Note: Within nine months of the publication of the mention of the grant of the European patent in the European Patent Bulletin, any person may give notice to the European Patent Office of opposition to that patent, in accordance with the Implementing Regulations. Notice of opposition shall not be deemed to have been filed until the opposition fee has been paid. (Art. 99(1) European Patent Convention).
Description

Technical Field

[0001] The disclosure relates to prodrugs of acyloxyalkyl carbamate trans-4-(aminomethyl)-cyclohexanecarboxylic acid, pharmaceutical compositions thereof to treat various diseases or disorders. The disclosure also relates to such prodrugs suitable for oral and topical administration including for oral administration using sustained release dosage forms.

Background

[0002] Tranexamic acid (1) (trans-4-(aminomethyl)-cyclohexanecarboxylic acid, Cyklokapron®):

\[
\text{H}_2\text{N} \quad \text{\begin{picture}(100,150)
  \put(100,0){\circle{100}}
  \put(100,0){\line(0,1){100}}
  \put(100,0){\line(1,0){100}}
  \end{picture}} \quad \text{OH}
\]

is an antifibrinolytic agent that reversibly blocks lysine binding sites on plasminogen and plasmin, and acts to prevent proteolytic degradation of fibrin clots which form in the normal physiologic process of hemostasis. Both plasminogen and plasmin are activators of fibrinolysis and active clot-lysing agents. Tranexamic acid thus helps to stabilize fibrin clots, which in turn maintains coagulation and helps to control bleeding.

[0003] Tranexamic acid is used clinically to control excess bleeding, for example, heavy bleeding associated with cardiac surgery, upper gastrointestinal hemorrhage, blood loss in patients with advanced cancer (both acute hemorrhagic events and low-volume chronic bleeding), excessive bleeding that occurs during dental procedures in hemophiliacs, and for heavy bleeding during menstruation, i.e., menorrhagia (see Wellington and Wagstaff, Drugs, 2003, 63, 1417-1433; Dunn and Goa, Drugs, 1999, 57, 1005-1032; Pereira and Phan, The Oncologist, 2004, 9, 561-570).


[0005] The plasminogen activation system is also a predominant protease pathway responsible for extracellular matrix (ECM) degradation. Cancer dissemination and metastasis is synonymous with invasive cell migration, a process in which the ECM plays the dual role of the substratum on which the cells move as well as the physical obstacle that the cells have to surpass. To degrade the physical obstacle that the ECM poses in the direction of migration, cells use proteolytic enzymes such as plasminogen and plasmin capable of hydrolyzing the ECM components (Stonelake et al., Br. J. Cancer, 1997, 75, 951-959; Dunbar et al., Expert Opin. Investig. Drugs, 2000, 9, 2085-2092; Sidenius and Blasi, Cancer Metastasis Rev., 2003, 22, 205-222). Plasmin inhibitory compounds such as tranexamic acid, therefore, show utility as anti-metastatic agents either alone or in combination with cytotoxic anticancer agents (Tsutsumi and Konishi, Jpn. Kokai Tokkyo Koho, 2002114673).

[0006] Menorrhagia is defined as blood loss >80 mL per menstrual cycle and affects many women and represents a significant health problem. Prevalence rates are believed to be similar across the Western world, and in the U.K. at least one in 20 women aged between 34 and 49 years will consult their general practitioners because of menstrual disorders. Menorrhagia accounts for 60% of primary-care consultations for menstrual problems and 12% of all gynecology referrals (Peto et al., Fam. Pract., 1993, 10, 207-211; McPherson and Andersson, eds., Women’s problems in general, practice, Oxford: Oxford University Press, 1983, pp 21-41; Bradlow et al., Patterns of referral, Oxford: Oxford Health Services Research Unit, 1992). While various pathological mechanisms may contribute to the cause of menorrhagia, approximately...
50% of women with heavy menstrual blood loss have no underlying anatomical or endocrinological abnormality. In such women fibrinolytic activity \textit{in utero} is higher than in women with normal menstrual blood loss, with this increased fibrinolysis resulting from elevated levels of endometrium-derived plasmin and plasminogen activators (Gleeson, Am. J. Obstet. Gynecol., 1994, 171, 178-183; Dockery et al., Eur. J. Obstet. Gynecol. Reprod. Biol., 1987, 24, 309-318).

Despite the availability of clinically effective antifibrinolytic agents such as tranexamic acid (which has been shown to reduce menstrual blood loss by \( \sim 50\% \)), approximately 60% of women with menorrhagia undergo hysterectomy within 5 years of referral to a gynecologist (Coulter et al., Br. J. Obstet. Gynaecol., 1991, 98, 789-796). Women suffering from menorrhagia are typically treated orally with tranexamic acid concurrently with menstruation (4-7 days). Doses of 500-1500 mg tranexamic acid tablets administered three or four times daily are typical. Intravenous dosage formulations are also available for use as a continuous infusion in the surgical setting. The requirement for frequent daily oral administration results from the suboptimal pharmacokinetic properties of tranexamic acid, which includes modest oral bioavailability (\( \sim 30\% \)) and a rapid terminal elimination half-life of \( \sim 2 \) hours.

Sustained released oral dosage formulations are a conventional solution to the problem of rapid systemic drug clearance, as is well known in the art (See, e.g., "Remington’s Pharmaceutical -Sciences," Philadelphia College of Pharmacy and Science, 19th Edition, 1995). Osmotic delivery systems are also recognized methods for sustained drug delivery (see e.g., Verma et al., Drug Dev. Ind. Pharm., 2000, 26, 695-708). Successful application of these technologies depends on the drug of interest having an effective level of absorption from the large intestine (also referred to herein as the colon), where the dosage form spends a majority of its time during its passage through the gastrointestinal tract. Tranexamic acid is poorly absorbed following rectal administration in humans (Almer et al., J. Clin. Pharm., 1992, 32, 49-54), consistent with limited permeability of the drug across the colonic mucosa. Development of an oral controlled release formulation for tranexamic acid should considerably improve the convenience, efficacy and side effect profile of antifibrinolytic therapy. However, the rapid passage of conventional dosage forms through the proximal absorptive region of the small intestine has thus far prevented the successful application of sustained release technologies to this drug. Heasley \textit{et al.} have described delayed release oral formulations of tranexamic acid based on the use of enteric polymer coatings that are designed to retard the dissolution of the drug by 1-2 hours until the dosage form has passed from the stomach to the small intestine (U.S. Patent Application No. 2005/002825). Such formulations are said to reduce the adverse gastrointestinal reactions that may accompany oral tranexamic acid therapy (including nausea, vomiting, diarrhea, dyspepsia and cramping). However these formulations would not be expected to substantially alter the elimination half-life of the drug, and hence overcome the requirement for frequent daily dosing.

There is a significant need for new prodrugs of tranexamic acid that are well absorbed in the large intestine and hence suitable for oral sustained release formulations, thus improving the convenience, efficacy and side effect profile of antifibrinolytic therapy. Moreover, since the zwitterionic character of tranexamic acid limits the permeability of the compound across the epidermal barrier, there is also a need for more lipophilic prodrug derivatives of tranexamic acid which would provide for more effective topical administration in the treatment of skin disorders such as wound healing, epidermal hyperplasia, skin roughening, unwanted skin pigmentation, etc.

One solution to the incomplete gastrointestinal absorption of tranexamic acid is through design of prodrug derivatives (see Svahn et al., J. Med Chem., 1986, 29, 448-453; Svahn \textit{et al.}, European Patent No. 0 079 827 B1; Svahn et al., U.S. Patent No. 4,483,867; Jonsson, International Publication No. WO94/15904; Svahn et al., Arzneim-Forsch., 1988, 38, 735-738; Edlund \textit{et al.}, Br. J. Obstet. Gynaecol., 1995, 102, 913-917). The prodrug 1-(ethoxycarbonyloxyethyl)trans-4-(aminomethyl)-cyclohexanecarboxylate (i.e.,Kabi 2161) showed markedly improved oral bioavailability of tranexamic acid in human patients, and was effective in reducing menstrual blood loss in women suffering from idiopathic menorrhagia.

There is a significant need for new prodrugs of tranexamic acid that are well absorbed in the large intestine and hence suitable for oral sustained release formulations, thus improving the convenience, efficacy and side effect profile of antifibrinolytic therapy. Moreover, since the zwitterionic character of tranexamic acid limits the permeability of the compound across the epidermal barrier, there is also a need for more lipophilic prodrug derivatives of tranexamic acid which would provide for more effective topical administration in the treatment of skin disorders such as wound healing, epidermal hyperplasia, skin roughening, unwanted skin pigmentation, etc.

The needs described above, among other needs, can be satisfied by the disclosure herein of acyloxyalkyl carbamate prodrugs of tranexamic acid, pharmaceutical composition of acyloxyalkyl carbamate prodrugs of tranexamic acid to treat various medical pathologies. The disclosure also provides prodrugs suitable for oral and topical administration including, for oral administration using sustained release dosage forms.

In one aspect, compounds of Formula (I) are provided.
Compounds of Formula (II) are disclosed herein,

pharmaceutically acceptable salts thereof, and pharmaceutically acceptable solvates of any of the foregoing, wherein:

X is selected from fluoro, chloro, bromo, iodo, and R$^{20}$SO$_3^-$, wherein R$^{20}$ is selected from C$_{1-6}$ alkyl, C$_{5-7}$ aryl, and substituted C$_{5-7}$ aryl; and
R$^2$, R$^3$ and R$^4$ are as defined above.

Methods of synthesizing a compound of Formula (I) are disclosed herein, comprising:
contacting a compound of Formula (II), a compound of Formula (III) and at least one equivalent of a reactant selected from an organic base, an inorganic base, and combinations thereof, to provide a compound of Formula (I), pharmaceutically acceptable salts thereof, and pharmaceutically acceptable solvates of any of the foregoing, wherein:

X, R¹, R², R³ and R⁴ are as defined above.

[0015] Methods of synthesizing a compound of Formula (I) are disclosed herein, comprising:

contacting a compound of Formula (IV) with a compound of Formulae (V) to provide a compound of Formula (I), pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate of any of the foregoing, wherein:

R⁵ and R⁶ are independently selected from hydrogen, acylamino, acyloxy, alkoxycarbonylamino, alkoxycarbonyloxy, alkyl, substituted alkyl, alkoxy, substituted alkoxy, aryl, substituted aryl, arylalkyl, substituted arylalkyl, carbamoyloxy, dialkylamino, heteroaryl, substituted heteroaryl, hydroxy, and sulfonamido, or R⁵ and R⁶ together with the atoms to which they are bonded form a substituted cycloalkyl, substituted cycloheteroalkyl, or substituted aryl ring; and R¹, R², R³ and R⁴ are as defined above.

[0016] Alternative methods of synthesizing a compound of Formula (I) are also disclosed comprising contacting a compound of Formula (XV) with an oxidant, to provide a compound of Formula (I), or pharmaceutically acceptable salts thereof, or pharmaceutically acceptable solvates of any of the foregoing.
wherein R¹, R², R³ and R⁴ are as defined above.

[0017] In another aspect, pharmaceutical compositions comprising at least one pharmaceutically acceptable vehicle and a therapeutically effective amount of at least one compound of Formula (I), a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate of any of the foregoing, are provided.

[0018] In another aspect, oral dosage forms, comprising at least one tranexamic acid prodrug of Formula (I), a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate of any of the foregoing, are provided.

[0019] In another aspect, sustained release oral dosage forms, comprising at least one prodrug of Formula (I), a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate of any of the foregoing, are provided.

[0020] In another aspect, topical dosage forms are provided, comprising at least one compound of Formula (I), a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate of any of the foregoing, formulated in a pharmaceutically acceptable topical vehicle.

[0021] In another aspect, the invention relates to use of a therapeutically effective amount of at least one compound according to said one aspect in the preparation of a medicament for treating excessive bleeding, including heavy bleeding associated with cardiac surgery, upper gastrointestinal hemorrhage, blood loss in patients with advanced cancer, excessive bleeding that occurs during dental procedures, for example in hemophiliacs, and heavy bleeding during menstruation, i.e., menorrhagia.

[0022] In another aspect, the invention relates to use of a therapeutically effective amount of at least one compound according to said one aspect in the preparation of a medicament for treating skin disorders such as wound healing, epidermal hyperplasia, skin roughening and unwanted skin pigmentation.

[0023] In another aspect, the invention relates to use of a therapeutically effective amount of at least one compound according to said one aspect in the preparation of a medicament for treating tumor metastasis in a patient suffering from a disorder, such as a malignant disorder, either alone or in combination with one or more cytotoxic agents. Preferred embodiments are defined in the dependent claims.

Brief Description of the Drawings

[0024] The skilled artisan will understand that the drawings, described herein, are for illustration purposes only.

[0025] Figure 1 shows the pharmacokinetics profile of released tranexamic acid (---) and remaining tranexamic acid prodrug 13 (- - - -) following intracolonic administration of tranexamic acid prodrug 13.

