylate (I-110) in a similar manner to method C, general procedure 3 (general scheme 4) as a yellow viscous oil (580 mg, 97% purity, 88%) used in the next step without further purification.

¹H NMR (500 MHz, Chloroform-*d*) δ 0.82-1.28 (m, 10H), 1.37-1.50 (m, 10H), 1.51-1.80 (m, 8H), 1.79-1.96 (m, 1H), 1.94-2.08 (m, 1H), 2.52-2.94 (m, 2H), 3.01-3.26 (m, 4H),

3.41-3.78 (m, 1H), 3.99-4.21 (m, 2H), 4.19-4.28 (m, 1H), 6.11-7.14 (m, 1H), 7.85-8.25 (m, 1H).

LC-MS (METCR1410): 97% (UV), Rt= 1.20-1.29 min (multiple peaks), m/z (ESI⁺)= 398.2 [M+H-^tBu]⁺

3-(*N*-cyclohexylformamido)-*N*-(cyclohexylmethyl)-2-hydroxypentanamide (I-183)

[0297] The title compound was synthesized from 3-(cyclohexylamino)-*N*-(cyclohexylmethyl)-2-hydroxypentanamide (I-111) in a similar manner to method C, general procedure 3 (general scheme 4) as a yellow viscous oil (460 mg, 88% purity, 98%) used in the next step without further purification.

¹H NMR (500 MHz, Chloroform-*d*) δ 0.75-1.03 (m, 4H), 1.06-1.55 (m, 11H), 1.54-1.99 (m, 13H), 3.01-3.35 (m, 2H), 3.71-3.92 (m, 1H), 4.18-4.33 (m, 1H), 6.12-7.13 (m, 1H), 8.05-8.26 (m, 1H).

LC-MS (METCR1410): 88% (UV), Rt= 1.13-1.24 min (multiple peaks), m/z (ESI⁺)= 339.2 [M+H]⁺

tert-Butyl 3-[(*N*-(1-[(cyclohexylmethyl)carbamoyl]-1-hydroxybutan-2-yl)formamido)-methyl]azetidine-1-carboxylate (I-184)

[0298] The title compound was synthesized from *tert*-butyl 3-[(1-[(cyclohexylmethyl)carbamoyl]-1-hydroxybutan-2-yl)amino)methyl]azetidine-1-carboxylate (I-112) in a similar manner to method C, general procedure 3 (general scheme 4) as an orange gum (475 mg, 60% purity, 53%) used in the next step without further purification.

¹H NMR (250 MHz, Chloroform-*d*) δ 0.75-1.07 (m, 6H), 1.05-1.35 (m, 5H), 1.43 (d, *J* = 2.8 Hz, 11H), 1.61-1.81 (m, 6H), 2.91-3.21 (m, 1H), 3.30-3.81 (m, 4H), 3.78-4.42 (m, 4H), 6.47-7.09 (m, 1H), 8.00-8.29 (m, 1H).

LC-MS (METCR1410): 60% (UV), Rt= 1.11 min, m/z (ESI⁺)= 426.3 [M+H]⁺

N-(Cyclopropylmethyl)-3-[*N*-(cyclopropylmethyl)formamido]-2-hydroxy-5-methylhexanamide (I-185)

[0299] The title compound was synthesized from *N*-(cyclopropylmethyl)-3-[(cyclopropylmethyl)amino]-2-hydroxy-5-methylhexanamide (I-113) in a similar manner to method C, general procedure 3 (general scheme 4) as a colourless viscous oil (252 mg, 96% purity, 91%) used in the next step without further purification.

¹H NMR (500 MHz, Chloroform-*d*) δ 0.21 (dq, *J* = 4.7, 10.7 Hz, 3H), 0.26-0.41 (m, 1H), 0.44-0.76 (m, 4H), 0.82-1.03 (m, 7H), 1.02-1.20 (m, 1H), 1.31-1.44 (m, 1H), 1.46-1.68

(m, 1H), 1.78-2.01 (m, 1H), 2.95-3.45 (m, 4H), 4.00 (td, $J = 3.9, 10.3, 10.7$ Hz, 1H), 4.28-4.48 (m, 1H), 6.98-7.18 (m, 1H), 7.96-8.33 (m, 1H).

LC-MS (METCR1410): 96% (UV), $R_t = 1.00-1.12$ min (multiple peaks), m/z (ESI⁺) = 297.6 [M+H]⁺

N-(Cyclopropylmethyl)-2-hydroxy-5-methyl-3-{*N*-[(oxan-4-yl)methyl]formamido}hexanamide (I-186)

[0300] The title compound was synthesized from *N*-(cyclopropylmethyl)-2-hydroxy-5-methyl-3-{[(oxan-4-yl)methyl]amino}hexanamide (I-114) in a similar manner to method C, general procedure 3 (general scheme 4) as a colourless viscous oil (400 mg, 77% purity, quantitative) used in the next step without further purification.

LC-MS (METCR1410): 76% (UV), $R_t = 0.96-1.04$ min (multiple peaks), m/z (ESI⁺) = 341.2 [M+H]⁺

N-(Cyclopropylmethyl)-2-hydroxy-5-methyl-3-(*N*-{[(3*S*)-oxolan-3-yl]methyl}formamido)-hexanamide (I-187)

[0301] The title compound was synthesized from *N*-(cyclopropylmethyl)-2-hydroxy-5-methyl-3-({[(3*S*)-oxolan-3-yl]methyl}amino)hexanamide (I-115) in a similar manner to method C, general procedure 3 (general scheme 4) as a colourless viscous oil (310 mg, 80% purity by ¹H NMR, 80%) used in the next step without further purification.

¹H NMR (250 MHz, Chloroform-*d*) δ 0.13-0.29 (m, 2H), 0.43-0.58 (m, 2H), 0.81-1.01 (m, 7H), 1.35-1.62 (m, 2H), 1.76-1.94 (m, 1H), 1.97-2.23 (m, 1H), 2.65-2.95 (m, 1H), 3.02-3.98 (m, 10H), 4.18-4.29 (m, 1H), 6.06 (d, $J = 3.0$ Hz, 1H), 7.03-7.18 (m, 1H), 7.99-8.26 (m, 1H).

LC-MS (METCR0990): 96% (UV), $R_t = 1.35-1.55$ min (multiple peaks), m/z (ESI⁺) = 327.0 [M+H]⁺

N-(Cyclopropylmethyl)-2-hydroxy-5-methyl-3-(*N*-{[(3*R*)-oxolan-3-yl]methyl}formamido)-hexanamide (I-188)

[0302] The title compound was synthesized from *N*-(cyclopropylmethyl)-2-hydroxy-5-methyl-3-({[(3*R*)-oxolan-3-yl]methyl}amino)hexanamide (I-116) in a similar manner to method C, general procedure 3 (general scheme 4) as a colourless viscous oil (277 mg, 80% purity by ¹H NMR, 72%) used in the next step without further purification.

¹H NMR (250 MHz, Chloroform-*d*) δ 0.14-0.27 (m, 2H), 0.43-0.57 (m, 2H), 0.79-1.03 (m, 7H), 1.35-1.61 (m, 2H), 1.75-1.95 (m, 1H), 1.96-2.18 (m, 1H), 2.60-2.85 (m, 1H),

3.01-3.99 (m, 10H), 4.17-4.29 (m, 1H), 6.07 (d, $J = 2.9$ Hz, 1H), 7.02-7.17 (m, 1H), 8.02-8.25 (m, 1H).

LC-MS (METCR0990): 96% (UV), $R_t = 1.35$ -1.55 min (multiple peaks), m/z (ESI⁺) = 327.0 [M+H]⁺

N-(Cyclopropylmethyl)-2-hydroxy-3-[*N*-(3-methoxypropyl)formamido]-5-methylhexanamide (I-189)

[0303] The title compound was synthesized from *N*-(cyclopropylmethyl)-2-hydroxy-3-[(3-methoxypropyl)amino]-5-methylhexanamide (I-117) in a similar manner to method C, general procedure 3 (general scheme 4) as a colourless viscous oil (269 mg, 85% purity by ¹H NMR, 100%) used in the next step without further purification.

¹H NMR (500 MHz, Chloroform-*d*) δ 0.16-0.28 (m, 2H), 0.45-0.56 (m, 2H), 0.85-0.92 (m, 6H), 0.92-1.10 (m, 1H), 1.33-1.59 (m, 2H), 1.73-1.99 (m, 3H), 2.01-2.10 (m, 1H), 3.07-3.20 (m, 2H), 3.21-3.45 (m, 6H), 3.49-3.91 (m, 2H), 4.24-4.34 (m, 1H), 7.01-7.18 (m, 1H), 8.01-8.26 (m, 1H).

LC-MS (METCR1410): 96% (UV), $R_t = 0.90$ -1.10 min (multiple peaks), m/z (ESI⁺) = 315.2 [M+H]⁺

N-(Cyclopropylmethyl)-2-hydroxy-5-methyl-3-{*N*-[(oxolan-3-yl)methyl]formamido}-hexanamide (I-190)

[0304] The title compound was synthesized from *N*-(cyclopropylmethyl)-2-hydroxy-5-methyl-3-{[(oxolan-3-yl)methyl]amino}hexanamide (I-118) in a similar manner to method C, general procedure 3 (general scheme 4) as a colourless viscous oil (237 mg, 98% purity by ¹H NMR, quantitative) used in the next step without further purification.

¹H NMR (500 MHz, Chloroform-*d*) δ 0.17-0.27 (m, 2H), 0.46-0.57 (m, 2H), 0.86-0.93 (m, 6H), 0.93-1.01 (m, 1H), 1.37-1.46 (m, 1H), 1.47-1.58 (m, 1H), 1.82-1.92 (m, 1H), 2.00-2.19 (m, 1H), 2.66-2.84 (m, 1H), 3.07-3.86 (m, 8H), 3.87-3.96 (m, 2H), 4.18-4.29 (m, 1H), 6.07 (d, $J = 6.0$ Hz, 1H), 7.03-7.14 (m, 1H), 8.04 (s, 1H).