[0026] Figure 2 shows the pharmacokinetics profile of tranexamic acid following oral administration of tranexamic acid prodrug 13. The levels of prodrug 13 following oral gavage administration were below the level of detection.

Detailed Description

Definitions

[0027] Unless otherwise indicated, all numbers expressing quantities of ingredients, reaction conditions, and so forth used in the specification and claims are to be understood as being modified in all instances by the term "about" Accordingly, unless indicated to the contrary, the numerical parameters set forth in the following specification and attached claims are approximations that may vary depending upon the properties sought to be obtained. At the very least, and not as an attempt to limit the application of the doctrine of equivalents to the scope of the claims, each numerical parameter should at least be construed in light of the number of reported significant digits and by applying ordinary rounding techniques.

[0028] Notwithstanding that the numerical ranges and parameters setting forth the broad scope of the embodiments are approximations, the numerical values set forth in the specific examples are reported as precisely as possible. Any numerical values, however, inherently contain certain errors necessarily resulting from in the error inherent in measurements.

[0029] The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter disclosed.

[0030] To the extent the definitions of terms in the publications, patents, and patent applications incorporated herein by reference are not the same as the definitions set forth in this specification, the definitions in this specification control for the entire specification, including the claims. Any other definitions in the publications, patents, and patent applications incorporated herein by reference that are not explicitly provided in this specification apply only to the embodiments discussed in the publications, patents, and patent applications incorporated herein by reference.

[0031] A dash ("-"), that is not between two letters or symbols is used to indicate a point of attachment for a substituent. For example, -CONCH₂ is attached through the carbon atom.

[0032] "Acyl" by itself or as part of another substituent refers to a radical - C(O)R³⁰, where R³⁰ is hydrogen, alkyl, heteroalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkylalkyl, cycoheteroaalkylalkyl, aryalkyl, heteroaryl, aryalkyl, or heteroaryl-


alkyl, which may be substituted, as defined herein. Examples of acyl groups include formyl, acetyl, cyclohexylcarbonyl, cyclohexylmethylcarbonyl, benzoyl, benzylcarbonyl. In certain embodiments, an acyl group is C1-3 acyl.

[0033] “Acylamino” by itself or as part of another substituent refers to a radical NR31C(O)R32 where R31 and R32 are independently hydrogen, alkyl, cycloalkyl, cyclohexylcarbonyl, aryl, arylalkyl, heteroaryl, heteroaryl, or heteroaryalkyl, which may be substituted as defined herein. Examples of acylamino groups include formamido, acetamido and benzamido.

[0034] “1-Acetoxy-Alkyl Carbamate” refers to an N-1-(acyloxy)alkoxycarbonyl derivative of tranexamic acid as encompassed by compounds of Formula (I) disclosed herein.

[0035] “Alkyl” by itself or as part of another substituent refers to a saturated or unsaturated, branched or straight-chain monovalent hydrocarbon radical derived by the removal of one hydrogen atom from a single carbon atom of a parent alkane, alkene, or alkyne. Examples of alkyl groups include methyl; ethyls such as ethanly, ethenly, and ethyny; propyls such as propan-1-yl, propan-2-yl, prop-1-en-1-yl, prop-1-en-2-yl, prop-2-en-1-yl (allyl), prop-1-en-1-yl, prop-2-en-1-yl, etc.; butyls such as butan-1-yl, butan-2-yl, 2-methyl-prop-1-yl, 2-methyl-prop-2-yl, but-1-en-1-yl, but-1-en-2-yl, 2-methyl-prop-1-en-1-yl, but-2-en-1-yl, but-2-en-2-yl, buta-1,3-dien-1-yl, buta-1,3-dien-2-yl, but-1-en-1-yl, but-1-en-3-yl, but-3-en-1-yl.

[0036] The term “alkyl” is specifically intended to include groups having any degree or level of saturation, i.e., groups having exclusively single carbon-carbon bonds, groups having one or more double carbon-carbon bonds, groups having one or more triple carbon-carbon bonds and groups having mixtures of single, double and triple carbon-carbon bonds. Where a specific level of saturation is intended, the expressions “alkyl,” “alkenyl,” and “alkynyl” are used. In certain embodiments, an alkyl group comprises from 1 to 20 carbon atoms, in certain embodiments, from 1 to 6 carbon atoms, and in certain embodiments, from 1 to 3 carbon atoms. In certain embodiments, alkyl is C1-6 alkyl, C1-4 alkyl, C1-3 alkyl, methyl, ethyl, n-propyl, iso-propyl, n-butyl, isobutyl, sec-butyl, tert-butyl, or alkyl.

[0037] “Alkenyl” by itself or as part of another substituent refers to a saturated branched or straight-chain alkyl radical derived by the removal of one hydrogen atom from a single carbon atom of a parent alkane. Examples of alkenyl groups include methanly, ethenly, propanlys such as propan-1-yl, propan-2-yl (isopropyl); butanlys such as butan-1-yl, butan-2-yl (sec-butyl), 2-methyl-prop-1-yl (isobutyl), 2-methyl-prop-2-yl (t-butyl).

[0038] “Alkynyl” by itself or as part of another substituent refers to an unsaturated branched or straight-chain alkyl radical having at least one carbon-carbon double bond derived by the removal of one hydrogen atom from a single carbon atom of a parent alkene. The group may be in either the cis or trans conformation about the double bond(s). Examples of alkynyl groups include ethenly; propenlys such as prop-1-en-1-yl, prop-1-en-2-yl, prop-2-en-1-yl (allyl), prop-2-en-2-yl; butynlys such as but-1-en-1-yl, but-1-en-2-yl, 2-methyl-prop-1-en-1-yl, but-2-en-1-yl, but-2-en-2-yl, buta-1,3-dien-1-yl, buta-1,3-dien-2-yl.

[0039] “Alkyll” by itself or as part of another substituent refers to a saturated alkane or straight-chain alkyl radical having at least one carbon-carbon triple bond derived by the removal of one hydrogen atom from a single carbon atom of a parent alkane. Examples of alkyll groups include ethynyl; propynlys such as prop-1-en-1-yl, prop-2-en-1-yl; butynlys such as but-1-en-1-yl, but-1-en-3-yl, but-3-en-1-yl.

[0040] “Acloyxy” by itself or as part of another substituent refers to a radical -OC(O)R33 where R33 is alkyl, cycloalkyl, cyclohexylcarbonyl, aryl, arylalkyl, heteroaryl, heteroaryl, or heteroaryalkyl, which may be substituted as defined herein. Examples of acloyxy groups include acetoxy, isobutyroyloxy, benzoyloxy, phenylacetoxy.

[0041] “Alkoyxy” by itself or as part of another substituent refers to a radical -OR where R34 is alkyl, cycloalkyl, cycloalkylalkyl, aryl, or arylalkyl, which may be substituted, as defined herein. Examples of alkoyxy groups include methoxy, ethoxy, propoxy, butoxy, cyclohexyloxy.

[0042] “Alkoxycarbonyl” by itself or as part of another substituent refers to a radical -C(O)OR35 where R35 is an alkyl or substituted alkyl group, as defined herein. Examples of alkoxycarbonyl groups include methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl. In certain embodiments, an alkoxycarbonyl group is C1-3 alkoxycarbonyl.

[0043] “Alkoxycarbonylamino” by itself or as part of another substituent refers to a radical -NR36C(O)R37 where R36 represents an alkyl, substituted alkyl, cycloalkyl, or substituted cycloalkyl group and R37 is alkyl, cycloalkyl, cyclohexylalkyl, aryl, arylalkyl, heteroaryl, heteroaryl, or heteroaryalkyl, which may be substituted, as defined herein. Examples of alkoxycarbonylamino groups include methoxycarbonylamino, tert-butoxycarbonylamino, and benzyloxycarbonylamino.

[0044] “Alkoxycarbonyloxy” by itself or as part of another substituent refers to a radical -OC(O)-OR38 where R38 is an alkyl, substituted alkyl, cycloalkyl, or substituted cycloalkyl group, as defined herein. Examples of alkoxycarbonyloxy groups include methoxycarbonyloxy, ethoxycarbonyloxy, and cyclohexylocarbonyloxy.

[0045] “Alkylamino” by itself or as part of another substituent refers to a radical NR39 where R39 is an alkyl, substituted alkyl, cycloalkyl, or substituted cycloalkyl group, as defined herein. In certain embodiments, an alkylamino group is C1-3 alkylamino.

[0046] “Aryl” by itself or as part of another substituent refers to a monovalent aromatic hydrocarbon radical derived by the removal of one hydrogen atom from a single carbon atom of a parent aromatic ring system. Aroyl encompasses...
5- and 6-membered carbocyclic aromatic rings, for example, benzene; bicyclic ring systems wherein at least one ring is carbocyclic and aromatic, for example, naphthalene, indane, and tetralin; and tricyclic ring systems wherein at least one ring is carbocyclic and aromatic, for example, fluorene. Aryl encompasses multiple ring systems having at least one carbocyclic aromatic ring fused to at least one carbocyclic aromatic ring, cycloalkyl ring, or heterocycloalkyl ring. For example, aryl includes 5- and 6-membered carbocyclic aromatic rings fused to a 5- to 7-membered heterocycloalkyl ring containing one or more heteroatoms chosen from N, O, and S. For such fused, bicyclic ring systems wherein only one of the rings is a carbocyclic aromatic ring, the point of attachment may be at the carbocyclic aromatic ring or the heterocycloalkyl ring. Examples of aryl groups include groups derived from aceanthrylene, acenaphthenylene, acenaphthylene, anthracene, azulene, benzene, chrysene, coronene, fluoranthen, fluorene, hexacene, hexaphene, hexalene, as-indacene, s-indacene, indene, naphthalene, octacene, octaphene, octalene, ovelane, penta-2,4-diene, pentacene, pentalene, pentaphene, perylene, phenalene, phenanthenre, picene, pleiadene, pyrene, pyranthren, rubicene, triphenylene, trinaphthalene. In certain embodiments, an aryl group may have from 5 to 20 carbon atoms, and in certain embodiments, from 5 to 12 carbon atoms. Aryl, however, does not encompass or overlap in any way with heteroaryl, separately defined herein. Hence, a multiple ring system in which one or more carbocyclic aromatic rings is fused to a heterocycloalkyl aromatic ring, is heteroaryl, not aryl, as defined herein. In certain embodiments, aryl is C₆-10 aryl or phenyl.

[0047] "Arylalkyl" by itself or as part of another substituent refers to an acyclic alkyl radical in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or sp² carbon atom, is replaced with an aryl group. Examples of arylalkyl groups include benzyl, 2-phenylethen-1-yl, 2-phenylethen-1-yl, naphthylmethyl, 2-naphthylenethen-1-yl, 2-naphthylenethen-1-yl, where specific alkyl moieties are intended, the nomenclature arylalkyl, arylalkeny1, or ary1alkny1 is used. In certain embodiments, an ary1alkyl group is C₇-30 arylalkyl, e.g., the alkanyl, alkenyl, or alkynyl moiety of the ary1alkyl group is C₁-10 and the aryl moiety is C₆-20; and in certain embodiments, an ary1alkyl group is C₇-20 ary1alkyl, e.g., the alkanyl, alkenyl, or alkynyl moiety of the ary1alkyl group is C₁-8 and the aryl moiety is C₆-12. In certain embodiments, ary1alkyl is C₇₋₁₆ ary1alkyl or benzyl.

[0048] "Aryldialkylsilyl" by itself or as part of another substituent refers to the radical -SiR₄₀R₄₁R₄₂ where one of R₄₀, R₄₁, and R₄₂ is aryl or substituted aryl as defined herein and the other two of R₄₀, R₄₁, and R₄₂ are alkyl or substituted alkyl, as defined herein. In certain embodiments, an aryldialkylsilyl group is C₇₋₁₄ aryldialkylsilyl.

[0049] “AUC” is the area under the plasma drug concentration-versus-time curve extrapolated from zero time to infinity.

[0050] “Cmax” is the highest drug concentration observed in plasma following an extravascular dose of drug.

[0051] "Carbamoyloxy" by itself or as part of another substituent refers to a radical -OC(O)₂NR₄₅R₄₆ where R₄₅ and R₄₆ are independently hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, or substituted aryl, as defined herein.

[0052] "Carbamoyloxy" by itself or as part of another substituent refers to a radical -OC(O)₂NR₄₅R₄₆ where R₄₅ and R₄₆ are independently selected from hydrogen, alkyl, cycloalkyl, cyclohexaalkyl, aryl, aryalkyl, heteroaryl, heteroary1, which may be substituted, as defined herein, or R₄₅ and R₄₆ together with the atoms to which they are bonded form a cyclohexaalkyl or heteroaryl ring.

[0053] "Cleave" refers to breakage of chemical bonds and is not limited to chemical or enzymatic reactions or mechanisms unless clearly intended by the context.

[0054] "Compounds" refers to compounds encompassed by structural Formulae (I) - (XIX) disclosed herein and includes any specific compounds within these formulae whose structure is disclosed herein. Compounds may be identified either by their chemical structure and/or chemical name. When the chemical structure and chemical name conflict, the chemical structure is determinative of the identity of the compound. The compounds described herein may contain one or more chiral centers and/or double bonds and therefore, may exist as stereoisomers, such as double-bond isomers, i.e., geometric isomers, enantiomers and diastereomers. Accordingly, the chemical structures depicted herein encompass all possible enantiomers and stereoisomers of the illustrated compounds including the stereochemically pure form (e.g., geometrically pure, enantiomerically pure or diastereomerically pure) and enantiomeric and other stereoisomeric mixtures. Enantiomeric and stereoisomeric mixtures may be resolved into their component enantiomers or stereoisomers using separation techniques or stereocontrolled synthesis techniques well known to the skilled artisan. The compounds may also exist in several tautomeric forms that the enol form, the keto form and mixtures thereof. Accordingly, the chemical structures depicted herein encompass all possible tautomeric forms of the illustrated compounds. The compounds described also include isotopically labeled compounds where one or more atoms have an atomic mass different from the atomic mass found in nature. Examples of isotopes that may be incorporated into the compounds disclosed herein include ²H, ³H, ¹¹C, ¹³C, ¹⁴C, ¹⁵N, ¹⁷O, and ¹⁸O. Compounds may exist in unsolvated forms as well as solvated forms, including hydrated forms and as N-oxides. In general, compounds may be hydrated, solvated, or N-oxides. Certain compounds may exist in multiple crystalline or amorphous forms. In general, all physical forms are equivalent for the uses contemplated herein and are intended to be within the scope of the present disclosure. Further, it should be understood, when partial structures of the compounds are illustrated, an asterisk (*) indicates the point of attachment of the partial structure to the rest of the molecule.

[0055] "Cycloalkoxy carbonyl" by itself or as part of another substituent refers to a radical -C(O)OR₄⁷ where R₄⁷
represents an cycloalkyl or substituted cycloalkyl group as defined herein. Examples of cycloalkoxy carbonyl groups include cyclobutyloxycarbonyl, cyclohexyloxycarbonyl.

[0056] "Cycloalkyl" by itself or as part of another substituent refers to a partially saturated or unsaturated cyclic alkyl radical. Where a specific level of saturation is intended, the nomenclature "cycloalkanyl" or "cycloalkenyl" is used. Examples of cycloalkyl groups include groups derived from cyclopropane, cyclobutane, cyclopentane, cyclohexane. In certain embodiments, a cycloalkyl group is C_{3-15} cycloalkyl, and in certain embodiments, C_{5-12} cycloalkyl. In certain embodiments, a cycloalkyl group is C_{3-7} cycloalkyl or cyclohexyl.

[0057] "Cy cloheteroaryl" by itself or as part of another substituent refers to a partially saturated or unsaturated cyclic alkyl radical in which one or more carbon atoms (and any associated hydrogen atoms) are independently replaced with the same or different heteroatom. Examples of heteroatoms to replace the carbon atom(s) include, but are not limited to, N, P, O, S and Si. Where a specific level of saturation is intended, the nomenclature "cy cloheteroaryl" or "cy cloheteroarylalkyl" is used. Examples of cycloheteroarylalkyl groups include, but are not limited to, groups derived from epoxides, azirines, thiranes, imidazolidine, morpholine, piperazine, piperidine, pyrazoline, pyrrolidine, quinuclidine.

[0058] "Dialkylamino" by itself or as part of another substituent refers to the radical NR^{48}R^{49} where R^{48} and R^{49} are independently alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, cyclohexylalkyl, substituted cyclohexylalkyl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, or substituted heteroarylalkyl, or R^{48} and R^{49} together with the nitrogen to which they are attached form a cycloalkyl or substituted cycloalkyl ring. In certain embodiments, a dialkylamino group is C_{1-3} dialkylamino.

[0059] "1-Haloalkyl carbamate" refers to an N-1-haloalkoxycarbonyl derivative of tranexamic acid as encompassed by compounds of Formula (II) disclosed herein.

[0060] "Heteroaryl" by itself or as part of another substituent refer to an alkyl group in which one or more of the carbon atoms (and any associated hydrogen atoms) are independently replaced with the same or different heteroatomic groups. Examples of heteroatomic groups include -O-, -S-, -O-O-, -S-S-, -O-S-, =N-N=, -N=N-, -N=N-NR^{52}R^{53}, -PR^{54}-, -P(O)_{2}-, -POR^{55}-, -OP(O)_{2}-, -SO-, -SO_{2}-, -SnR^{56}R^{57}-, where R^{51}, R^{53}, R^{55}, R^{56}, R^{57}, and R^{58} independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, cyclohexylalkyl, substituted cyclohexylalkyl, cyclohexylalkyl, substituted cyclohexylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, or substituted heteroarylalkyl. Where a specific level of saturation is intended, the nomenclature "heteroaryalkyl," "heteroalkenyl," or "heteroalkynyl" is used.

[0061] "Heteroaryl" by itself or as part of another substituent refers to a monovalent heteroaromatic radical derived by the removal of one hydrogen atom from a single atom of a parent heteroaromatic ring system. Heteroaryl encompasses multiple ring systems having at least one aromatic ring fused to at least one other ring, which may be aromatic or non-aromatic in which at least one ring atom is a heteroatom. Heteroaryl encompasses 5- to 7-membered aromatic, monocyclic rings containing one or more, for example, from 1 to 4, or in certain embodiments, from 1 to 3, heteroatoms chosen from N, O, and S, with the remaining ring atoms being carbon; and bicyclic heterocycloalkyl rings containing one or more, for example, from 1 to 4, or in certain embodiments, from 1 to 3, heteroatoms chosen from N, O, and S, with the remaining ring atoms being carbon and wherein at least one heteroatom is present in an aromatic ring. For example, heteroaryl includes a 5- to 7-membered heterocycloalkyl, aromatic ring fused to a 5- to 7-membered cycloalkyl ring. For such fused, bicyclic heteroaryl ring systems wherein only one of the rings contains one or more heteroatoms, the point of attachment may be at the heteroaromatic ring or the cycloalkyl ring. In certain embodiments, when the total number of N, S, and O atoms in the heteroaryl group exceeds one, the heteroatoms are not adjacent to one another. In certain embodiments, the total number of N, S, and O atoms in the heteroaryl group is not more than two. In certain embodiments, the total number of N, S, and O atoms in the aromatic heterocycle is not more than one. Heteroaryl does not encompass or overlap with aryl as defined herein.

[0062] Examples of heteroaryl groups include groups derived from acridine, arsindole, carbazole, β-carboline, chromane, chromene, cinnoline, furan, imidazole, indazole, indole, indoline, indolizine, isobenzofuran, isochromene, isocinole, isoindole, isouinoline, isothiazole, isoxazole, naphthyridine, oxadiazole, oxazole, perimidine, phenanthridine, phenanthrolines, phenazine, phthalazine, pteridine, pyrine, pyrazine, pyrazole, pyridazine, pyridine, pyrimidine, pyrrole, pyrrolizine, quinazoline, quinoline, quinolinine, quinoxaline, tetrazole, thiadiazole, thiazole, thiophene, triazole, xanthene. In certain embodiments, a heteroaryl group is from 5- to 20-membered heteroaryl, and in certain embodiments from 5- to 10-membered heteroaryl. In certain embodiments heteroaryl groups are those derived from thiophene, pyrrole, benzo thiophene, benzofuran, indole, pyridine, quinoline, imidazole, oxazole, and pyrazine.

[0063] "Heteroarylalkyl" by itself or as part of another substituent refers to an acyclic alkyl radical in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or sp{sup 3} carbon atom, is replaced with a heteroaryl group. Where specific alkyl moieties are intended, the nomenclature heteroarylalkyl, heteroarylalkenyl, or heteroarylalkynyl is used. In certain embodiments, a heteroarylalkyl group is a 6- to 30-membered heteroarylalkyl, e.g., the alkanyl, alkenyl, or alkynyl moiety of the heteroarylalkyl is 1- to 10-membered and the heteroaryl moiety is 5- to 20-membered heteroaryl, and in certain embodiments, 6- to 20-membered heteroarylalkyl, e.g., the alkanyl, alkenyl, or alkynyl moiety of the heteroarylalkyl is 1- to 8-membered and the heteroaryl moiety is 5- to 12-membered heteroaryl.
10

[0064] "Immediately preceding embodiments" means the embodiments disclosed in the same paragraph.

[0065] "Parent aromatic ring system" refers to an unsaturated cyclic or polycyclic ring system having a conjugated π electron system. Included within the definition of "parent aromatic ring system" are fused ring systems in which one or more of the rings are aromatic and one or more of the rings are saturated or unsaturated, such as, fluorene, indane, indene, phenalene. Examples of parent aromatic ring systems include aceanthrylene, acenaphthylene, acephenanthrylene, anthracene, azulene, benzene, chrysene, coronene, fluoranthene, fluorene, hexacene, hexalene, as-indacene, α-indacene, indane, indene, naphthalene, octacene, octaphene, octalene, ovalene, penta-2,4-diene, pentaacene, pentalene, pentaphene, perylene, phenalene, phenanthrene, picene, pleiadene, pyrene, pyranthrene, rubicene, triphenylene, triphenalene.

[0066] "Parent heteroaromatic ring system" refers to a parent aromatic ring system in which one or more carbon atoms (and any associated hydrogen atoms) are independently replaced with the same or different heteroatom. Examples of heteroatoms to replace the carbon atoms include N, P, O, S, Si. Specifically included within the definition of "parent heteroaromatic ring systems" are fused ring systems in which one or more of the rings are aromatic and one or more of the rings are saturated or unsaturated, such as, arsindole, benzodioxan, benzofuran, chromane, chromone, indole, indoline, xanthene. Examples of parent heteroaromatic ring systems include arsindole, carbazole, β-carboline, chromane, chromene, cinnoline, furan, imidazole, indazole, indole, indoline, indolizine, isobenzofuran, isochromene, isoindole, isoindoline, isoquinoline, isothiazole, isoaxazole, naphthyridine, oxadiazole, oxazole, perimidine, phenanthridine, phenanthrolene, phenazine, phthalazine, piperidine, purine, pyran, pyrazine, pyrazole, pyridazine, pyridine, pyrimidine, pyrole, pyrrole, quinazoline, quinolone, quinoxaline, tetrazole, thiazole, thiophene, triazole, xanthene.

[0067] "Patient" includes mammals, such as for example, humans.

[0068] "Pharmaceutical composition" refers to at least one compound and a pharmaceutically acceptable vehicle, with which the compound is administered to a patient.

[0069] "Pharmaceutically acceptable" refers to approved or approvable by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopoeia or other generally recognized pharmacopoeia for use in animals, including humans.

[0070] "Pharmaceutically acceptable salt" refers to a salt of a compound which possesses the desired pharmacological activity of the parent compound. Such salts include: (1) acid addition salts, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid; or formed with organic acids such as acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethane-disulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 1,2-ethanesulfonyl acid, 2-hydroxyethanesulfonyl acid, 4-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, 4-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo[2.2.2]-oct-2-ene-1-carboxylic acid, glucoheptonic acid, 3-phenylpropionic acid, trimethyleacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid; or (2) salts formed when an acidic proton present in the parent compound is replaced by a metal ion, e.g., an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base such as ethanolidine, diethanolamine, triethanolamine, N-methylglucamine.

[0071] "Pharmaceutically acceptable vehicle" refers to a pharmaceutically acceptable diluent, a pharmaceutically acceptable adjuvant, a pharmaceutically acceptable excipient, a pharmaceutically acceptable carrier, or a combination of any of the foregoing with which a compound of the present disclosure may be administered to a patient and which does not destroy the pharmacological activity thereof and which is nontoxic when administered in doses sufficient to provide a therapeutically effective amount of the compound.

[0072] "Protecting group" refers to a grouping of atoms, which when attached to a reactive group in a molecule masks, reduces, or prevents that reactivity. Examples of protecting groups can be found in Green et al., "Protective Groups in Organic Chemistry," (Wiley, 2nd ed. 1991) and Harrison et al., "Compendium of Synthetic Organic Methods," Vols. 1-8 (John Wiley and Sons, 1971-1996). Examples of amino protecting groups include, but are not limited to, formyl, acetyl, trifluoroacetyl, benzyl, benzoxycarbonyl (CBZ), tert-butoxycarbonyl (Boc), trimethylsilyl (TMS), 2-trimethylsilyl-ethanesulfonyl (SES), trityl and substituted trityl groups, alloxycarbonyl, 9-fluorenlymethylxycarbonyl (FMOC), nitroveratryloxycarbonyl (NVOC). Examples of hydroxy protecting groups include those in which the hydroxy group is either acylated or alkylated such as benzyl, and trityl ethers as well as alkyl ethers, tetrahydropyranyl ethers, trialkylsilyl ethers,
"Solvate" refers to a molecular complex of a compound with one or more solvent molecules in a stoichiometric or non-stoichiometric amount. Such solvent molecules are those commonly used in the pharmaceutical art, which are known to be innocuous to the recipient, e.g., water, ethanol. A molecular complex of a compound or moiety of a compound and a solvent can be stabilized by non-covalent intra-molecular forces such as, electrostatic forces, van der Waals forces, or hydrogen bonds. The term "hydrate" refers to a complex where the one or more solvent molecules are water including monohydrates and hemi-hydrates.