LC-MS (METCR1410): 100% (UV), $R_t = 0.90$ -1.10 min (two peaks), m/z (ESI⁺) = 327.2 [M+H]⁺

N-(Cyclopropylmethyl)-2-hydroxy-5-methyl-3-{*N*-[(oxolan-2-yl)methyl]formamido}-hexanamide (I-191)

[0305] The title compound was synthesized from *N*-(cyclopropylmethyl)-2-hydroxy-5-methyl-3-[[{(oxolan-2-yl)methyl]amino}hexanamide (I-119) in a similar manner to method C, general procedure 3 (general scheme 4) as a pale yellow solid (176 mg, 99% purity, 93%) used in the next step without further purification.

¹H NMR (500 MHz, Chloroform-d) δ 0.14-0.26 (m, 2H), 0.44-0.56 (m, 2H), 0.80-1.02 (m, 7H), 1.07-1.57 (m, 4H), 1.61-2.31 (m, 4H), 2.89-3.46 (m, 3H), 3.53-4.42 (m, 5H), 5.42-6.19 (m, 1H), 7.10-7.26 (m, 1H), 8.01-8.30 (m, 1H).

LC-MS (METCR1410): 99% (UV), Rt= 0.92-1.08 min (multiple peaks), m/z (ESI⁺)= 327.2 [M+H]⁺

3-Cyclopropyl-*N*-(cyclopropylmethyl)-2-hydroxy-3-{*N*-[(oxan-4-yl)methyl]formamido}-propanamide (I-192)

[0306] The title compound was synthesized from 3-cyclopropyl-*N*-(cyclopropylmethyl)-2-hydroxy-3-[[{(oxan-4-yl)methyl]amino}propanamide (I-120) in a similar manner to method C, general procedure 3 (general scheme 4) as a colourless viscous oil (321 mg, 95% purity by ¹H NMR, 72%) used in the next step without further purification.

¹H NMR (500 MHz, Chloroform-d) δ 0.18-0.34 (m, 4H), 0.46-0.63 (m, 4H), 0.93-1.04 (m, 1H), 1.15-1.32 (m, 2H), 1.57-1.63 (m, 2H), 1.64-1.72 (m, 1H), 1.85-1.99 (m, 1H), 3.01-3.26 (m, 5H), 3.38 (tdd, *J* = 2.0, 5.33, 11.6 Hz, 2H), 3.98 (dd, *J* = 3.7, 11.6 Hz, 2H), 4.23-4.27 (m, 1H), 6.30-6.40 (m, 1H), 7.18-7.23 (m, 1H), 7.94-8.53 (m, 1H).

LC-MS (METCR1410): 97% (UV), Rt= 0.84-0.92 min (two peaks), m/z (ESI⁺)= 325.5 [M+H]⁺

3-(*N*-Benzylformamido)-3-cyclopropyl-*N*-(cyclopropylmethyl)-2-hydroxypropanamide (I-193)

[0307] The title compound was synthesized from 3-(benzylamino)-3-cyclopropyl-*N*-(cyclopropylmethyl)-2-hydroxypropanamide (I-121) in a similar manner to method C, general procedure 3 (general scheme 4) as a colourless viscous oil (273 mg, 95% purity by ¹H NMR, 89%) used in the next step without further purification.

¹H NMR (500 MHz, Chloroform-d) δ -0.43-0.14 (m, 1H), 0.08-0.15 (m, 1H), 0.17-0.34 (m, 3H), 0.40-0.54 (m, 3H), 0.86-1.00 (m, 1H), 1.61-1.66 (m, 1H), 2.93-3.09 (m, 2H), 3.10-3.20 (m, 1H), 4.23 (m, 1H), 4.39-5.14 (m, 2H), 6.12-6.19 (m, 1H), 6.87-7.18 (m, 1H), 7.25-7.40 (m, 5H), 8.29-8.54 (m, 1H).

LC-MS (METCR1410): 99% (UV), Rt= 0.96-1.08 min (multiple peaks), m/z (ESI⁺)= 317.5 [M+H]⁺

N-(Cyclopropylmethyl)-2-hydroxy-3-{*N*-[(oxan-4-yl)methyl]formamido}-5-phenylpentanamide (I-194)

[0308] The title compound was synthesized from *N*-(cyclopropylmethyl)-2-hydroxy-3-[[oxan-4-yl)methyl]amino]-5-phenylpentanamide (I-124) in a similar manner to method C, general procedure 3 (general scheme 4) as a yellow viscous oil (310 mg, 95% purity by ¹H NMR, quantitative) used in the next step without further purification.

¹H NMR (500 MHz, Chloroform-d) δ 0.18-0.25 (m, 2H), 0.43-0.57 (m, 2H), 0.91-1.01 (m, 1H), 1.18-1.24 (m, 1H), 1.46-1.65 (m, 3H), 1.81-1.94 (m, 1H), 1.99-2.08 (m, 1H), 2.13-2.27 (m, 1H), 2.49-2.69 (m, 2H), 2.87-3.23 (m, 4H), 3.26-3.43 (m, 2H), 3.78-4.00 (m, 3H), 4.25-4.32 (m, 1H), 6.24 (m, 1H), 7.05-7.18 (m, 3H), 7.18-7.22 (m, 1H), 7.26-7.31 (m, 2H), 7.97-8.34 (m, 1H).

LC-MS (METCR1410): 99% (UV), Rt= 0.96-1.12 min (multiple peaks), m/z (ESI⁺)= 389.3 [M+H]⁺

N-[(3-Chlorophenyl)methyl]-2-hydroxy-3-(*N*-methylformamido)butanamide (I-195)

[0309] The title compound was synthesized from *N*-[(3-chlorophenyl)methyl]-2-hydroxy-3-(methylamino)butanamide (I-125) in a similar manner to method C, general procedure 3 (general scheme 4) as a colourless viscous oil (296 mg, 95% purity by ¹H NMR, 93%) used in the next step without further purification.

¹H NMR (500 MHz, Chloroform-d) δ 1.22-1.32 (m, 3H), 2.88-3.07 (m, 3H), 3.98 (m, 1H), 4.37-4.51 (m, 3H), 6.12 (s, 1H), 7.10-7.19 (m, 1H), 7.21-7.30 (m, 3H), 7.36-7.49 (m, 1H), 7.98-8.19 (m, 1H).

LC-MS (METCR1278): 100% (UV), Rt= 1.50-1.70 min (multiple peaks), m/z (ESI⁺)= 285.0/287.0 [M+H]⁺

3-(*N*-Benzylformamido)-*N*-(cyclopropylmethyl)-2-hydroxy-5-methoxypentanamide (I-196)

[0310] The title compound was synthesized from 3-(benzylamino)-*N*-(cyclopropylmethyl)-2-hydroxy-5-methoxypentanamide (I-122) in a similar manner to method C, general procedure 3 (general scheme 4) as a yellow viscous oil (153 mg) used in the next step without further purification.

3-(*N*-Benzylformamido)-*N*-(cyclopropylmethyl)-2-hydroxy-3-(oxan-4-yl)propanamide (I-197)

[0311] The title compound was synthesized from 3-(benzylamino)-*N*-(cyclopropylmethyl)-2-hydroxy-3-(oxan-4-yl)propanamide (I-123) in a similar manner to method C, general procedure 3 (general scheme 4) as a colourless viscous oil (101 mg) used in the next step without further purification.

GENERAL PROCEDURE 4 (GENERAL SCHEME 4): Oxidation

Method A: Dess-Martin Oxidation

N-[(3-Chlorophenyl)methyl]-3-[*N*-(2-methoxyphenyl)formamido]-2-oxobutanamide (FP 1)

[0312] To a stirred solution of *N*-[(3-chlorophenyl)methyl]-2-hydroxy-3-[*N*-(2-methoxyphenyl)formamido]butanamide (I-126, 75% purity, 60 mg, 0.12 mmol) in DCM (1 mL) was added DMP (76 mg, 0.18 mmol). The reaction was stirred at RT for 1 h. The solution was washed with saturated NaHCO₃ (3 mL) and the aqueous layer extracted with DCM (2 x 5 mL). The combined organic layer was dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude material was purified by preparative LC (acidic pH, standard elution method) to afford 11 mg of *N*-[(3-chlorophenyl)methyl]-3-[*N*-(2-methoxyphenyl)formamido]-2-oxobutanamide as a yellow viscous oil (100% purity, 25%).

¹H NMR (500 MHz, Chloroform-*d*) δ 1.31-1.51 (m, 3H), 3.59-3.89 (m, 3H), 4.42-4.57 (m, 2H), 4.98-5.49 (m, 1H), 6.95-7.06 (m, 2H), 7.11-7.18 (m, 1H), 7.19 (dt, *J* = 2.0, 6.6 Hz, 1H), 7.22-7.33 (m, 3H), 7.36 (ddd, *J* = 1.7, 7.6, 8.2 Hz, 1H), 7.56 (dd, *J* = 1.7, 7.8 Hz, 1H), 7.97-8.65 (m, 1H).

LC-MS (METCR1416): 100% (UV), *R*_t = 4.17 min, *m/z* (ESI⁺) = 375.0/377.0 [M+H]⁺
(3*R*)-*N*-[(3-chlorophenyl)methyl]-3-[*N*-(2-methoxyphenyl)formamido]-2-oxobutanamide and (3*S*)-*N*-[(3-chlorophenyl)methyl]-3-[*N*-(2-methoxyphenyl)formamido]-2-oxobutanamide (FP 2-3) ((*R*) and (*S*) assignments arbitrary)

[0313] *N*-[(3-Chlorophenyl)methyl]-3-[*N*-(2-methoxyphenyl)formamido]-2-oxobutanamide (FP 1, 96% purity, 140 mg, 0.36 mmol) was purified by chiral separation on SFC [Column: YMC Amylose-C (20 mm x 250 mm, 5 μm) at 40 °C; Isocratic eluent: 30:70 MeOH/CO₂; Flow rate: 50 mL/min; Detector wavelength; 210 nm; Dilution solvent: MeOH; Injection volume: 500 μL]. The samples were redissolved in DCM (2 mL) and

transferred to barcoded vials. The solvent was removed under a stream of air and the residues dried *in vacuo* at 40 °C to afford 32 mg of Enantiomer 1 (FP 2) as a yellow viscous oil (74% ee, 17%) and 30 mg of Enantiomer 2 (FP 3) as a yellow viscous oil (73% ee, 15%).