"Substantially one enantiomer" refers to a compound containing 1 or more stereogenic centers such that the enantiomeric excess (e.e.) of the compound is at least about 90%, in certain embodiments greater than about 95%, in certain embodiments greater than about 98%, and in certain embodiments greater than about 99%.

Each substituent is independently selected from C1-3 alkyl, -OH, -NH2, -SH, C1-3 alkoxy, C1-3 acyl, C1-3 thioalkyl, C1-3 alkoxycarbonyl, C1-3 alkylamino, and C1-3 dialkylamino, as defined herein.

"Thioalkyl" by itself or as part of another substituent refers to a radical -SR67 where R67 is alkyl or substituted alkyl, as defined herein. In certain embodiments, a thioalkyl group is C1-3 thioalkyl.

"Treating" or "treatment" of any disease or disorder refers to arresting or ameliorating a disease, disorder, or at least one of the clinical symptoms of a disease or disorder, reducing the risk of acquiring a disease, disorder, or at least one of the clinical symptoms of a disease or disorder, reducing the development of a disease, disorder or at least one of the clinical symptoms of a disease or disorder, or reducing the risk of developing a disease or disorder or at least one of the clinical symptoms of a disease or disorder. "Treating" or "treatment" also refers to inhibiting the disease or disorder, either physically, (e.g., stabilization of a discernible symptom), physiologically, (e.g., stabilization of a physical parameter), or both, and to inhibiting at least one physical parameter which may or may not be discernible to the patient. In certain embodiments, "treatment" or "treatment" refers to delaying the onset of the disease or disorder or at least one or more symptoms thereof in a patient which may be exposed to or predisposed to a disease or disorder even though that patient does not yet experience or display symptoms of the disease or disorder.

"Theraeutically effective amount" refers to the amount of a compound that, when administered to a subject for treating a disease or disorder, or at least one of the clinical symptoms of a disease or disorder, is sufficient to affect such treatment of the disease, disorder, or symptom. The "therapeutically effective amount" may vary depending, for example, on the compound, the disease, disorder, and/or symptoms of the disease or disorder, severity of the disease, disorder, and/or symptoms of the disease or disorder, the age, weight, and/or health of the patient to be treated, and the judgment of the prescribing physician. An appropriate amount in any given instance may be readily ascertained by those skilled in the art or capable of determination by routine experimentation.

"Trialkylsilyl" by itself or as part of another substituent refers to a radical -SiR68R69R70 where R68, R69, and R70 are independently selected from alkyl and substituted alkyl, as defined herein. In certain embodiments, a trialkylsilyl group is C3-12 trialkylsilyl.

**Compounds**

Certain embodiments of the present disclosure provide a compound of Formula (I)"
of C<sub>1</sub>-<sub>3</sub> alkyl, -OH, -NH<sub>2</sub>, -SH, C<sub>1</sub>-<sub>3</sub> alkoxy, C<sub>1</sub>-<sub>3</sub> acyl, C<sub>1</sub>-<sub>3</sub> thioalkyl, C<sub>1</sub>-<sub>3</sub> alkoxy carbonyl, C<sub>1</sub>-<sub>3</sub> alkylamino, and C<sub>1</sub>-<sub>3</sub> dialkylamino.

In certain embodiments of a compound of Formula (I), R<sup>1</sup> is selected from C<sub>1</sub>-<sub>4</sub> alkyl, substituted C<sub>1</sub>-<sub>4</sub> alkyl, phenyl, substituted phenyl, cyclohexyl, and substituted cyclohexyl. Each substituent group of R<sup>1</sup> is independently selected from at least one of C<sub>1</sub>-<sub>3</sub> alkyl, -OH, -NH<sub>2</sub>, -SH, C<sub>1</sub>-<sub>3</sub> alkoxy, C<sub>1</sub>-<sub>3</sub> acyl, C<sub>1</sub>-<sub>3</sub> thioalkyl, C<sub>1</sub>-<sub>3</sub> alkoxy carbonyl, C<sub>1</sub>-<sub>3</sub> alkylamino, and C<sub>1</sub>-<sub>3</sub> dialkylamino.

In certain embodiments of a compound of Formula (I), R<sup>2</sup> and R<sup>3</sup> are independently selected from hydrogen, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, phenyl, o-tolyl, and cyclohexyl.

In certain embodiments of a compound of Formula (I), R<sup>4</sup> is selected from hydrogen, methyl, ethyl, n-propyl, isopropyl, phenyl, and cyclohexyl.

In certain embodiments of a compound of Formula (I), R<sup>2</sup> and R<sup>3</sup> are independently selected from hydrogen, methyl, ethyl, n-propyl, isopropyl, phenyl, and cyclohexyl. In certain embodiments of a compound of Formula (I), R<sup>2</sup> is hydrogen, and R<sup>3</sup> is selected from methyl, ethyl, n-propyl, isopropyl, phenyl, and cyclohexyl.

In certain embodiments of a compound of Formula (I), R<sup>1</sup> is selected from methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, phenyl, o-tolyl, and cyclohexyl. R<sup>2</sup> is hydrogen, and R<sup>3</sup> is selected from hydrogen, methyl, ethyl, n-propyl, isopropyl, phenyl, and cyclohexyl. In certain embodiments of a compound of Formula (I), R<sup>1</sup> is selected from methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, phenyl, o-tolyl, and cyclohexyl, R<sup>2</sup> is hydrogen, and R<sup>3</sup> is selected from methyl, ethyl, n-propyl, isopropyl, phenyl, and cyclohexyl.

In certain embodiments of a compound of Formula (I), R<sup>2</sup> is hydrogen. In certain embodiments of a compound of Formula (I), each of R<sup>2</sup> and R<sup>3</sup> is other than hydrogen. When each of R<sup>2</sup> and R<sup>3</sup> is hydrogen, a metabolite of certain acyloxyalkylcarbamate promoieties may be formaldehyde. In some embodiments for methods of treatment comprising administering large amounts of a compound of Formula (I) it may be desirable that the amount of toxic metabolites of the promoiety such as formaldehyde be minimized or eliminated.

In certain embodiments of a compound of Formula (I), the compound is selected from:

trans-4-[(2-Methylpropanoyloxy)methoxycarbonyl]aminomethyl]-cyclohexanecarboxylic acid;
trans-4-[(2,2-Dimethylpropanoyloxy)methoxycarbonyl]aminomethyl]-cyclohexanecarboxylic acid;
trans-4-[(3-Methylbutanoyloxy)methoxycarbonyl]aminomethyl]-cyclohexanecarboxylic acid;
trans-4-[(Benzyloxoy)methoxycarbonyl]aminomethyl]-cyclohexanecarboxylic acid;
trans-4-[(3-Methylbutanoyloxy)methoxycarbonyl]aminomethyl]-cyclohexanecarboxylic acid;
trans-4-[(2,2-Dimethylpropanoyloxy)propoxy]carbonyl] aminomethyl] - cyclohexanecarboxylic acid;
trans-4-[(1-(2-Methylpropanoyloxy)-2-methylpropoxycarbonyl]aminomethyl] - cyclohexanecarboxylic acid;
trans-4-[(1-(2-Methylpropanoyloxy)-2-methylpropoxycarbonyl]aminomethyl] - cyclohexanecarboxylic acid;
trans-4-[(1-(2-Methylpropanoyloxy)-2-methylpropoxycarbonyl]aminomethyl] - cyclohexanecarboxylic acid;
trans-4-[(1-(2-Methylpropanoyloxy)-2-methylpropoxycarbonyl]aminomethyl] - cyclohexanecarboxylic acid;
trans-4-[(1-(2-Methylpropanoyloxy)-2-methylpropoxycarbonyl]aminomethyl] - cyclohexanecarboxylic acid;
trans-4-[(1-(2-Methylpropanoyloxy)-2-methylpropoxycarbonyl]aminomethyl] - cyclohexanecarboxylic acid;
trans-4-[(1-(2-Methylpropanoyloxy)-2-methylpropoxycarbonyl]aminomethyl] - cyclohexanecarboxylic acid;
trans-4-[(1-(2-Methylpropanoyloxy)-2-methylpropoxycarbonyl]aminomethyl] - cyclohexanecarboxylic acid;
trans-4-[(1-(2-Methylpropanoyloxy)-2-methylpropoxycarbonyl]aminomethyl] - cyclohexanecarboxylic acid;
trans-4-[(1-Cyclohexylcarbonyloxy)ethoxycarbonyl]aminomethyl]-cyclohexanecarboxylic acid;
trans-4-[(1-Benzoyloxy)ethoxycarbonyl]aminomethyl]-cyclohexanecarboxylic acid;
trans-4-[(1-2-Methylbenzoyloxy)ethoxycarbonyl]aminomethyl]-cyclohexanecarboxylic acid;
trans-4-[(1-Butanoyloxy)butoxycarbonyl]aminomethyl]-cyclohexanecarboxylic acid;
trans-4-[(1-3-Methylbutanoyloxy)butoxycarbonyl]aminomethyl]-cyclohexanecarboxylic acid;
trans-4-[(1-2,2-Dimethylpropanoyloxy)butoxycarbonyl]aminomethyl]-cyclohexanecarboxylic acid;
trans-4-[(1-Benzoyloxy)butoxycarbonyl]aminomethyl]-cyclohexanecarboxylic acid;
trans-4-[(1-Propionyloxy)propoxycarbonyl]aminomethyl]-cyclohexanecarboxylic acid;
trans-4-[(1-Butanoyloxy)propoxycarbonyl]aminomethyl]-cyclohexanecarboxylic acid;
trans-4-[(1-2,2-Dimethylpropanoyloxy)propoxycarbonyl]aminomethyl]-cyclohexanecarboxylic acid;
trans-4-[(1-Benzyloxy)propoxycarbonyl]aminomethyl]-cyclohexanecarboxylic acid;
trans-4-[(1-Propanoyloxy)propoxycarbonyl]aminomethyl]-cyclohexanecarboxylic acid;
trans-4-[(1-Butanoyloxy)2-methylpropoxycarbonyl]aminomethyl]-cyclohexanecarboxylic acid;
trans-4-[(1-Propionyloxy)2-methylpropoxycarbonyl]aminomethyl]-cyclohexanecarboxylic acid;
trans-4-[(1-Acetoxy)ethoxycarbonyl]aminomethyl]-cyclohexanecarboxylic acid;
trans-4-[(1-Propanoyloxy)ethoxycarbonyl]aminomethyl]-cyclohexanecarboxylic acid;
trans-4-[(1-Butanoyloxy)-1-cyclohexylmethoxycarbonyl]aminomethyl]-cyclohexanecarboxylic acid;
trans-4-[(1-Benzyloxy)-1-cyclohexylmethoxycarbonyl]aminomethyl]-cyclohexanecarboxylic acid;
trans-4-[(1-2-Methylpropanoyloxy)-1-cyclohexylmethoxycarbonyl]aminomethyl]-cyclohexanecarboxylic acid;
trans-4-[(1-Propionyloxy)1-cyclohexylmethoxycarbonyl]aminomethyl]-cyclohexanecarboxylic acid;
trans-4-[(1-Acetoxy)butoxycarbonyl]aminomethyl]-cyclohexanecarboxylic acid;
trans-4-[(1-Propanoyloxy)butoxycarbonyl]aminomethyl]-cyclohexanecarboxylic acid;
trans-4-[(1-2,2-Dimethylpropanoyloxy)butoxycarbonyl]aminomethyl]-cyclohexanecarboxylic acid;
trans-4-[(1-Acetoxy)butoxycarbonyl]aminomethyl]-cyclohexanecarboxylic acid;
trans-4-[(1-Propanoyloxy)propoxycarbonyl]aminomethyl]-cyclohexanecarboxylic acid;
trans-4-[(1-2-Methylpropanoyloxy)propoxycarbonyl]aminomethyl]-cyclohexanecarboxylic acid;
trans-4-[(1-Acetoxy)propoxycarbonyl]aminomethyl]-cyclohexanecarboxylic acid;
trans-4-[(1-Propanoyloxy)propoxycarbonyl]aminomethyl]-cyclohexanecarboxylic acid;
trans-4-[(1-2,2-Dimethylpropanoyloxy)propoxycarbonyl]aminomethyl]-cyclohexanecarboxylic acid;
trans-4-[(1-Acetoxy)propoxycarbonyl]aminomethyl]-cyclohexanecarboxylic acid;
trans-4-[(1-Propanoyloxy)propoxycarbonyl]aminomethyl]-cyclohexanecarboxylic acid;
including pharmaceutically acceptable salts thereof and pharmaceutically acceptable solvates of any of the foregoing.

A compound of Formula (II) is described therein:

![Chemical Structure](image)

X is selected from fluoro, chloro, and R²SO₃⁻ wherein R²⁺ is selected from C₁-₆ alkyl, C₅-₇ aryl, and substituted C₅-₇ aryl. The parameters R₂ to R₄ are as defined above.