Enantiomer 1 (FP 2)

¹H NMR (500 MHz, Chloroform-d) δ 1.36 (d, *J* = 7.0 Hz, 3H), 3.83 (s, 3H), 4.43-4.56 (m, 2H), 5.05 (q, *J* = 7.0 Hz, 1H), 6.98 (dd, *J* = 8.3, 1.1 Hz, 1H), 7.02 (td, *J* = 7.6, 1.2 Hz, 1H), 7.12-7.17 (m, 1H), 7.17-7.22 (m, 1H), 7.24-7.28 (m, 2H), 7.28-7.32 (m, 1H), 7.34-7.39 (m, 1H), 7.56 (dd, *J* = 7.8, 1.7 Hz, 1H), 8.02 (s, 1H).

LC-MS (MET-uPLC-AB-101): 95% (UV), *R*_t = 3.41 min, *m/z* (ESI⁺) = 375.0/377.0 [M+H]⁺

LC-MS (CAM-F1): 86% (UV), *R*_t = 5.02 min, 74% ee

Enantiomer 2 (FP 3)

¹H NMR (500 MHz, Chloroform-d) δ 1.36 (d, *J* = 7.0 Hz, 3H), 3.83 (s, 3H), 4.44-4.56 (m, 2H), 5.05 (q, *J* = 7.0 Hz, 1H), 6.98 (dd, *J* = 8.3, 1.1 Hz, 1H), 7.02 (td, *J* = 7.6, 1.2 Hz, 1H), 7.11-7.17 (m, 1H), 7.17-7.21 (m, 1H), 7.24-7.28 (m, 2H), 7.28-7.31 (m, 1H), 7.34-7.38 (m, 1H), 7.56 (dd, *J* = 7.7, 1.7 Hz, 1H), 8.02 (s, 1H).

LC-MS (MET-uPLC-AB-101): 94% (UV), *R*_t = 3.41 min, *m/z* (ESI⁺) = 375.1/377.0 [M+H]⁺

LC-MS (CAM-F1): 84% (UV), *R*_t = 6.66 min, 73% ee

N[(3-Chlorophenyl)methyl]-3-[*N*-(3-methoxyphenyl)formamido]-2-oxo butanamide (FP 4)

[0314] The title compound was synthesized from *N*[(3-chlorophenyl)methyl]-2-hydroxy-3-[*N*-(3-methoxyphenyl)formamido]butanamide (I-127) in a similar manner to method A, general procedure 4 (general scheme 4) as a colourless viscous oil (90 mg, 96% purity, 33%) after purification by flash column chromatography on normal phase silica (10 g SNAP KP-SIL cartridge, 0-50% EtOAc in heptane gradient).

¹H NMR (500 MHz, Chloroform-d) δ 1.47 (d, *J* = 6.9 Hz, 3H), 3.84 (s, 3H), 4.42-4.54 (m, 2H), 4.94 (q, *J* = 6.9 Hz, 1H), 6.90-6.93 (m, 1H), 6.96-7.00 (m, 2H), 7.06-7.13 (m, 1H), 7.16-7.20 (m, 1H), 7.24-7.26 (m, 1H), 7.26-7.28 (m, 1H), 7.28-7.30 (m, 1H), 7.31-7.37 (m, 1H), 8.19 (s, 1H).

LC-MS (MET-uPLC-AB-101): 96% (UV), *R*_t = 3.43 min, *m/z* (ESI⁺) = 375.0/377.0 [M+H]⁺

N[(3-Chlorophenyl)methyl]-3-[*N*-(4-methoxyphenyl)formamido]-2-oxobutanamide (FP 5)

[0315] The title compound was synthesized from *N*-[(3-chlorophenyl)methyl]-2-hydroxy-3-[*N*-(4-methoxyphenyl)formamido]butanamide (I-128) in a similar manner to method A, general procedure 4 (general scheme 4) as a yellow viscous oil (156 mg, 99% purity, 58%) after purification by flash column chromatography on normal phase silica (10 g SNAP KP-SIL cartridge, 0-40% EtOAc in heptane gradient).

¹H NMR (500 MHz, Chloroform-d) δ 1.43 (d, J = 6.9 Hz, 3H), 3.83 (s, 3H), 4.43-4.55 (m, 2H), 4.91 (q, J = 6.9 Hz, 1H), 6.92-6.97 (m, 2H), 7.08-7.15 (m, 1H), 7.16-7.20 (m, 1H), 7.24-7.28 (m, 2H), 7.28-7.30 (m, 1H), 7.32-7.38 (m, 2H), 8.11 (s, 1H).

LC-MS (MET-uPLC-AB-101): 99% (UV), R_t = 3.39 min, m/z (ESI⁺) = 375.0/377.0 [M+H]⁺
N-[(3-Chlorophenyl)methyl]-2-oxo-3-(*N*-phenylformamido)butanamide (FP 6)

[0316] The title compound was synthesized from *N*-[(3-chlorophenyl)methyl]-2-hydroxy-3-(*N*-phenylformamido)butanamide (I-129) in a similar manner to method A, general procedure 4 (general scheme 4) as a yellow viscous oil (83 mg, 95% purity, 36%) after purification by flash column chromatography on normal phase silica (10 g SNAP KP-SIL cartridge, 0-40% EtOAc in heptane gradient).

¹H NMR (500 MHz, Chloroform-d) δ 1.47 (d, J = 6.9 Hz, 3H), 4.42-4.55 (m, 2H), 4.94 (q, J = 6.9 Hz, 1H), 7.08-7.15 (m, 1H), 7.16-7.20 (m, 1H), 7.24-7.28 (m, 2H), 7.28-7.30 (m, 1H), 7.36-7.40 (m, 1H), 7.40-7.48 (m, 4H), 8.18 (s, 1H).

LC-MS (MET-uPLC-AB-101): 95% (UV), R_t = 3.37 min, m/z (ESI⁺) = 345.0/347.0 [M+H]⁺
N-[(3-Chlorophenyl)methyl]-3-[*N*-(5-fluoro-2-methoxyphenyl)formamido]-2-oxobutanamide (FP 7)

[0317] The title compound was synthesized from *N*-[(3-chlorophenyl)methyl]-3-[*N*-(5-fluoro-2-methoxyphenyl)formamido]-2-hydroxybutanamide (I-130) in a similar manner to method A, general procedure 4 (general scheme 4) as a yellow viscous oil (87 mg, 95% purity, 38%) after purification by flash column chromatography on normal phase silica (10 g SNAP KP-SIL cartridge, 0-40% EtOAc in heptane gradient).

¹H NMR (500 MHz, Chloroform-d) δ 1.34-1.53 (m, 3H), 3.59-3.83 (m, 3H), 4.41-4.57 (m, 2H), 4.97-5.45 (m, 1H), 6.84-6.94 (m, 1H), 6.99-7.10 (m, 1H), 7.10-7.16 (m, 1H), 7.16-7.21 (m, 1H), 7.25-7.28 (m, 2H), 7.29-7.31 (m, 1H), 7.41 (dd, J = 3.1, 8.5 Hz, 1H), 8.00-8.59 (m, 1H).

LC-MS (MET-uPLC-AB-101): 95% (UV), R_t = 3.49 min, m/z (ESI⁺) = 393.0/395.0 [M+H]⁺

N[(3-Chlorophenyl)methyl]-3-[*N*-(4-fluoro-2-methoxyphenyl)formamido]-2-oxobutanamide (FP 8)

[0318] The title compound was synthesized from *N*[(3-chlorophenyl)methyl]-3-[*N*-(4-fluoro-2-methoxyphenyl)formamido]-2-hydroxybutanamide (I-131) in a similar manner to method A, general procedure 4 (general scheme 4) as an off-white powder (100 mg, 99% purity, 30%) after purification by flash column chromatography on normal phase silica (10 g SNAP KP-SIL cartridge, 0-100% EtOAc in heptane gradient) followed by trituration in heptane.

¹H NMR (500 MHz, Chloroform-*d*) δ 1.36-1.50 (m, 3H), 3.46-3.88 (m, 3H), 4.41-4.56 (m, 2H), 4.96-5.59 (m, 1H), 6.66-6.80 (m, 2H), 7.10-7.19 (m, 2H), 7.25-7.28 (m, 2H), 7.28-7.30 (m, 1H), 7.57 (t, *J* = 8.8 Hz, 1H), 8.00-8.58 (m, 1H).

LC-MS (MET-uPLC-AB-101): 99% (UV), *R*_t = 3.53 min, *m/z* (ESI⁺) = 393.0/395.1 [M+H]⁺
N[(3-Chlorophenyl)methyl]-3-[*N*-(2-methoxyphenyl)formamido]-3-methyl-2-oxobutanamide (FP 9)

[0319] The title compound was synthesized from *N*[(3-chlorophenyl)methyl]-2-hydroxy-3-[*N*-(2-methoxyphenyl)formamido]-3-methylbutanamide (I-132) in a similar manner to method A, general procedure 4 (general scheme 4) as a brown solid (45 mg, 99% purity, 19%) after purification by flash column chromatography on normal phase silica (10 g SNAP KP-SIL cartridge, 0-40% EtOAc in heptane gradient).

¹H NMR (500 MHz, Chloroform-*d*) δ 1.32 (s, 3H), 1.67 (s, 3H), 3.85 (s, 3H), 4.48 (d, *J* = 6.3 Hz, 2H), 6.99 (dd, *J* = 8.3, 1.1 Hz, 1H), 7.00-7.05 (m, 1H), 7.10-7.18 (m, 1H), 7.18-7.21 (m, 1H), 7.23-7.29 (m, 2H), 7.30-7.33 (m, 1H), 7.36-7.41 (m, 1H), 7.71 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.93 (s, 1H).

LC-MS (MET-uPLC-AB-101): 99% (UV), *R*_t = 3.79 min, *m/z* (ESI⁺) = 389.1/391.0 [M+H]⁺
N[(3-Chlorophenyl)methyl]-3-[*N*-(2-methoxyphenyl)formamido]-2-oxo-3-phenylpropanamide (FP 10)

[0320] The title compound was synthesized from *N*[(3-chlorophenyl)methyl]-2-hydroxy-3-[*N*-(2-methoxyphenyl)formamido]-3-phenylpropanamide (I-133) in a similar manner to method A, general procedure 4 (general scheme 4) as a brown glass (124 mg, 98% purity, 50%) after purification by flash column chromatography on normal phase silica (10 g SNAP KP-SIL cartridge, 0-40% EtOAc in heptane gradient).

¹H NMR (500 MHz, Chloroform-d) δ 3.54 (s, 3H), 4.40-4.52 (m, 2H), 6.48-6.54 (m, 1H), 6.67 (dd, J = 8.3, 1.0 Hz, 1H), 6.90 (td, J = 7.6, 1.2 Hz, 1H), 7.13-7.23 (m, 8H), 7.23-7.26 (m, 3H), 7.46 (dd, J = 7.8, 1.7 Hz, 1H), 8.14-8.43 (m, 1H).

LC-MS (MET-uPLC-AB-101): 98% (UV), R_t = 3.75 min, m/z (ESI⁺) = 437.0/439.0 [M+H]⁺
N-[2-(3-Chlorophenyl)propan-2-yl]-3-[*N*-(2-methoxyphenyl)formamido]-2-oxobutanamide (FP 11)

[0321] The title compound was synthesized from *N*-[2-(3-chlorophenyl)propan-2-yl]-2-hydroxy-3-[*N*-(2-methoxyphenyl)formamido]butanamide (I-134) in a similar manner to method A, general procedure 4 (general scheme 4) as an off-white powder (70 mg, 97% purity, 34%) after purification by flash column chromatography on normal phase silica (10 g SNAP KP-SIL cartridge, 0-100% EtOAc in heptane gradient) followed by trituration in heptane.

¹H NMR (500 MHz, Chloroform-d) δ 1.31-1.49 (m, 3H), 1.70 (s, 3H), 1.74 (s, 3H), 3.70-3.88 (m, 3H), 4.78-5.39 (m, 1H), 6.93-6.98 (m, 2H), 7.05 (s, 1H), 7.18-7.22 (m, 1H), 7.23-7.27 (m, 1H), 7.27-7.34 (m, 2H), 7.37-7.43 (m, 2H), 7.99-8.56 (m, 1H).

LC-MS (MET-uPLC-AB-101): 97% (UV), R_t = 3.77 min, m/z (ESI⁺) = 403.1/405.1 [M+H]⁺
N-[(3-Chlorophenyl)methyl]-3-[*N*-(2-methoxyphenyl)formamido]-2-oxopentanamide (FP 12)

[0322] The title compound was synthesized from *N*-[(3-chlorophenyl)methyl]-2-hydroxy-3-[*N*-(2-methoxyphenyl)formamido]pentanamide (I-135) in a similar manner to method A, general procedure 4 (general scheme 4) as a yellow viscous oil (53 mg, 96% purity, 42%) after purification by flash column chromatography on normal phase silica (10 g SNAP KP-SIL cartridge, 0-40% EtOAc in heptane gradient).

¹H NMR (500 MHz, Chloroform-d) δ 0.89-1.13 (m, 3H), 1.70-1.81 (m, 1H), 1.90-2.01 (m, 1H), 3.56-3.82 (m, 3H), 4.46-4.54 (m, 2H), 4.98 (t, J = 6.7 Hz, 1H), 6.88-6.99 (m, 1H), 7.00-7.06 (m, 1H), 7.13-7.22 (m, 2H), 7.23-7.31 (m, 3H), 7.31-7.37 (m, 1H), 7.58 (dd, J = 1.7, 7.8 Hz, 1H), 8.04-8.63 (m, 1H).

LC-MS (MET-uPLC-AB-101): 96% (UV), R_t = 3.54 min, m/z (ESI⁺) = 389.1/391.1 [M+H]⁺
N-[(3-Chlorophenyl)methyl]-3-[*N*-(2-methoxyphenyl)formamido]-5-methyl-2-oxohexanamide (FP 13)

[0323] The title compound was synthesized from *N*-[(3-chlorophenyl)methyl]-2-hydroxy-3-[*N*-(2-methoxyphenyl)formamido]-5-methylhexanamide (I-136) in a similar

manner to method A, general procedure 4 (general scheme 4) as an off-white powder (39 mg, 97% purity, 28%) after purification by flash column chromatography on normal phase silica (10 g SNAP KP-SIL cartridge, 0-40% EtOAc in heptane gradient) followed by trituration in heptane.

¹H NMR (500 MHz, Chloroform-d) δ 0.73-1.02 (m, 6H), 1.46-1.64 (m, 2H), 1.80-1.96 (m, 1H), 3.52-3.84 (m, 3H), 4.44-4.57 (m, 2H), 5.16-5.39 (m, 1H), 6.87-6.99 (m, 1H), 6.99-7.06 (m, 1H), 7.11-7.23 (m, 2H), 7.23-7.32 (m, 3H), 7.31-7.38 (m, 1H), 7.54 (dd, $J = 1.6, 7.8$ Hz, 1H), 8.04-8.65 (m, 1H).

LC-MS (MET-uPLC-AB-101): 97% (UV), $R_t = 3.93$ min, m/z (ESI⁺) = 417.1/419.1 [M+H]⁺
3-[*N*-(2-Methoxyphenyl)formamido]-2-oxobutanamide (FP 14)

[0324] The title compound was synthesized from 2-hydroxy-3-[*N*-(2-methoxyphenyl)formamido]butanamide (I-137) in a similar manner to method A, general procedure 4 (general scheme 4) as a yellow oil (5 mg, 98% purity, 26%) after purification by flash column chromatography on normal phase silica (10 g SNAP KP-SIL cartridge, 0-100% EtOAc in heptane gradient).

¹H NMR (500 MHz, Chloroform-d) δ 1.31-1.48 (m, 3H), 3.67-3.86 (m, 3H), 5.02-5.44 (m, 1H), 5.44-5.68 (m, 1H), 6.54-6.86 (m, 1H), 6.96-7.00 (m, 1H), 7.02 (td, $J = 1.3, 7.6$ Hz, 1H), 7.29-7.39 (m, 1H), 7.53 (dd, $J = 1.7, 7.7$ Hz, 1H), 8.00-8.63 (m, 1H).

LC-MS (MET-uPLC-AB-101): 98% (UV), $R_t = 1.94$ min, m/z (ESI⁺) = 251.2 [M+H]⁺
3-(*N*-Cyclohexylformamido)-*N*-(2-methylpropyl)-2-oxobutanamide (FP 15)

[0325] The title compound was synthesized from 3-(*N*-cyclohexylformamido)-2-hydroxy-*N*-(2-methylpropyl)butanamide (I-138) in a similar manner to method A, general procedure 4 (general scheme 4) as a colourless oil (72 mg, 96% purity, 29%) after purification by flash column chromatography on normal phase silica (25 g SNAP KP-SIL cartridge, 0-100% EtOAc in heptane gradient) followed by preparative LC (acidic pH, standard elution method).

¹H NMR (500 MHz, Chloroform-d) δ 0.85-0.98 (m, 6H), 1.08-1.21 (m, 1H), 1.22-1.40 (m, 2H), 1.44-1.84 (m, 7H), 1.84-1.94 (m, 2H), 2.02-2.12 (m, 2H), 3.03-3.24 (m, 2H), 3.31-4.18 (m, 1H), 4.23-5.20 (m, 1H), 6.59-7.00 (m, 1H), 8.02-8.26 (m, 1H).

LC-MS (MET-uPLC-AB-101): 96% (UV), $R_t = 3.09$ min, m/z (ESI⁺) = 283.2 [M+H]⁺
3-[*N*-(cyclopropylmethyl)formamido]-*N*-(2-methylpropyl)-2-oxobutanamide (FP 16)

[0326] The title compound was synthesized from 3-[*N*-(cyclopropylmethyl)formamido]-2-hydroxy-*N*-(2-methylpropyl)butanamide (I-139) in a similar manner to method A, general procedure 4 (general scheme 4) as a yellow oil (27 mg, 94% purity, 9%) after purification by flash column chromatography on normal phase silica (10 g SNAP KP-SIL cartridge, 0-100% EtOAc in heptane gradient) followed by preparative LC (acidic pH, standard elution method).

¹H NMR (500 MHz, Chloroform-*d*) δ 0.17-0.36 (m, 2H), 0.39-0.74 (m, 2H), 0.82-1.14 (m, 7H), 1.45-1.57 (m, 3H), 1.74-1.88 (m, 1H), 3.03-3.36 (m, 4H), 4.36-5.23 (m, 1H), 6.64-6.99 (m, 1H), 7.94-8.31 (m, 1H).