In certain embodiments of a compound of Formula (II), X is chloro.

In certain embodiments of a compound of Formula (II), R² is selected from hydrogen, C₁-₆ alkyl, substituted C₁-₆ alkyl, C₃-₇ cycloalkyl, substituted C₃-₇ cycloalkyl, C₆-₁₀ aryl, substituted C₆-₁₀ aryl, C₇-₁₆ arylalkyl, substituted C₇-₁₆ arylalkyl, C₁₂-₁₈ trialkylsilyl, and C₁₇-₁₄ arylalkylsilyl. Each substituent group of R² is independently selected from at least one of C₁-₃ alkyl, -OH, NH₂, -SH, C₁-₃ alkoxy, C₁-₃ acyl, C₁-₃ thioalkyl, C₁-₃ alkoxycarbonyl, C₁-₃ alkyloxyamino, and C₁-₃ dialkylamino.

In certain embodiments of a compound of Formula (II), R³ is selected from hydrogen, methyl, ethyl, tert-butyl, allyl, benzyl, 4-methoxybenzyl, diphenylmethyl, triphenylmethyl, triethysilyl, trisopropylsilyl, tert-butyldimethylsilyl, and phenyldimethylsilyl.

In certain embodiments of a compound of Formula (II), R⁴ is selected from hydrogen, allyl, benzyl, and trimethylsilyl.

In certain embodiments of a compound of Formula (II), R⁴ is hydrogen.

R² and R³ are independently selected from hydrogen, C₁-₆ alkyl, substituted C₁-₆ alkyl, C₆-₁₀ aryl, substituted C₆-₁₀ aryl, C₃-₇ cycloalkyl, and substituted C₃-₇ cycloalkyl. Each substituent group of R² and/or R³ is independently selected from at least one of C₁-₃ alkyl, -OH, NH₂, -SH, C₁-₃ alkoxy, C₁-₃ acyl, C₁-₃ thioalkyl, C₁-₃ alkoxycarbonyl, C₁-₃ alkylamino, and C₁-₃ dialkylamino.

In certain embodiments of a compound of Formula (II), R² and R³ are independently selected from hydrogen,
In certain embodiments of a compound of Formula (II), R² is hydrogen, and R³ is selected from hydrogen, methyl, ethyl, n-propyl, isopropyl, phenyl, and cyclohexyl.

In certain embodiments of a compound of Formula (II), R² and R³ are independently selected from hydrogen, C₁₋₆ alkyl, substituted C₁₋₆ alkyl, C₆₋₁₀ aryl, substituted C₆₋₁₀ aryl, C₃₋₇ cycloalkyl, and substituted C₃₋₇ cycloalkyl, and R⁴ is selected from hydrogen, C₁₋₆ alkyl, substituted C₁₋₆ alkyl, C₃₋₇ cycloalkyl, substituted C₃₋₇ cycloalkyl, C₆₋₁₀ aryl, substituted C₆₋₁₀ aryl, C₇₋₁₆ arylalkyl, substituted C₇₋₁₆ arylalkyl, C₁₋₁₂ trialkylsilyl, and substituted C₁₋₁₂ trialkylsilyl. In certain of the immediately preceding embodiments, each substituent group of R² and/or R³ is independently selected from at least one of C₁₋₃ alkyl, -OH, NH₂, -SH, C₁₋₃ alkoxy, C₁₋₃ acyl, C₁₋₃ thioalkyl, C₁₋₃ alkoxy carbonyl, C₁₋₃ alkylamino, and C₁₋₃ dialkylamino.

In certain embodiments of a compound of Formula (II), R² is hydrogen, R³ is selected from hydrogen, methyl, ethyl, n-propyl, isopropyl, phenyl, and cyclohexyl, and R⁴ is hydrogen.

Compounds of Formula (II) are useful intermediates in the synthesis of compounds of Formula (I) as described below.

**Synthesis**

Compounds of the present disclosure may be obtained via the synthetic methods illustrated in Schemes 1-9. Those of ordinary skill in the art will appreciate that a synthetic route to the disclosed compounds consists of attaching promoieties to tranexamic acid.


Accordingly, starting materials useful for preparing compounds and intermediates thereof, and/or for practicing methods described herein are commercially available or may be prepared by well-known synthetic methods. Accordingly, the methods presented in the Schemes herein are illustrative.

Intermediate (V), useful in the preparation of 1-haloalkyl carbamates of Formula (II), may be generated according to the reactions detailed in Scheme 1:
The amino group of tranexamic acid is protected under standard conditions with a protecting group (Pg) to afford compound (VII). The carboxylic acid moiety of compound (VII) is esterified to yield compound (VIII), either via alkylation or silylation with R^4 -X, where X is selected from fluoro, chloro, bromo, iodo, and R^{20}SO_3^- wherein R^{20} is selected from C_{1-6} alkyl, C_{5-7} aryl, and substituted C_{5-7} aryl, or any other suitable leaving group, or via condensation with alcohol R^4-OH under standard acylation conditions (e.g., in the presence of a coupling agent such as a carbodiimide, via an acyl halide, acid anhydride, or other activated ester intermediate). Removal of the protecting group from compound (VIII) under standard deprotection conditions affords compound (V).

In certain embodiments, a compound of Formula (II) is prepared by acylation of compound (V) with compound (IX) (see Scheme 2), where X is a halide and Z is a leaving group (e.g., halide, p-nitrophenolate, imidazolyl, etc.). In certain embodiments, X is F, Cl, Br, or I. In some of these embodiments, Z is Cl. In certain embodiments, X and Z are each Cl. The acylation reaction may be performed in the presence of an inorganic base or an organic base (e.g., tertiary amine bases, such as triethylamine, tributylamine, disopropylethylamine, dimethylisopropylamine, N-methylmorpholine, N-methylpyrrolidine, N-methylpiperidine, pyridine, 2-methylpyridine, 2,6-dimethylpyridine, 4-dimethylaminopyridine, 1, 4-diazabicyclo[2.2.2]octane, 1,8-diazabicyclo[5.4.0]undeca-7-ene or 1,5-diazabicyclo[4.3.0]undeca-7-ene), and combinations of any of the foregoing. Suitable solvents for acylation include dichloromethane, dichloroethane, chloroform, toluene, dimethylformamide, dimethylacetamide, N-methylpyrrolidinone, dimethyl sulfoxide, pyridine, ethyl acetate, isopropyl acetate, acetonitrile, acetone, 2-butanol, methyl tert-butyl ether, and combinations of any of the foregoing. Alternatively, biphasic solvent mixtures comprising water and including one or more of dichloromethane, dichloroethane, chloroform, toluene, ethyl acetate, isopropyl acetate, or methyl tert-butyl ether, can be utilized. Temperatures for performing the reaction of Scheme 2 can range from about -20°C to about 50 °C, and in certain embodiments can range from about -20°C to about 25 °C.
In certain embodiments, a compound of Formula (II), where R^4 is trialkylsilyl or aryldialkylsilyl, can be prepared directly from tranexamic acid by silylation (e.g., using a silyl halide or silylamide reagent) followed by acylation of the resulting intermediate with compound (IX) (see Scheme 3). Suitable solvents for performing this reaction include dichloromethane, dichloroethane, chloroform, toluene, pyridine, acetonitrile, and combinations of any of the foregoing. Suitable bases for performing this reaction include triethylamine, tributylamine, diisopropylethylamine, dimethylisopropylamine, N-methylmorpholine, N-methylpyrrolidine, N-methylpiperidine, pyridine, 2-methylpyridine, 2,6-dimethylpyridine, 4-dimethylaminopyridine, 1,4-diazabicyclo[2.2.2]octane, 1, 8-diazabicyclo[5.4.0]undec-7-ene, 1,5-diazabicyclo[4.3.0]undec-7-ene, and combinations of any of the foregoing. Temperatures for performing the reaction of Scheme 3 can range from about -78 °C to about 50 °C, and in certain embodiments can range from about -20 °C to about 25 °C.

In certain embodiments, N-1-acyloxyalkyl carbamates of Formula (I) can be prepared from compounds of Formula (II) by treatment with carboxylic acids of Formula (III) in the presence of an organic or inorganic base, or other metal salt, as illustrated in Scheme 4.

Parameters R_1 to R_4 are as defined above.
In certain embodiments of compounds of Formulae (I), (II), and (III) in the method of Scheme 4, X is chloro, R₁ is selected from methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, phenyl, o-tolyl, and cyclohexyl, R₂ is hydrogen, R₃ is selected from hydrogen, methyl, ethyl, n-propyl, isopropyl, phenyl, and cyclohexyl, and R₄ is hydrogen.

In certain embodiments of the method of Scheme 4, the ratio of a compound of Formula (II) to a compound of Formula (III) can range from about 1:1 to about 1:20. In certain embodiments, the ratio of a compound of Formula (II) to a compound of Formula (III) can range from about 1:1 to about 1:5. In certain embodiments, the ratio of a compound of Formula (II) to a compound of Formula (III) is about 1:1.

In certain embodiments of the method of Scheme 4, compounds of Formulae (II) and (III) and a metal salt are contacted with a solvent. In certain embodiments in which a compound of Formula (I), a compound of Formula (II) and a metal salt are contacted with a solvent, the ratio of a compound of Formula (II) to a compound of Formula (III) can range from about 1:1 to about 1:20, in certain embodiments, from about 1:1 to about 1:5, and in certain embodiments, the ratio of a compound of Formula (II) to a compound of Formula (III) is about 1:1. In certain embodiments, the solvent can be dichloromethane, dichloroethane, chloroform, toluene, dimethylformamide, dimethylacetamide, N-methylpyrrolidinone, dimethyl sulfoxide, pyridine, ethyl acetate, acetonitrile, acetone, 2-butaneone, methyl tert-butyl ether, methanol, ethanol, isopropanol, tert-butanol, water, hexamethylphosphoramide, and combinations of any of the foregoing. In certain embodiments, the metal salt can be a salt of Ag, Hg, Na, K, Li, Cs, Ca, Mg, Zn, and combinations of any of the foregoing.

In certain embodiments of the method of Scheme 4, compounds of Formulae (II) and (III) and an organic base are contacted with a solvent. In certain embodiments in which a compound of Formula (II), a compound of Formula (III) and an organic base are contacted with a solvent, the ratio of a compound of Formula (II) to a compound of Formula (III) can range from about 1:1 to about 1:20, in certain embodiments, from about 1:15 to about 1:20, and in certain embodiments, can range from about 1:1 to about 1:5. In certain embodiments in which a compound of Formula (II), a compound of Formula (III) and an organic base are contacted with a solvent, the ratio of a compound of Formula (II) to a compound of Formula (III) is about 1:1, and in certain embodiments, is about 1:10. In some embodiments, the solvent can be dichloromethane, dichloroethane, chloroform, toluene, dimethylformamide, dimethylacetamide, N-methylpyrrolidinone, dimethyl sulfoxide, pyridine, ethyl acetate, acetonitrile, acetone, 2-butaneone, methyl tert-butyl ether, methanol, ethanol, isopropanol, tert-butanol, water, hexamethylphosphoramide, and combinations of any of the foregoing. In certain embodiments, the organic base can be triethylamine, tributylamine, diisopropylethylamine, dimethylisopropylamine, N-methylmorpholine, N-methylpyrrolidine, N-methylpiperidine, pyridine, 2-methylpyridine, 2,6-dimethylpyridine, 4-dimethylaminopyridine, 1,4-diazabicyclo[2.2.2]octane, 1,8-diazabicyclo[5.4.0]undec-7-ene, 1,5-diazabicyclo[4.3.0]undec-7-ene, and combinations of any of the foregoing.

In some embodiments of the method of Scheme 4, a compound of Formula (III) is a liquid under the conditions of contacting with a compound of Formula (II). In certain embodiments, a compound of Formula (III) further serves as a solvent for the reaction with a compound of Formula (II). In certain embodiments, a compound of Formula (III) can be acetic acid, methoxyacetic acid, ethoxyacetic acid, propionic acid, butyric acid, isobutyric acid, pivalic acid, valeric acid, isovaleric acid, 2-methylbutyric acid, cyclobutanecarboxylic acid, cyclopentanecarboxylic acid, or cyclohexanecarboxylic acid.

In some embodiments of the method of Scheme 4, a compound of Formula (II), a compound of Formula (III), and a metal salt can be contacted at a temperature ranging from about -25°C to about 120 °C. In certain embodiments, the temperature can range from about 0 °C to about 5 °C.

In certain other embodiments of the method of Scheme 4, a compound of Formula (II), a compound of Formula (III), and an organic base can be contacted at a temperature ranging from about -25°C to about 120 °C. In certain embodiments, the temperature can range from about 0 °C to about 25 °C.

In some embodiments of the method of Scheme 4, a compound of Formula (II), a compound of Formula (III), and an organic base can be contacted with a catalytic amount of an iodide salt. In certain embodiments, the iodide salt can be sodium iodide, potassium iodide, tetramethylammonium iodide, tetraethylammonium iodide, or tetrabutylammonium iodide.