LC-MS (MET-uPLC-AB-101): 94% (UV), *R*_t= 2.5 min, *m/z* (ESI⁺)= 255.2 [M+H]⁺

N[(3-Chlorophenyl)methyl]-3-(*N*-cyclohexylformamido)-2-oxobutanamide (FP 17)

[0327] The title compound was synthesized from *N*[(3-chlorophenyl)methyl]-3-(*N*-cyclohexylformamido)-2-hydroxybutanamide (I-140) in a similar manner to method A, general procedure 4 (general scheme 4) as a colourless viscous oil (16 mg, 94% purity, 21%) after purification by flash column chromatography on normal phase silica (10 g SNAP KP-SIL cartridge, 0-50% EtOAc in heptane gradient) followed by preparative LC (acidic pH, standard elution method).

¹H NMR (500 MHz, Chloroform-*d*) δ 1.07-1.21 (m, 1H), 1.28-1.39 (m, 2H), 1.43-1.66 (m, 5H), 1.66-1.73 (m, 1H), 1.78-1.93 (m, 2H), 2.01-2.11 (m, 2H), 3.30-4.15 (m, 1H), 4.21-5.21 (m, 1H), 4.36-4.54 (m, 2H), 6.89-7.02 (m, 1H), 7.12-7.17 (m, 1H), 7.21-7.31 (m, 3H), 8.01-8.27 (m, 1H).

LC-MS (MET-uPLC-AB-101): 94% (UV), *R*_t= 3.56 min, *m/z* (ESI⁺)= 351.1/353.0 [M+H]⁺

N[(3-Chlorophenyl)methyl]-3-[*N*-(cyclohexylmethyl)formamido]-2-oxobutanamide (FP 18)

[0328] The title compound was synthesized from *N*[(3-chlorophenyl)methyl]-3-[*N*-(cyclohexylmethyl)formamido]-2-hydroxybutanamide (I-141) in a similar manner to method A, general procedure 4 (general scheme 4) as a colourless viscous oil (34 mg, 96% purity, 26%) after purification by flash column chromatography on normal phase silica (10 g SNAP KP-SIL cartridge, 0-40% EtOAc in heptane gradient) followed by preparative LC (acidic pH, standard elution method).

¹H NMR (500 MHz, Chloroform-*d*) δ 0.82-0.96 (m, 2H), 1.10-1.36 (m, 3H), 1.44-1.56 (m, 3H), 1.61-1.82 (m, 6H), 2.96-3.18 (m, 1H), 3.25-3.36 (m, 1H), 4.22-5.11 (m, 1H),

4.38-4.49 (m, 2H), 6.96-7.05 (m, 1H), 7.12-7.17 (m, 1H), 7.23-7.30 (m, 3H), 7.83-8.30 (m, 1H).

LC-MS (MET-uPLC-AB-101): 96% (UV), Rt= 3.89 min, m/z (ESI⁺)= 365.1/367.1 [M+H]⁺
N[(3-Chlorophenyl)methyl]-3-[*N*-(2-methoxyphenyl)formamido]-2-oxopropanamide (FP 19)

[0329] The title compound was synthesized from *N*[(3-chlorophenyl)methyl]-2-hydroxy-3-[*N*-(2-methoxyphenyl)formamido]propanamide (I-142) in a similar manner to method A, general procedure 4 (general scheme 4) as a yellow viscous oil (107 mg, 93% purity by ¹H NMR, 52%) after purification by flash column chromatography on normal phase silica (25 g SNAP Ultra cartridge, 10-100% EtOAc in heptane gradient) followed by preparative LC (acidic pH, standard elution method).

¹H NMR (500 MHz, Chloroform-*d*) δ 3.78-3.88 (m, 3H), 4.45 (d, *J* = 6.3 Hz, 2H), 4.99-5.13 (m, 2H), 6.92-7.02 (m, 2H), 7.11-7.23 (m, 2H), 7.26-7.30 (m, 4H), 7.30-7.36 (m, 1H), 8.22-8.34 (m, 1H)

LC-MS (METCR1600): 92% (UV), Rt= 4.58 min, m/z (ESI⁺)= 361.1/363.1 [M+H]⁺
3-(*N*-Benzylformamido)-*N*[(3-chlorophenyl)methyl]-2-oxobutanamide (FP 20)

[0330] The title compound was synthesized from 3-(*N*-benzylformamido)-*N*[(3-chlorophenyl)methyl]-2-hydroxybutanamide (I-143) in a similar manner to method A, general procedure 4 (general scheme 4) as a yellow viscous oil (88 mg, 100% purity, 53%) after purification by flash column chromatography on normal phase silica (10 g SNAP KP-SIL cartridge, 0-45% EtOAc in heptane gradient) then on reverse phase silica (12 g SNAP Ultra C18 cartridge, acidic pH, standard elution method).

¹H NMR (500 MHz, Chloroform-*d*) δ 1.13-1.48 (m, 3H), 4.16-5.19 (m, 5H), 6.62-7.06 (m, 1H), 7.12-7.31 (m, 6H), 7.32-7.43 (m, 3H), 8.14-8.48 (m, 1H).

LC-MS (METCR1600): 100% (UV), Rt= 4.20-5.00 min (two peaks), m/z (ESI⁺)= 359.1/361.1 [M+H]⁺

N[(3-Chlorophenyl)methyl]-2-oxo-3-[*N*-(propan-2-yl)formamido]butanamide (FP 21)

[0331] The title compound was synthesized from *N*[(3-chlorophenyl)methyl]-2-hydroxy-3-[*N*-(propan-2-yl)formamido]butanamide (I-144) in a similar manner to method A, general procedure 4 (general scheme 4) as a yellow viscous oil (87 mg, 100% purity, 52%) after purification by flash column chromatography on normal phase silica (10 g SNAP KP-SIL cartridge, 0-45% EtOAc in heptane gradient).

¹H NMR (500 MHz, Chloroform-d) δ 1.00-1.45 (m, 6H), 1.45-1.60 (m, 3H), 3.84 (hept, J = 6.8 Hz, 1H), 4.19-5.19 (m, 3H), 6.91-7.04 (m, 1H), 7.12-7.19 (m, 1H), 7.21-7.32 (m, 3H), 8.02-8.26 (m, 1H).

LC-MS (METCR1600): 100% (UV), R_t = 4.38 min, m/z (ESI⁺) = 311.1/313.2 [M+H]⁺
N[(3-Chlorophenyl)methyl]-3-[*N*(oxan-4-yl)formamido]-2-oxobutanamide (FP 22)

[0332] The title compound was synthesized from *N*[(3-chlorophenyl)methyl]-2-hydroxy-3-[*N*(oxan-4-yl)formamido]butanamide (I-145) in a similar manner to method A, general procedure 4 (general scheme 4) as an off-white powder (20 mg, 90% purity, 11%) after purification by flash column chromatography on normal phase silica (10 g SNAP KP-SIL cartridge, 0-100% EtOAc in heptane gradient) followed by preparative LC (neutral pH, standard elution method) and trituration in heptane.

¹H NMR (500 MHz, Chloroform-d) δ 1.45-1.64 (m, 3H), 1.86-2.10 (m, 4H), 3.37-3.50 (m, 2H), 3.59-3.69 (m, 1H), 3.93-4.14 (m, 2H), 4.20-5.19 (m, 1H), 4.37-4.53 (m, 2H), 6.93-7.03 (m, 1H), 7.11-7.18 (m, 1H), 7.20-7.32 (m, 3H), 8.05-8.26 (m, 1H).

LC-MS (MET-uPLC-AB-101): 90% (UV), R_t = 2.58 min, m/z ((ESI⁺) = 353.1/355.1 [M+H]⁺

N[(3-Chlorophenyl)methyl]-3-[*N*(2,2-dimethylpropyl)formamido]-2-oxobutanamide (FP 23)

[0333] The title compound was synthesized from *N*[(3-chlorophenyl)methyl]-3-[*N*(2,2-dimethylpropyl)formamido]-2-hydroxybutanamide (I-146) in a similar manner to method A, general procedure 4 (general scheme 4) as a colourless viscous oil (64 mg, 98% purity, 29%) after purification by flash column chromatography on normal phase silica (10 g SNAP KP-SIL cartridge, 0-40% EtOAc in heptane gradient) followed by preparative LC (acidic pH, standard elution method).

¹H NMR (500 MHz, DMSO-d₆) δ 0.83-0.97 (m, 9H), 1.31-1.61 (m, 3H), 2.81-3.16 (m, 1H), 3.18-3.33 (m, 1H), 4.22-4.89 (m, 3H), 7.18-7.25 (m, 1H), 7.27-7.39 (m, 3H), 7.90-8.20 (m, 1H), 9.00-9.44 (m, 1H).

LC-MS (MET-uPLC-AB-101): 98% (UV), R_t = 3.56 min, m/z (ESI⁺) = 339.2/341.2 [M+H]⁺
N[(3-Chlorophenyl)methyl]-3-{*N*[(oxan-4-yl)methyl]formamido}-2-oxobutanamide (FP 24)

[0334] The title compound was synthesized from *N*[(3-chlorophenyl)methyl]-2-hydroxy-3-{*N*[(oxan-4-yl)methyl]formamido}butanamide (I-147) in a similar manner to

method A, general procedure 4 (general scheme 4) as a yellow viscous oil (75 mg, 96% purity, 39%) after purification by flash column chromatography on normal phase silica (10 g SNAP KP-SIL cartridge, 0-40% EtOAc in heptane gradient).

¹H NMR (500 MHz, Chloroform-d) δ 1.19-1.32 (m, 2H), 1.44-1.57 (m, 3H), 1.63-1.71 (m, 2H), 1.77-2.02 (m, 1H), 3.04-3.23 (m, 1H), 3.25-3.44 (m, 3H), 3.90-4.04 (m, 2H), 4.25-5.14 (m, 1H), 4.38-4.49 (m, 2H), 6.98-7.08 (m, 1H), 7.12-7.17 (m, 1H), 7.23-7.31 (m, 3H), 7.85-8.31 (m, 1H).

LC-MS (MET-uPLC-AB-101): 96% (UV), Rt= 2.72 min, m/z (ESI⁺)= 367.1/369.1 [M+H]⁺

N-(Cyclohexylmethyl)-3-[*N*-(2-methoxyphenyl)formamido]-2-oxobutanamide (FP 25)

[0335] The title compound was synthesized from *N*-(cyclohexylmethyl)-2-hydroxy-3-[*N*-(2-methoxyphenyl)formamido]butanamide (I-148) in a similar manner to method A, general procedure 4 (general scheme 4) as an off-white powder (254 mg, 100% purity, 79%) after trituration in EtOAc and purification of the filtrate by flash column chromatography on normal phase silica (50 g SNAP KP-SIL cartridge, 0-100% TBME in heptane gradient).

¹H NMR (500 MHz, Chloroform-d) δ 0.90-1.01 (m, 2H), 1.10-1.29 (m, 3H), 1.32-1.50 (m, 3H), 1.50-1.54 (m, 1H), 1.63-1.69 (m, 1H), 1.69-1.78 (m, 4H), 3.09-3.27 (m, 2H), 3.68-3.87 (m, 3H), 5.02-5.45 (m, 1H), 6.81-6.91 (m, 1H), 6.95-7.00 (m, 1H), 7.00-7.07 (m, 1H), 7.32-7.39 (m, 1H), 7.55-7.64 (m, 1H), 7.96-8.61 (m, 1H).

LC-MS (MET-uPLC-AB-101): 100% (UV), Rt= 3.58 min, m/z (ESI⁺)= 347.2 [M+H]⁺

N[2-(3-Chlorophenyl)propan-2-yl]-2-oxo-3-[*N*-(propan-2-yl)formamido]butanamide (FP 26)

[0336] The title compound was synthesized from *N*[2-(3-chlorophenyl)propan-2-yl]-2-hydroxy-3-[*N*-(propan-2-yl)formamido]butanamide (I-149) in a similar manner to method A, general procedure 4 (general scheme 4) as a colourless viscous oil (40 mg, 97% purity, 35%) after purification by flash column chromatography on normal phase silica (10 g SNAP KP-SIL cartridge, 0-40% EtOAc in heptane gradient) followed by preparative LC (acidic pH, standard elution method).

¹H NMR (500 MHz, Chloroform-d) δ 1.01-1.33 (m, 6H), 1.45-1.54 (m, 3H), 1.62-1.70 (m, 3H), 1.74-1.76 (m, 3H), 3.71-4.01 (m, 1H), 4.12-4.54 (m, 1H), 6.67-6.99 (m, 1H), 7.20-7.23 (m, 1H), 7.25-7.28 (m, 2H), 7.35-7.39 (m, 1H), 8.10-8.26 (m, 1H).

LC-MS (MET-uPLC-AB-101): 97% (UV), Rt= 3.28 min, m/z (ESI⁺)= 339.2/341.2 [M+H]⁺

N-[2-(3-Chlorophenyl)propan-2-yl]-3-(*N*-cyclohexylformamido)-2-oxobutanamide (FP 27)

[0337] The title compound was synthesized from *N*-[2-(3-chlorophenyl)propan-2-yl]-3-(*N*-cyclohexylformamido)-2-hydroxybutanamide (I-150) in a similar manner to method A, general procedure 4 (general scheme 4) as an off-white powder (19 mg, 98% purity, 18%) after purification by flash column chromatography on normal phase silica (10 g SNAP KP-SIL cartridge, 0-40% EtOAc in heptane gradient) followed by preparative LC (acidic pH, standard elution method).

¹H NMR (500 MHz, Chloroform-*d*) δ 1.03–1.18 (m, 1H), 1.24–1.35 (m, 2H), 1.39–1.55 (m, 5H), 1.64 (s, 3H), 1.64–1.70 (m, 1H), 1.72–1.77 (m, 3H), 1.80–1.89 (m, 3H), 1.90–1.96 (m, 1H), 3.21–4.13 (m, 1H), 4.15–5.15 (m, 1H), 6.81 (s, 1H), 7.20–7.24 (m, 1H), 7.24–7.28 (m, 2H), 7.32–7.37 (m, 1H), 8.08–8.28 (m, 1H).

LC-MS (MET-uPLC-AB-101): 98% (UV), *R*_t= 3.89 min, *m/z* (ESI⁺)= 379.2/381.2 [M+H]⁺
3-[*N*-(2-Methoxyphenyl)formamido]-2-oxo-*N*-(propan-2-yl)butanamide (FP 28)

[0338] The title compound was synthesized from 2-hydroxy-3-[*N*-(2-methoxyphenyl)-formamido]-*N*-(propan-2-yl)butanamide (I-152) in a similar manner to method A, general procedure 4 (general scheme 4) as a yellow viscous oil (108 mg, 97% purity, 56%) after purification by flash column chromatography on normal phase silica (10 g SNAP KP-SIL cartridge, 0-40% EtOAc in heptane gradient).

¹H NMR (500 MHz, Chloroform-*d*) δ 1.20-1.25 (m, 6H), 1.32-1.50 (m, 3H), 3.70-3.86 (m, 3H), 4.01-4.14 (m, 1H), 5.06-5.45 (m, 1H), 6.54-6.81 (m, 1H), 6.90-6.99 (m, 1H), 7.00-7.15 (m, 1H), 7.28-7.38 (m, 1H), 7.55-7.61 (m, 1H), 7.99-8.61 (m, 1H).

LC-MS (MET-uPLC-AB-101): 97% (UV), *R*_t= 2.62 min, *m/z* (ESI⁺)= 293.1 [M+H]⁺
3-[*N*-(2,2-Dimethylpropyl)formamido]-2-oxo-*N*-(propan-2-yl)butanamide (FP 29)

[0339] The title compound was synthesized from 3-[*N*-(2,2-dimethylpropyl)formamido]-2-hydroxy-*N*-(propan-2-yl)butanamide (I-153) in a similar manner to method A, general procedure 4 (general scheme 4) as an off-white solid (88 mg, 100% purity, 52%) after trituration in 1:1 EtOAc/heptane and purification of the filtrate by flash column chromatography on normal phase silica (50 g SNAP KP-SIL cartridge, 0-100% TBME in heptane gradient).

¹H NMR (500 MHz, Chloroform-d) δ 0.91-1.05 (m, 9H), 1.17-1.24 (m, 6H), 1.50-1.67 (m, 3H), 2.78-3.20 (m, 1H), 3.23-3.53 (m, 1H), 3.94-4.12 (m, 1H), 4.17-5.05 (m, 1H), 6.37-6.81 (m, 1H), 7.88-8.30 (m, 1H).

LC-MS (MET-uPLC-AB-101): 100% (UV), Rt= 2.72 min, m/z (ESI⁺)= 257.2 [M+H]⁺
N-(Cyclopropylmethyl)-4-methyl-3-[*N*-(2-methylpropyl)formamido]-2-oxopentanamide (FP 30)

[0340] The title compound was synthesized from *N*-(cyclopropylmethyl)-2-hydroxy-4-methyl-3-[*N*-(2-methylpropyl)formamido]pentanamide (I-155) in a similar manner to method A, general procedure 4 (general scheme 4) as a colourless glass (40 mg, 98% purity, 49%) after purification by preparative LC (acidic pH, standard elution method) followed by flash column chromatography on normal phase silica (10 g SNAP KP-SIL cartridge, 0-50% EtOAc in heptane gradient).

¹H NMR (500 MHz, Chloroform-d) δ 0.20-0.26 (m, 2H), 0.51-0.57 (m, 2H), 0.76-1.03 (m, 13H), 1.78-2.04 (m, 1H), 2.31-2.51 (m, 1H), 3.02-3.21 (m, 4H), 4.46-4.78 (m, 1H), 6.76-7.07 (m, 1H), 8.01-8.42 (m, 1H).

LC-MS (METCR1600): 98% (UV), Rt= 4.59 min, m/z (ESI⁺)= 283.3 [M+H]⁺
N-(Cyclopropylmethyl)-3-[*N*-(2,2-dimethylpropyl)formamido]-4-methyl-2-oxopentanamide (FP 31)

[0341] The title compound was synthesized from *N*-(cyclopropylmethyl)-3-[*N*-(2,2-dimethylpropyl)formamido]-2-hydroxy-4-methylpentanamide (I-156) in a similar manner to method A, general procedure 4 (general scheme 4) as a colourless glass (58 mg, 100% purity, 82%) after purification by flash column chromatography on normal phase silica (10 g SNAP KP-SIL cartridge, 0-50% EtOAc in heptane gradient).

¹H NMR (500 MHz, Chloroform-d) δ 0.20-0.26 (m, 2H), 0.49-0.57 (m, 2H), 0.86 (s, 6H), 0.96-1.07 (m, 10H), 2.31-2.54 (m, 1H), 2.82-3.45 (m, 4H), 4.35-4.90 (m, 1H), 6.82-7.13 (m, 1H), 8.00-8.56 (m, 1H).

LC-MS (METCR1600): 100% (UV), Rt= 4.8 min, m/z (ESI⁺)= 297.4 [M+H]⁺
(3R)-*N*-(Cyclopropylmethyl)-3-[*N*-(2,2-dimethylpropyl)formamido]-4-methyl-2-oxopentanamide and (3S)-*N*-(cyclopropylmethyl)-3-[*N*-(2,2-dimethylpropyl)formamido]-4-methyl-2-oxopentanamide (FP 32-33) ((R) and (S) assignments arbitrary)

[0342] *N*-(cyclopropylmethyl)-3-[*N*-(2,2-dimethylpropyl)formamido]-4-methyl-2-oxopentanamide (FP 31) (100% purity, 40.8 mg, 0.138 mmol) was purified by chiral

separation on Gilson LC [Column: Chiralpakas (250 mm x 20 mm, 10 μ M) at RT; Isocratic eluent: 85:15 heptane:EtOH; Flow rate: 9 mL/min; Detector wavelength: 210/254 nm; Injection volume: 300 -1000 μ L] to afford 8.9 mg of enantiomer 1 (FP 32) as a yellow viscous oil (95% ee, 20%) and 10.1 mg of enantiomer 2 (FP 33) as a yellow viscous oil (99% ee, 24%).