In some embodiments of the method of Scheme 4, R₄ can be a carboxylic acid protecting group that can be removed under mild conditions to provide a compound of Formula (I) where R₄ is hydrogen. Carboxylic acid protecting groups removable via mild acidic hydrolysis, fluoride ion-promoted hydrolysis, catalytic hydrogenolysis, transfer hydrogenolysis, or other transition metal-mediated deprotection reactions can be used. In some embodiments, R₄ can be trimethylsilyl, allyl; or benzyl.

In certain embodiments, a compound of Formula (I) can be prepared as illustrated in Scheme 5.
Chloroformate (X) is treated with an aromatic leaving group such as p-nitrophenol in the presence of base to provide p-nitrophenylcarbonate (XI). Halide interchange provides iodide (XII), which is reacted with a metal or tetraalkylammonium salt of a carboxylic acid to afford compound (XIII). Treatment of (XIII) with tranexamic acid derivative (V), optionally in the presence of trimethylsilyl chloride, affords a compound of Formula (I).

Another method for synthesis of compounds of Formula (I) proceeds via carbonylation of tranexamic acid derivative (V) to an intermediate carboxylic acid species, which is captured by an in situ alkylation reaction in an adaptation of methods disclosed in the art (Butcher, Synlett, 1994, 825-6; Ferres et al., U.S. Patent 4,036,829). Carbon dioxide gas is bubbled into a solution containing tranexamic acid derivative (V) and a base (e.g., Cs$_2$CO$_3$, Ag$_2$CO$_3$, or AgO) in a solvent such as DMF or NMP. An activated halide is added, optionally, in the presence of iodide ion as a catalyst, and the carbonylation continued until the reaction is completed. This method is illustrated in Scheme 6 for the preparation of a compound of Formula (I) from halide (XIV).

can be beneficial since prodrugs of Formula (I) may be labile. Thus, performing the oxidation under anhydrous reaction conditions can avoid hydrolysis of the reactive products.

Parameters R₁ to R₄ are as defined above.

[0135] In certain embodiments of compounds of Formulae (I) and (XV) in the method of Scheme 7, R¹ is selected from methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, phenyl, o-tolyl, and cyclohexyl, R² is hydrogen, R³ is selected from hydrogen, methyl, ethyl, n-propyl, isopropyl, phenyl, and cyclohexyl, and R⁴ is hydrogen.

[0136] In the method of Scheme 7 oxidation can be performed in the liquid phase, and in certain embodiments, in the presence of a solvent. Choosing a solvent for oxidation of a compound of Formula (XV) is well within the ambit of one of skill in the art. Generally, a useful solvent will dissolve, at least partially, both the oxidant and a compound of Formula (XV) and will be inert to the reaction conditions. Useful solvents can be anhydrous and include, dichloromethane, dichloroethane, chloroform, ethyl acetate, isopropyl acetate, toluene, chlorobenzene, xylene, acetonitrile, diethyl ether, methyl tert-butyl ether, acetic acid, cyclohexane, and hexanes. Combinations of the above solvents can also be used in the oxidation of a compound of Formula (XV) to a compound of Formula (I).

[0137] In some embodiments, the anhydrous oxidant is an anhydrous peroxyacid generated in situ by reaction of a urea-hydrogen peroxide complex (UHP) with a carboxylic acid anhydride. In certain embodiments, the anhydrous oxidant is an anhydrous peroxyacidsulfonic acid generated in situ by reaction of a urea-hydrogen peroxide complex with a sulfonic acid anhydride. The UHP complex serves as a source of anhydrous hydrogen peroxide and has been used in a variety of oxidative transformations in anhydrous organic solvents (Cooper et al., Synlett., 1990, 533-535; Balicki et al., Synth. Commun., 1993, 23, 3149; Astudillo et al., Heterocycles, 1993, 36, 1075-1080; Varma et al., Org. Lett., 1999, 1, 189-191). However, other suitable sources of anhydrous hydrogen peroxide can also be used in the reaction instead of the UHP-complex (e.g., the 1,4-diazabicyclo[2.2.2]octane-hydrogen peroxide complex).

[0138] A useful oxidant is anhydrous peroxycarboxylic acid, generated in situ by reacting the UHP-complex with trifluorocarboxylic anhydride (Cooper et al., Synlett., 1990, 533-535; Benjamin et al., J. Am. Chem. Soc., 2002, 124, 827-833). Anhydrous peroxyacids (XVII) can be prepared by treating carboxylic acid anhydrides (XVI) with anhydrous hydrogen peroxide, and in certain embodiments, with the UHP-complex. Similarly, anhydrous peroxyacidsulfonic acids (XIX) can be prepared by reacting sulfonic acid anhydrides (XVIII) with anhydrous hydrogen peroxide, and in certain embodiments, with the UHP-complex. Preparation of anhydrous peroxyacids (XVII) and peroxyacidsulfonic acids (XIX) is illustrated in Scheme 8.
The UHP-complex and a carboxylic acid anhydride (XVI) or a sulfonic acid anhydride (XVIII) can be reacted in dichloromethane or other suitable solvent at temperatures ranging from about -25 °C to about 100 °C to generate the corresponding anhydrous peroxyacid oxidant. The peroxyacid oxidant can be generated first and subsequently reacted with a ketocarbamate (XV). In some embodiments, a carboxylic acid anhydride (XVI) is added to a stirred suspension or solution containing the UHP-complex and a ketocarbamate (XV) to generate the peroxycarboxylic acid, which reacts in situ with the ketocarbamate (XV) to give compound (I). In certain embodiments, the molar ratio of UHP-complex and carboxylic acid anhydride (XVI) is about 6:1. In certain embodiments, the molar ratio of UHP-complex and carboxylic acid anhydride (XVI) can range from about 5:1 to about 1:1. In certain embodiments, the molar ratio of UHP-complex and acid anhydride (XVI) can range from about 2:1 to about 1:1.

In some embodiments of the method of Scheme 8, the molar ratio of the peroxyacid oxidant to a compound of Formula (XV) can range from about 8:1 to about 1:1. In certain embodiments, the molar ratio of the peroxyacid oxidant to a compound of Formula (XV) can range from about 4:1 to about 1:1. In certain embodiments, the molar ratio of the peroxyacid oxidant to a compound of Formula (XV) can range from about 2:1 to about 1:1. In certain embodiments, when the oxidant is peroxytrifluoroacetic acid or another substituted peroxyacetic acid, the molar ratio of the peroxyacid oxidant to a compound of Formula (XV) is about 2:1.

Further, in the method of Scheme 8 the use of additives in the oxidation of a compound of Formula (XV) to a compound of Formula (I) is also contemplated. For example, additives can either catalyze the reaction or stabilize the final product or both. In some embodiments, a Lewis acid or a protic acid or any combination of Lewis acid or protic acid can be used in the oxidation of a compound of Formula (XV) and in certain embodiments, in the presence of a solvent. Examples of Lewis acids include, but are not limited to, BF₃, SeO₂, MeReO₃, MnO₂, SnCl₄, Sc(OTf)₃, Ti(O-Pr)₄, Al₂O₃, and Fe₂O₃. Examples of protic acids include, but are not limited to, trifluoroacetic acid, acetic acid, p-toluenesulfonic acid, methanesulfonic acid, trifluoromethanesulfonic acid, hydrochloric acid, and sulfuric acid. In certain embodiments,
the Lewis acid and/or protic acid can catalyze oxidation by increasing the electrophilicity of the carbonyl group in Formula (XV).

[0142] In certain embodiments of the method of Scheme 8, the oxidation can be conducted in the presence of an anhydrous base. In certain embodiments, the base can stabilize acid sensitive products by reacting with acidic by-products formed during oxidation.

[0143] Generally, in the method of Scheme 8 the temperature of the reaction can be optimized by methods known to those of ordinary skill in the art. In certain embodiments, the oxidation of a compound of Formula (XV) can be carried out at a temperature ranging from about -25 °C to about 100 °C, and in certain embodiments, from about 0 °C to about 25 °C.

[0144] A feature of this method of synthesis of a compound of Formula (I) is that oxidation of a ketocarbamate derivative (XV) proceeds stereospecifically, with retention of configuration at the carbon atom initially adjacent to the carbonyl group in the ketocarbamate derivative (XV). This stereospecificity can be exploited in a stereoselective synthesis of prodrug derivatives of Formula (I).

[0145] Another method for synthesis of a compound of Formula (I), illustrated in Scheme 9, relies upon reaction of tranexamic acid, or a compound of Formula (V), with a 1-(acyloxy)-alkyl N-hydroxysuccinimidyl carbonate compound of Formula (IV), as described in the co-pending application Gallop et al., U.S. Application Publication No. 2005/0222431:

![Scheme 9](image)

wherein R¹, R², R³ and R⁴ are as defined herein, and R⁵ and R⁶ are independently selected from hydrogen, acylamino, acyloxy, alkoxy carbonylamino, alkoxy carbonyloxy, alkyl, substituted alkyl, alkoxy, substituted alkoxy, ary1, substituted ary1, ary1alkyl, substituted ary1alkyl, carbamoyloxy, dialkylamino, heteroaryl, substituted heteroaryl, hydroxy, and sulfonamido, or R⁵ and R⁶ together with the atoms to which they are bonded form a substituted cycloalkyl, substituted cyclohexyloxyalkyl, or substituted ary1 ring. In certain of the immediately preceding embodiments, the substituent group of R¹, R², R³, R⁴, R⁵, and/or R⁶ is selected from at least one of C₁₋₃ alkyl, -OH, -NH₂, -SH, C₁₋₃ alkoxy, C₁₋₃ acyl, C₁₋₃ thioalkyl, C₁₋₃ alkoxy carbonyl, C₁₋₃ alkyamino, and C₁₋₃ dialkylamino.

[0146] In certain embodiments of compounds of Formula (I), (IV), and (V) of the method of Scheme 9, R¹ is selected from methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, phenyl, o-tolyl, and cyclohexyl, R² is hydrogen, R³ is selected from hydrogen, methyl, ethyl, n-propyl, phenyl, and cyclohexyl, R⁴ is hydrogen, and R⁵ and R⁶ are each hydrogen.

[0147] In some embodiments, the method of Scheme 9 can be carried out in a solvent. Useful solvents include, acetone, acetonitrile, dichloromethane, dichloroethane, chloroform, toluene, tetrahydrofuran, dioxane, dimethylformamide, dimethylacetamide, N-methylpyrrolidinone, dimethyl sulfoxide, pyridine, ethyl acetate, methyl tert-butyl ether, methanol, ethanol, isopropanol, tert-butanol, water, and combinations of any of the foregoing. In certain embodiments, the solvent can be acetone, acetonitrile, dichloromethane, toluene, tetrahydrofuran, pyridine, methyl tert-butyl ether, methanol, ethanol, isopropanol, tert-butanol, water, and combinations of any of the foregoing. In certain embodiments, the solvent can be a combination of acetone and water. In certain embodiments, the solvent can be a combination of acetone and water, with a volume ratio of acetone to water ranging from about 1:5 to about 5:1. In certain embodiments, the solvent can be a combination of methyl tert-butyl ether and water. In certain embodiments, the solvent can be a combination of methyl tert-butyl ether and water, with a volume ratio of methyl tert-butyl ether to water ranging from about 2:1 to about 20:1. In certain embodiments, the solvent can be a combination of methyl tert-butyl ether and water, wherein the methyl tert-butyl ether contains from about 10% to about 50% acetonitrile by volume. In certain embodiments, the solvent can be dichloromethane, water, or a combination thereof. In certain embodiments, the solvent is a biphasic combination of dichloromethane and water. In certain embodiments, the solvent can be a biphasic combination of dichloromethane and water containing from about 0.001 equivalents to about 0.1 equivalents of a phase transfer catalyst.

In certain embodiments, the phase transfer catalyst is a tetraalkylammonium salt, and in certain embodiments, the phase transfer catalyst is a tetraalkylammonium salt.

[0148] The method of Scheme 9 can be carried out at a temperature ranging from about -20 °C to about 40 °C. In certain embodiments, the temperature can range from about -20 °C to about 25 °C. In certain embodiments, the temperature
can range from about 0 °C to about 25 °C. In certain embodiments, the temperature can range from about 25 °C to about 40 °C.

In certain embodiments of the method of Scheme 9, the reaction can be performed in the absence of a base.

In certain embodiments of the method of Scheme 9, the reaction can be performed in the presence of an inorganic base. In some embodiments, the reaction can be performed in the presence of an alkali metal bicarbonate or alkali metal carbonate salt. In certain embodiments, the reaction can be performed in the presence of sodium bicarbonate.

In certain embodiments of the method of Scheme 9, the reaction can be performed in the presence of an organic base. In certain embodiments, the reaction can be performed in the presence of triethylamine, tributylamine, diisopropylethylamine, N-methylmorpholine, or pyridine. 2,6-dimethylpyridine, 4-dimethylaminopyridine, 1,4-diazabicyclo[2.2.2]octane, 1,8-diazabicyclo[5.4.0]undec-7-ene, 1,5-diazabicyclo[4.3.0]undec-7-ene, or a combination of any of the foregoing. In certain embodiments, the reaction can be performed in the presence of triethylamine, diisopropylethylamine, N-methylmorpholine, or pyridine.

Pharmaceutical Compositions

Pharmaceutical compositions comprising a therapeutically effective amount of one or more tranexamic acid prodrug compounds of Formula (I), optionally in purified form, together with suitable amounts of pharmaceutically acceptable vehicle, so as to provide a form for proper administration to a patient are provided herein. Suitable pharmaceutical vehicles include excipients such as starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol.

Compositions of the present disclosure, if desired, can also contain minor amounts of wetting agents, emulsifying agents, or pH buffering agents. In addition, auxiliary, stabilizing, thickening, lubricating, and coloring agents can be included.

Pharmaceutical compositions can be manufactured, for example, by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping, and lyophilizing processes. Pharmaceutical compositions can be formulated in a conventional manner using one or more physiologically acceptable carriers, diluents, excipients, and auxiliaries, which facilitate processing of compounds disclosed herein into preparations, which can be used pharmaceutically.

Proper formulation can be dependent upon the route of administration chosen.

The present pharmaceutical compositions can take the form of, for example, solutions, suspensions, emulsion, tablets, pills, melts, capsules, tablets containing liquids, powders, sustained-release formulations, suppositories, emulsions, aerosols, sprays, suspensions, or any other form suitable for use. In some embodiments, a pharmaceutically acceptable vehicle can be a capsule (see e.g., Grosswald et al., U.S. Patent No. 5,698,155). Other examples of suitable pharmaceutical vehicles have been described in the art (see Remington’s Pharmaceutical Sciences, Philadelphia College of Pharmacy and Science, 19th Edition, 1995). In some embodiments, compositions can be formulated for oral delivery, for example, oral sustained release administration. In certain embodiments, compositions can be formulated for topical delivery, and in certain embodiments, for topical sustained release administration.

Pharmaceutical compositions for oral delivery can be in the form of, for example, tablets, lozenges, aqueous or oily suspensions, granules, powders, emulsions, capsules, syrups, or elixirs, for example. Oral administration compositions can contain one or more optional agents, sweetening agents such as fructose, aspartame or succharin, flavoring agents such as peppermint, oil of wintergreen, cherry coloring agents, and preserving agents, to provide a palatable preparation. Moreover, when in tablet or pill form, the compositions can be coated to delay disintegration and absorption in the gastrointestinal tract, thereby providing a sustained action over an extended period of time. Oral compositions can include standard vehicles such as mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate. Such vehicles may be of pharmaceutical grade.

For oral liquid preparations for example, suspensions, elixirs and solutions, suitable carriers, excipients or diluents include water, saline, alkylene glycols (e.g., propylene glycol), polyalkylene glycols (e.g., polyethylene glycol), oils, alcohols, slightly acidic buffers between about pH 4 and about pH 6 (e.g., acetate, citrate, ascorbate at between about 5 mM to about 50 mM). Additionally, flavoring agents, preservatives, coloring agents, bile salts, acylcarnitines, and the like can be added.

For topical formulations of tranexamic acid prodrug compounds of Formula (I) in the form of creams, gels, viscous lotions, transdermal patches, and/or sprays can be used as appropriate delivery forms. Such formulations can comprise one or more tranexamic acid prodrug compounds of Formula (I), optionally in purified form, together with a suitable amount of any pharmaceutically acceptable topical excipients including, but not limited to, gels, patches, lotions, creams, ointments, and liquids.

For topical administration include those for delivery via the mouth (buccal), nose (nasal), the rectum (rectal), the vagina (vaginal), and through the skin (dermal). Topical delivery systems also include transdermal patches containing at least one compound of Formula (I) to be administered. Delivery through the skin can be achieved by diffusion or by more active energy sources such as iontophoresis or electrotransport.

Compositions suitable for topical administration in the mouth include lozenges comprising a compound of
Formula (I) optionally in a flavored basis such as sucrose and acacia or tragacanth, pastilles comprising a compound of Formula (I) in an inert basis such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising a compound of Formula (I) administered in a suitable liquid vehicle.

[0160] Compositions suitable for topical administration to the skin include ointments, creams, gels, patches, pastes and sprays comprising a compound of Formula (I) to be administered in a pharmaceutical acceptable vehicle. Formulations of a compound of Formula (I) for topical use, such as in creams, ointments and gels, can include an oleaginous or water-soluble ointment base. For example, topical compositions can include vegetable oils, animal fats, and in certain embodiments, semisolid hydrocarbons obtained from petroleum. Topical compositions can further include white ointment, yellow ointment, cetetyl esters wax, oleic acid, olive oil, paraffin, petrolatum, white petrolatum, spermacte, starch glycerite, white wax, yellow wax, lanolin, anhydrous lanolin, and glyceryl monostearate. Various water-soluble ointment bases can also be used, including glycol ethers and derivatives, polyethylene glycols, polyoxyethyl stearete, and polysorbates.

[0161] Compositions for rectal administration can be in the form of a suppository with a suitable base comprising, for example, cocoa butter or a salicylate. Compositions suitable for vaginal administration can be provided as pessaries, tampons, creams, gels, pastes, foams, or spray formulations containing in addition to a compound of Formula (I) such vehicles as are known in the art to be appropriate. Compositions for nasal administration can be in the form of, for example, nasal solutions, sprays, aerosols, or inhalants, and can include in addition to at least one compound of Formula (I), vehicles suitable for nasal administration.

[0162] When a compound of Formula (I), is acidic, it can be included in any of the above-described formulations as the free acid, a pharmaceutically acceptable salt, a solvate, or a hydrate. Pharmaceutically acceptable salts can substantially retain the activity of the free acid, can be prepared by reaction with bases, and can be more soluble in aqueous and other protic solvents than the corresponding free acid form. In some embodiments, sodium salts of a compound of Formula (I) can be used in the above described formulations.

Sustained Release Oral Dosage Forms

[0163] The disclosed compounds may be used with a number of different dosage forms, which can be adapted to provide sustained release of a compound of Formula (I) upon oral administration.

[0164] In some embodiments, a dosage form can comprise beads that on dissolution or diffusion release a compound disclosed herein over an extended period of hours, in certain embodiments, over a period of at least 4 hours, in certain embodiments, over a period of at least 8 hours and in certain embodiments, over a period of at least 12 hours. The beads can have a central composition or core comprising a compound disclosed herein and pharmaceutically acceptable vehicles, including an optional lubricant, antioxidant, and buffer. The beads can be medical preparations with a diameter ranging from about 0.05 mm to about 2 mm. Individual beads can comprise doses of a compound disclosed herein, for example, doses of up to about 40 mg of the compound. The beads, in some embodiments, can be formed of non-cross-linked materials to enhance their discharge from the gastrointestinal tract. The beads can be coated with a release rate-controlling polymer that gives a timed-release profile.

[0165] The time-release beads can be manufactured into a tablet for therapeutically effective administration. The beads can be made into matrix tablets by the direct compression of a plurality of beads coated with, for example, an acrylic resin and blended with excipients such as hydroxypropylmethyl cellulose. The manufacture of beads has been disclosed in the art (Lu, Int. J. Pharm., 1994, 112, 117-124; "Pharmaceutical Sciences" by Remington, 14th Ed, pp. 1626-1628 (1970); Fincher, J. Pharm. Sci., 1968, 57, 1825-1835; and U.S. Patent No. 4,083,949) as has the manufacture of tablets ("Pharmaceutical Sciences," by Remington, 17th Ed, Ch. 90, pp 1603-1625 (1985)).

[0166] One type of sustained release oral dosage formulation that can be used with the disclosed compounds comprises an inert core, such as a sugar sphere, coated with an inner drug-containing layer and an outer membrane layer controlling drug release from the inner layer. A "sealcoat" can be provided between the inert core and the layer containing the active ingredient. When the core is of a water-soluble or water-swellable inert material, the sealcoat can be in the form of a relatively thick layer of a water-insoluble polymer. Such a controlled release bead can thus comprise: (i) a core unit of a substantially water-soluble or water-swellable inert material; (ii) a first layer on the core unit of a substantially water-insoluble polymer; (iii) a second layer covering the first layer and containing an active ingredient; and (iv) a third layer on the second layer of polymer effective for controlled release of the active ingredient, wherein the first layer is adapted to control water penetration into the core.

[0167] In certain embodiments, the first layer (ii) above can constitute more than about 2% (w/w) of the final bead composition, and in certain embodiments, more than about 3% (w/w), e.g., from about 3% to about 80% (w/w). The amount of the second layer (ii) above can constitute from about 0.05% to about 60% (w/w), and in certain embodiments from about 0.1 % to about 30% (w/w) of the final bead composition. The amount of the third layer (iv) above can constitute from about 1% to about 50% (w/w), in certain embodiments, from about 2% to about 25% (w/w) of the final bead composition. The core unit can have a size ranging from about 0.05 to about 2 mm. The controlled release beads can be provided in a multiple unit formulation, such as a capsule or a tablet.
[0168] The cores can comprise a water-soluble or swellable material and can be any such material that is conventionally used as cores or any other pharmaceutically acceptable water-soluble or water-swellable material made into beads or pellets. The cores can be spheres of materials such as sucrose/starch (Sugar Spheres NF), sucrose crystals, or extruded and dried spheres typically comprised of excipients such as microcrystalline cellulose and lactose. The substantially water-insoluble material in the first, or sealcoat layer can be a "GI insoluble" or "GI partially insoluble" film forming polymer (dispersed or dissolved in a solvent). Examples include ethyl cellulose, cellulose acetate, cellulose acetate butyrate, polymethacrylates such as ethyl acrylate/methyl methacrylate copolymer (Eudragit NE-30-D) and ammonio methacrylate copolymer types A and B (Eudragit RL30D and RS30D), and silicone elastomers. In certain embodiments, a plasticizer can be used together with the polymer. Examples of plasticizers include, dibutylysebacate, propylene glycol, triethylcitrate, tributylicitate, castor oil, acetylated monoglycerides, acetyl triethylcitrate, acetyl butylcitrate, diethyl phthalate, dibutyl phthalate, triacetin, and fractionated coconut oil (medium-chain triglycerides). The second layer containing the active ingredient can comprise an active ingredient with or without a polymer as a binder. The binder, when used, can be hydrophilic, and in certain embodiments can be water-soluble or water-insoluble. Examples of polymers that can be used in the second layer containing the active drug include hydrophilic polymers such as, polyvinylpyrrolidone (PVP), polyalkylene glycol such as polyethylene glycol, gelatine, polyvinyl alcohol, starch and derivatives thereof, cellulose derivatives, such as polyhydroxypropylmethyl cellulose (HPMC), hydroxypropyl cellulose, carboxymethyl cellulose, methyl cellulose, ethyl cellulose, hydroxyethyl cellulose, carboxethyl cellulose, carboxymethylhydroxyethyl cellulose, acryl acid polymers, polyalkylacrylates, or any other pharmaceutically acceptable polymer. The ratio of drug to hydrophilic polymer in the second layer can range from about 1:100 to about 100:1 (w/w). Suitable polymers for use in the third layer, or membrane, for controlling the drug release can be selected from water-insoluble polymers or polymers with pH-dependent solubility, such as, ethyl cellulose, hydroxypropylmethyl cellulose phthalate; cellulose acetate phthalate, cellulose acetate trimellitate, polymethacrylates, or mixtures thereof, optionally combined with plasticizers, such as those mentioned above. Optionally, the controlled release layer comprises, in addition to the polymers above, other substance (s) with different solubility characteristics, to adjust the permeability and thereby the release rate, of the controlled release layer. Examples of polymers that can be used as a modifier together with, for example, ethyl cellulose include, HPMC, hydroxyethyl cellulose, hydroxypropyl cellulose, methylcellulose, carboxymethylcellulose, polyethylene glycol, polyvinylpyrrolidone (PVP), polyvinyl alcohol, polymers with pH-dependent solubility, such as cellulose acetate phthalate or ammonio methacrylate copolymer, methacrylic acid copolymer, and combinations of any of the foregoing. Additives such as sucrose, lactose and pharmaceutical grade surfactants can also be included in the controlled release layer, if desired.

[0169] The preparation of the multiple unit formulation can comprise the additional step of transforming the prepared beads into a pharmaceutical formulation, such as by filling a predetermined amount of the beads into a capsule, or compressing the beads into tablets. Examples of multi-particulate sustained release dosage forms are described in, for example, U.S. Patent Nos. 6,627,223 and 5,229,135.


[0171] In certain embodiments, enteric-coated preparations can be used for oral sustained release administration. Examples of useful coating materials include polymers with a pH-dependent solubility (i.e., pH-controlled release), polymers with a slow or pH-dependent rate of swelling, dissolution or erosion (i.e., time-controlled release), polymers that are degraded by enzymes (i.e., enzyme-controlled release), and polymers that form firm layers that are destroyed by an increase in pressure (i.e., pressure-controlled release).