Enantiomer 1 (FP 32)

^1H NMR (500 MHz, Chloroform- d) δ 0.19-0.28 (m, 2H), 0.49-0.60 (m, 2H), 0.88 (s, 6H), 0.95-1.10 (m, 10H), 2.29-2.58 (m, 1H), 2.83-3.46 (m, 4H), 4.34-4.93 (m, 1H), 6.80-7.08 (m, 1H), 7.99-8.58 (m, 1H).

LC-MS (METCR1416): 97% (UV), R_t = 3.97 min, m/z (ESI $^+$)= 297.5 [M+H] $^+$

LC-MS (CAM-F2): 95% (UV), R_t = 15.24 min, 95% ee

Enantiomer 2 (FP 33)

^1H NMR (500 MHz, Chloroform- d) δ 0.24 (dq, J = 4.8, 15.4 Hz, 2H), 0.47-0.61 (m, 2H), 0.88 (s, 6H), 0.93-1.13 (m, 10H), 2.29-2.61 (m, 1H), 2.82-3.46 (m, 4H), 4.32-4.95 (m, 1H), 6.80-7.08 (m, 1H), 7.99-8.59 (m, 1H).

LC-MS (METCR1416): 99% (UV), R_t = 3.97 min, m/z (ESI $^+$)= 297.5 [M+H] $^+$

LC-MS (CAM-F2): 99% (UV), R_t = 6.66 min, 99% ee

N-(Cyclopropylmethyl)-4-methyl-3-{*N*-[(oxan-4-yl)methyl]formamido}-2-oxopentanamide (FP 34)

[0343] The title compound was synthesized from *N*-(cyclopropylmethyl)-2-hydroxy-4-methyl-3-{*N*-[(oxan-4-yl)methyl]formamido}pentanamide (I-157) in a similar manner to method A, general procedure 4 (general scheme 4) as a colourless glass (41 mg, 100% purity, 51%) after purification by flash column chromatography on normal phase silica (10 g SNAP KP-SIL cartridge, 0-50% EtOAc in heptane gradient).

^1H NMR (500 MHz, Chloroform- d) δ 0.19-0.27 (m, 2H), 0.50-0.58 (m, 2H), 0.90-1.04 (m, 7H), 1.16-1.66 (m, 4H), 1.80-2.00 (m, 1H), 2.30-2.51 (m, 1H), 3.02-3.42 (m, 6H), 3.86-4.00 (m, 2H), 4.43-4.82 (m, 1H), 6.80-7.08 (m, 1H), 7.98-8.40 (m, 1H).

LC-MS (METCR1600): 100% (UV), R_t = 4.06 min, m/z (ESI $^+$)= 325.3 [M+H] $^+$

N-[(3-Chlorophenyl)methyl]-3-[*N*-(2-methoxyphenyl)formamido]-4-methyl-2-oxopentanamide (FP 35)

[0344] The title compound was synthesized from *N*-[(3-chlorophenyl)methyl]-2-hydroxy-3-[*N*-(2-methoxyphenyl)formamido]-4-methylpentanamide (I-158) in a similar

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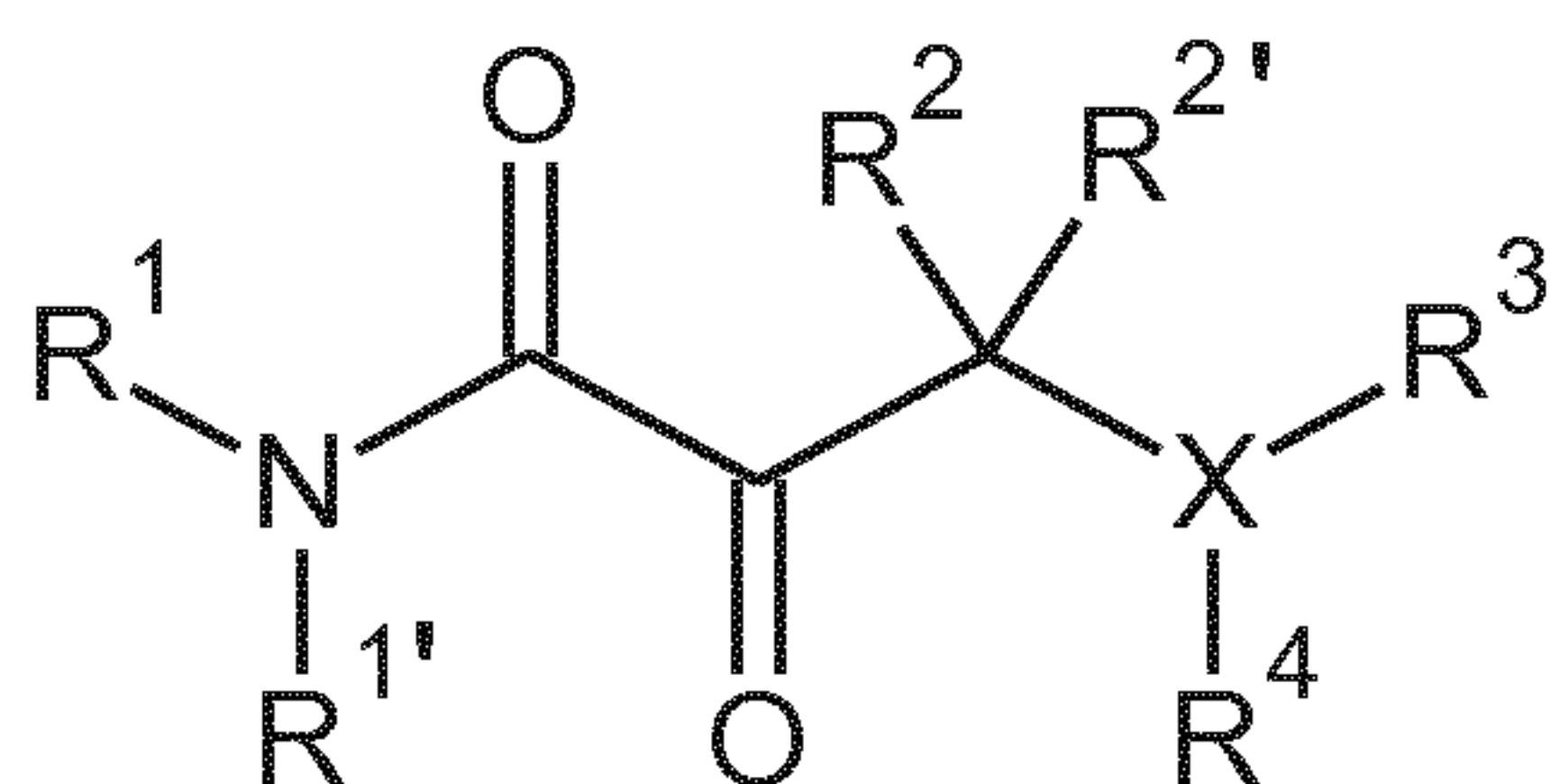
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Claims

1. A compound of general formula I,



wherein

R¹ denotes H, $-\text{C}(\text{O})\text{R}^a$, $-(\text{CH}_2)_n\text{C}(\text{O})\text{OR}^a$ or a group, optionally substituted by one or more, identical or different R^a and/or R^b , selected independently from one another among C_{1-8} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-10} aryl, 3-8 membered heterocycloalkyl, and 5-12 membered heteroaryl, and

R^{1'} denotes H or C_{1-4} alkyl,

or **R¹** and **R^{1'}** together with the adjacent nitrogen atom form a 4- to 10-membered heterocyclic group, which optionally may be substituted by one or more, identical or different R^a and/or R^b ;

X denotes $-(\text{CH}_2)_n\text{-N-}$ or O;

R² denotes H, $-\text{C}(\text{O})\text{R}^a$ or a group, optionally substituted by one or more, identical or different R^a and/or R^b , selected independently from one another among C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{4-16} cycloalkylalkyl, C_{6-10} aryl, C_{7-16} arylalkyl, 3-8 membered heterocycloalkyl, 5-12 membered heteroaryl and 6-18 membered heteroarylalkyl;

or **R²** forms together with **R³** a 5–7 membered heterocycloalkyl ring when X denotes $-\text{N-}$, wherein said heterocycloalkyl ring bears an oxo group, and is optionally substituted by one or more, identical or different R^a and/or R^b ;

R^{2'} denotes H or C_{1-6} alkyl;

R³ denotes H, $-\text{C}(\text{O})\text{R}^c$, or $-\text{SO}_2\text{R}^a$; and

R⁴ denotes H, or a group, optionally substituted by one or more, identical or different R^a and/or R^b , selected independently from one another among C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{4-16} cycloalkyl, C_{6-10} aryl, C_{7-16} arylalkyl, 3-8 membered heterocycloalkyl, 4-14 membered heterocycloalkylalkyl, 5-12 membered heteroaryl, and 6-18 membered heteroarylalkyl;

or **R**⁴ form together with **R**³ a 4-6-membered heterocycloalkyl ring when X denotes -N-, wherein said heterocycloalkyl ring bears an oxo group, and is optionally substituted by one or more, identical or different **R**^a and/or **R**^b; and **n** denotes 0, 1, 2 or 3;

each **R**^a independently of one another denotes hydrogen or a group, optionally substituted by one or more, identical or different **R**^b and/or **R**^c, selected from among C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₁₀cycloalkyl, C₄₋₁₆cycloalkylalkyl, C₆₋₁₀aryl, C₇₋₁₆arylalkyl, 3-8 membered heterocycloalkyl, 4-14 membered heterocycloalkylalkyl, 5-12 membered heteroaryl and 6-18 membered heteroarylalkyl;

each **R**^b is a suitable substituent and is selected in each case independently of one another from among =O, -OR^c, C₁₋₃haloalkyloxy, -OCF₃, =S, -SR^c, =NR^c, =NOR^c, =NNR^cR^c, =NN(R^g)C(O)NR^cR^c, -NR^cR^c, -ONR^cR^c, -N(OR^c)R^c, -N(R^g)NR^cR^c, halogen, -CF₃, -CN, -NC, -OCN, -SCN, -NO, -NO₂, =N₂, -N₃, -S(O)R^c, -S(O)OR^c, -S(O)₂R^c, -S(O)₂OR^c, -S(O)NR^cR^c, -S(O)₂NR^cR^c, -OS(O)R^c, -OS(O)₂R^c, -OS(O)₂OR^c, -OS(O)NR^cR^c, -OS(O)₂NR^cR^c, -O(CH₂)_p(CH₂)_pR^c, -C(O)R^c, -C(O)OR^c, -C(O)SR^c, -C(O)NR^cR^c, -C(O)N(R^g)NR^cR^c, -C(O)N(R^g)OR^c, -C(NR^g)NR^cR^c, -C(NOH)R^c, -C(NOH)NR^cR^c, -OC(O)R^c, -OC(O)OR^c, -OC(O)SR^c, -OC(O)NR^cR^c, -OC(NR^g)NR^cR^c, -SC(O)R^c, -SC(O)OR^c, -SC(O)NR^cR^c, -SC(NR^g)NR^cR^c, -N(R^g)C(O)R^c, -N[C(O)R^c]₂, -N(OR^g)C(O)R^c, -N(R^g)C(NR^g)R^c, -N(R^g)N(R^g)C(O)R^c, -N[C(O)R^c]NR^cR^c, -N(R^g)C(S)R^c, -N(R^g)S(O)R^c, -N(R^g)S(O)OR^c, -N(R^g)S(O)₂R^c, -N[S(O)₂R^c]₂, -N(R^g)S(O)₂OR^c, -N(R^g)S(O)₂NR^cR^c, -N(R^g)[S(O)₂]₂R^c, -N(R^g)C(O)OR^c, -N(R^g)C(O)SR^c, -N(R^g)C(O)NR^cR^c, -N(R^g)C(O)NR^gNR^cR^c, -N(R^g)N(R^g)C(O)NR^cR^c, -N(R^g)C(S)NR^cR^c, -[N(R^g)C(O)]₂R^c, -N(R^g)[C(O)]₂R^c, -N{[C(O)]₂R^c}₂, -N(R^g)[C(O)]₂OR^c, -N(R^g)[C(O)]₂NR^cR^c, -N{[C(O)]₂OR^c}₂, -N{[C(O)]₂NR^cR^c}₂, -[N(R^g)C(O)]₂OR^c, -N(R^g)C(NR^g)OR^c, -N(R^g)C(NOH)R^c, -N(R^g)C(NR^g)SR^c and -N(R^g)C(NR^g)NR^cR^c;

each **R**^c independently of one another denotes hydrogen or a group, optionally substituted by one or more, identical or different **R**^d and/or **R**^e, selected from among C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₁₀cycloalkyl, C₄₋₁₆cycloalkylalkyl, C₆₋₁₀aryl, C₇₋₁₆arylalkyl, 3-8 membered heterocycloalkyl, 4-14 membered

heterocycloalkylalkyl, 5-12 membered heteroaryl and 6-18 membered heteroarylalkyl;

each **R^d** denotes a suitable substituent and is selected in each case independently of one another from among =O, -OR^e, C₁₋₃haloalkyloxy, -OCF₃, =S, -SR^e, =NR^e, =NOR^e, =NNR^eR^e, =NN(R^g)C(O)NR^eR^e, -NR^eR^e, -ONR^eR^e, -N(OR^e)R^e, -N(R^g)NR^eR^e, halogen, -CF₃, -CN, -NC, -OCN, -SCN, -NO, -NO₂, =N₂, -N₃, -S(O)R^e, -S(O)OR^e, -S(O)₂R^e, -S(O)₂OR^e, -S(O)NR^eR^e, -S(O)₂NR^eR^e, -OS(O)R^e, -OS(O)₂R^e, -OS(O)₂OR^e, -OS(O)NR^eR^e, -OS(O)₂NR^eR^e, -C(O)R^e, -C(O)OR^e, -C(O)SR^e, -C(O)NR^eR^e, -C(O)N(R^g)NR^eR^e, -C(O)N(R^g)OR^e, -C(NR^g)NR^eR^e, -C(NOH)R^e, -C(NOH)NR^eR^e, -OC(O)R^e, -OC(O)OR^e, -OC(O)SR^e, -OC(O)NR^eR^e, -OC(NR^g)NR^eR^e, -SC(O)R^e, -SC(O)OR^e, -SC(O)NR^eR^e, -SC(NR^g)NR^eR^e, -N(R^g)C(O)R^e, -N[C(O)R^e]₂, -N(OR^g)C(O)R^e, -N(R^g)C(NR^g)R^e, -N(R^g)N(R^g)C(O)R^e, -N[C(O)R^e]NR^eR^e, -N(R^g)C(S)R^e, -N(R^g)S(O)R^e, -N(R^g)S(O)OR^e, -N(R^g)S(O)₂R^e, -N[S(O)₂R^e]₂, -N(R^g)S(O)₂OR^e, -N(R^g)S(O)₂NR^eR^e, -N(R^g)[S(O)₂]₂R^e, -N(R^g)C(O)OR^e, -N(R^g)C(O)SR^e, -N(R^g)C(O)NR^eR^e, -N(R^g)C(O)NR^gNR^eR^e, -N(R^g)N(R^g)C(O)NR^eR^e, -N(R^g)C(S)NR^eR^e, -[N(R^g)C(O)]₂R^e, -N(R^g)[C(O)]₂R^e, -N{[C(O)]₂R^e}₂, -N(R^g)[C(O)]₂OR^e, -N(R^g)[C(O)]₂NR^eR^e, -N{[C(O)]₂OR^e}₂, -N{[C(O)]₂NR^eR^e}₂, -[N(R^g)C(O)]₂OR^e, -N(R^g)C(NR^g)OR^e, -N(R^g)C(NOH)R^e, -N(R^g)C(NR^g)SR^e and -N(R^g)C(NR^g)NR^eR^e; and

each **R^e** independently of one another denotes hydrogen or a group selected from among C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₈cycloalkyl, C₆₋₁₀aryl, 3-8 membered heterocycloalkyl, and 5-12 membered heteroaryl; and

each **R^g** independently of one another denotes hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₈cycloalkyl, C₆₋₁₀aryl, 3-8 membered heterocycloalkyl, or 5-12 membered heteroaryl; and

p denotes independently from one another 1, 2, 3, or 4; and

provided that when X denotes O R³ is absent and

provided that when X denotes -N-, and

R¹ and R^{1'} denote hydrogen R³ and R⁴ are other than hydrogen; and

provided that R² is not benzyl, and

optionally in the form of the tautomers, the racemates, the enantiomers, the

diastereomers, hydrates, isotopes, and mixtures thereof, and optionally the pharmacologically acceptable salts thereof.

2. The compound according to claim 1, wherein X is N.
3. The compound according to claim 2, wherein R³ is -C(O)R^c.
4. The compound according to claim 1, wherein X is O.
5. The compound according to claim 4, wherein R⁴ is selected from optionally substituted C₁₋₆alkyl, C₃₋₆cycloalkyl, phenyl, C₇₋₁₆arylalkyl, 3-8 membered heterocycloalkyl, 4-14 membered heterocycloalkylalkyl, and 5-6 membered heteroaryl.
6. The compound according to claim 5, wherein R⁴ is C₁₋₆alkyl.
7. The compound according to claim 1, wherein R² forms together with R³ an oxo bearing pyrrolidinyl group.
8. The compound according to any one of claims 1 to 7, wherein R^{1'} is H.
9. The compound according to any one of claims 1 to 8, wherein R¹ is optionally substituted C₁₋₆alkyl, C₃₋₆cycloalkyl, or C₄₋₁₆cycloalkylalkyl.
10. The compound according to any one of claims 1 to 9, wherein R^{2'} is H.
11. The compound according to any one of claims 1 to 10, wherein R² is optionally substituted C₁₋₆alkyl.
12. The compound according to claim 1 chosen from Table 2.
13. The compound according to claim 1 chosen from compounds FP1 to FP349.
14. A compound of general formula I according to any one of claims 1 to 13, optionally in the form of the tautomers, the racemates, the enantiomers, the diastereomers, hydrates, isotopes, and mixtures thereof, or the pharmacologically acceptable salt thereof for use as medicament.
15. A compound of general formula I according to any one of claims 1 to 13, optionally in the form of the tautomers, the racemates, the enantiomers, the diastereomers, hydrates, isotopes, and mixtures thereof, or the pharmacologically acceptable salt thereof for use in the treatment or prevention of infectious diseases, cancer or obesity.
16. A compound of general formula I according to any one of claims 1 to 13, optionally in the form of the tautomers, the racemates, the enantiomers, the diastereomers,

hydrates, isotopes, and mixtures thereof, or the pharmacologically acceptable salt thereof for the treatment or prevention of picornavirus infections.

17. Pharmaceutical preparations containing as active substance one or more compounds of general formula I according to any one of claims 1 to 13 optionally in the form of the tautomers, the racemates, the enantiomers, the diastereomers, hydrates, isotopes, and mixtures thereof, or the pharmacologically acceptable salts thereof, optionally in combination with conventional excipients and/or carriers.
18. Pharmaceutical preparation comprising a compound of general formula I according to any one of claims 1 to 13, wherein the compounds are optionally present in the form of the tautomers, racemates, enantiomers, diastereomers, hydrates, isotopes, and mixtures thereof, or also as the respective pharmacologically acceptable salts of all the above mentioned forms, and at least one further active substance different from formula I.