[0172] In certain embodiments, drug-releasing lipid matrices can be used for oral sustained release administration. An example is when solid microparticles of a compound disclosed herein are coated with a thin controlled release layer of a lipid (e.g., glycerol behenate and/or glyceryl palmitostearate) as disclosed in Farah et al., U.S. Patent No. 6,375,987 and Joachim et al., U.S. Patent No. 6,379,700. The lipid-coated particles can optionally be compressed to form a tablet. Another controlled release lipid-based matrix material that is suitable for sustained release oral administration comprises polyglycolized glycerides as disclosed in Roussin et al., U.S. Patent No. 6,171,615.

[0173] In certain embodiments, waxes can be used for oral sustained release administration. Examples of suitable sustained compound-releasing waxes are disclosed in Cain et al., U.S. Patent No. 3,402,240 (carnauba wax, candelilla wax, esparto wax and ouricury wax); Shtohryn et al., U.S. Patent No. 4,820,523 (hydrogenated vegetable oil, bees wax, carnauba wax, paraffin, candelilla, ozokerite and combinations of any of the foregoing); and Walters, U.S. Patent No.
In certain embodiments, osmotic delivery systems can be used for oral sustained release administration (Verma et al., Drug Dev. Ind. Pharm., 2000, 26, 695-708). In some embodiments, OROS® systems made by Alza Corporation, Mountain View, CA can be used for oral sustained release delivery devices (Theeuwes et al., U.S. Patent No. 3,845,770; Theeuwes et al., U.S. Patent No. 3,916,899).

In certain embodiments, a controlled-release system can be placed in proximity of the target of a compound disclosed herein (e.g., within the spinal cord), thus requiring only a fraction of the systemic dose (See, e.g., Goodson, in "Medical Applications of Controlled Release," supra, vol. 2, pp. 115-138 (1984)). Other controlled-release systems discussed in Langer, Science, 1990, 249, 1527-1533 can also be used.

In certain embodiments, a dosage form can comprise a compound disclosed herein coated on a polymer substrate. The polymer can be an erodible, or a nonerodible polymer. The coated substrate can be folded onto itself to provide a bilayer polymer drug dosage form. For example, a compound disclosed herein can be coated onto a polymer such as a polypeptide, collagen, gelatin, polyvinyl alcohol, polyorthoester, polyacetyl, or a polyorthocarbonate and the coated polymer folded onto itself to provide a bilaminated dosage form. In operation, a bioerodible dosage form erodes at a controlled rate to dispense a compound disclosed herein over a sustained release period. Representative biodegradable polymers include biodegradable poly(amides), poly (amino acids), poly(esters), poly(lactic acid), poly(glycolic acid), poly(carbohydrate), poly(orthoester), poly(orthocarbonate), poly(acetyl), poly(anhydrides), biodegradable poly(di-hydroxypropanes), and poly(dioxinones) which are known in the art (Rosoff, Controlled Release of Drugs Chap. 2, pp. 53-95 (1989); and in U.S. Patent Nos. 3,811,444; 3,962,414; 4,066,747, 4,070,347; 4,079,038; and 4,093,709).

In certain embodiments, a dosage form can comprise a compound of Formula (I) loaded into a polymer that releases the compound by diffusion through a polymer, or by flux through pores or by rupture of a polymer matrix. The drug delivery polymeric dosage form can comprise from about 10 mg to about 500 mg of the compound homogenously contained in or on a polymer. The dosage form can comprise at least one exposed surface at the beginning of dose delivery. The non-exposed surface, when present, can be coated with a pharmaceutically acceptable material impermeable to the passage of the compound. The dosage form can be provided by procedures known in the art. An example of providing a dosage form comprises blending a pharmaceutically acceptable carrier such as polyethylene glycol, with a known dose of a compound at an elevated temperature, (e.g., 37 °C), and adding the blended composition to a silastic medical grade elastomer with a cross-linking agent, for example, octanoate, followed by casting in a mold. The step can be repeated for each optional successive layer. The system can be allowed to set for about 1 hour, to provide the dosage form. Representative polymers for manufacturing the dosage include olefinic polymers, vinyl polymers, addition polymers, condensation polymers, carbohydrate polymer and silicone polymers as represented by polyethylene, polypropylene, polyvinyl acetate, polypepnylacrylate, polyisobutylmethacrylate, poly alginate, polyamide and polysilicone. The polymers and procedures for manufacturing the polymers have been described in the art (Coleman et al., Polymers, 1990, 31, 1187-1231; Roerdink et al., Drug Carrier Systems, 1989, 9, 57-10; Leong et al., Adv. Drug Delivery Rev., 1987, 1, 199-233; Roff et al., Handbook of Common Polymers, 1971, CRC Press; and U.S. Patent No. 3,992,518).

In certain embodiments, a dosage form can comprise a plurality of pills. The time-release pills can provide a number of individual doses for providing various time doses for achieving a sustained-release produg delivery profile over an extended period of time up to about 24 hours. The matrix can comprise a hydrophilic polymer such as, a polysaccharide, agar, agarose, natural gum, alkali alginate including sodium alginate, carrageenan, fucoidan, furcellaran, laminaran, hynpea, gum arabic, gum ghatti, gum karaya, gum tragacanth, locust bean gum, pectin, amylopectin, gelatin, or a hydrophilic colloid. The hydrophilic matrix can comprise a plurality of 4 to 50 time release pills, each time release pill comprising a dose population of from about 10 ng, about 0.5 mg, about 1 mg, about 1.2 mg, about 1.4 mg, about 1.6 mg, about 5.0 mg, etc. The pills can comprise a release rate-controlling wall ranging from about 0.001 mm to about 10 mm thick to provide for the timed release of a compound disclosed herein over a sustained release period. Representative biodegradable polymers include biodegradable poly(amides), poly (amino acids), poly(esters), poly(lactic acid), poly(glycolic acid), poly(carbohydrate), poly(orthoester), poly(orthocarbonate), poly(acetyl), poly(anhydrides), biodegradable poly(di-hydroxypropanes), and poly(dioxinones) which are known in the art (Rosoff, Controlled Release of Drugs Chap. 2, pp. 53-95 (1989); and in U.S. Patent Nos. 3,811,444; 3,962,414; 4,066,747, 4,070,347; 4,079,038; and 4,093,709).

In certain embodiments, a dosage form can comprise an osmotic dosage form, which comprises a semipermeable wall that surrounds a therapeutic composition comprising the compound. In use within a patient, an osmotic dosage form comprising a homogenous composition, imbibes fluid through the semipermeable wall into the dosage form in response to the concentration gradient across the semipermeable wall. The therapeutic composition in the dosage form develops osmotic pressure differential that causes the therapeutic composition to be administered through an exit from the dosage form over a prolonged period of time up to about 24 hours (or even in some cases up to about 30 hours) to provide controlled and sustained compound release. These delivery platforms can provide an essentially zero order delivery profile as opposed to the spiked profiles of immediate release formulations.

In certain embodiments, the dosage form can comprise another osmotic dosage form comprising a wall sur-
EP 1 919 859 B1

rounding a compartment, the wall comprising a semipermeable polymeric composition permeable to the passage of fluid and substantially impermeable to the passage of compound present in the compartment, a compound-containing layer composition in the compartment, a hydrogel push layer composition in the compartment comprising an osmotic formulation for imbibing and absorbing fluid for expanding in size for pushing the compound composition layer from the dosage form, and at least one passageway in the wall for releasing the prodrug composition. The method delivers the compound by imbibing fluid through the semipermeable wall at a fluid imbibing rate determined by the permeability of the semipermeable wall and the osmotic pressure across the semipermeable wall causing the push layer to expand, thereby delivering the compound from the dosage form through the exit passageway to a patient over a prolonged period of time (up to about 24 or even about 30 hours). The hydrogel layer composition can comprise from about 10 mg to about 1000 mg of a hydrogel such as a member selected from the group consisting of a polyalkylene oxide of about 1,000,000 to about 8,000,000 weight-average molecular weight, which are selected from the group consisting of a polyethylene oxide of about 1,000,000 weight-average molecular weight, a polyethylene oxide of about 2,000,000 molecular weight, a polyethylene oxide of about 4,000,000 molecular weight, a polyethylene oxide of about 7,000,000 molecular weight, and a polypropylene oxide of the about 1,000,000 to about 8,000,000 weight-average molecular weight; or about 10 mg to about 1000 mg of an alkali carboxymethylcellulose of about 10,000 to about 6,000,000 weight average molecular weight, such as sodium carboxymethylcellulose or potassium carboxymethylcellulose. The hydrogel expansion layer comprises about 0 mg to about 350 mg, in present manufacture; about 0.1 mg to about 250 mg of a hydroxalkylcellulose of about 7,500 to about 4,500,00 weight-average molecular weight (e.g., hydroxyethylcellulose, hydroxypropylcellulose, hydroxybutylcellulose or hydroxypropylpentylcellulose) in present manufacture; about 1 mg to about 50 mg of an agent selected from the group consisting of sodium chloride, potassium chloride, potassium acid phosphate, tartaric acid, citric acid, raffinose, magnesium sulfate, magnesium chloride, urea, inositol, sucrose, glucose and sorbitol; 0 to about 5 mg of a colorant, such as ferric oxide; about 0 mg to about 30 mg, in present manufacture, 0.1 mg to 30 mg of a hydroxypropylalkylcellulose of about 9,000 to about 225,000 average-number molecular weight, selected from the group consisting of hydroxypropylcellulose, hydroxypropylpentylcellulose, hydroxypropylmethylcellulose, and hydroxypropylbutylcellulose; about 0.00 to about 1.5 mg of an antioxidant selected from the group consisting of ascorbic acid, butylated hydroxyanisole, butylated hydroxyquinone, butylhydroxyanisol; hydroxycoumarin, butylated hydroxytoluene, cephalin, ethyl gallate, propyl gallate, octyl gallate, lauryl gallate, propyl-hydroxybenzoate, trihydroxybutylrophenone, dimethylphenol, dibutylphenol, vitamin E, lecithin, and ethanolamine; and about 0.0 mg to about 7 mg of a lubricant selected from the group consisting of calcium stearate, magnesium stearate, zinc stearate, magnesium oleate, calcium palmitate, sodium suberate, potassium laurate, salts of fatty acids, salts of alicyclic acids, salts of aromatic acids, stearic acid, oleic acid, palmitic acid, a mixture of a salt of a fatty, alicyclic or aromatic acid, and a fatty, alicyclic, or aromatic acid.

[0181] In the osmotic dosage forms, the semipermeable wall can comprise a composition that is permeable to the passage of fluid and impermeable to the passage of prodrug. The wall is nontoxic and comprises a polymer selected from the group consisting of a cellulose acylate, cellulose diacylate, cellulose triacylate, cellulose acetate, cellulose diacetate and cellulose triacetate. The wall comprises about from 75 wt % (weight percent) to about 100 wt % of the cellulosic wall-forming polymer or, the wall can comprise additionally about 0.01 wt % to about 20 wt % of polyethylene glycol, or about from 1 wt % to about 25 wt % of a cellulose ether selected from the group consisting of hydroxypropylcellulose and a hydroxypropylalkyloxycellulose such as hydroxypropylmethylcellulose. The total weight percent of all components comprising the wall is equal to about 100 wt %. The internal compartment comprises the compound-containing composition alone or in layered position with an expandable hydrogel composition. The expandable hydrogel composition in the compartment increases in dimension by imbibing the fluid through the semipermeable wall, causing the hydrogel to expand and occupy space in the compartment, whereby the drug composition is pushed from the dosage form. The therapeutic layer and the expandable layer act together during the operation of the dosage form for the release of prodrug to a patient over time. The dosage form comprises a passageway in the wall that connects the exterior of the dosage form with the internal compartment. The osmotic powered dosage form can be made to deliver prodrug from the dosage form to the patient at a zero order rate of release over a period of up to about 24 hours.

[0182] The expression “passageway” as used herein comprises means and methods suitable for the metered release of the compound from the compartment of the dosage form. The exit means comprises at least one passageway, including an orifice, bore, aperture, pore, porous element, hollow fiber, capillary tube, channel, porous overlay, or porous element that provides for the osmotic controlled release of compound. The passageway includes a material that erodes or is leached from the wall in a fluid environment of use to produce at least one controlled-release dimensioned passageway. Representative materials suitable for forming a passageway, or a multiplicity of passageways comprise a leachable poly (glycolic) acid or poly(lactic) acid polymer in the wall, a gelatinous filament, poly(vinyl alcohol), leach-able polysaccharides, salts, and oxides. A pore passageway, or more than one pore passageway, can be formed by leaching a leachable compound, such as sorbitol, from the wall. The passageway possesses controlled-release dimensions, such as round, triangular, square, or elliptical, for the metered release of prodrug from the dosage form. The dosage form can be constructed with one or more passageways in spaced apart relationship on a single surface or on more than one surface
of the wall. The expression “fluid environment” denotes an aqueous or biological fluid as in a human patient, including the gastrointestinal tract. Passageways and equipment for forming passageways are disclosed in U.S. Patent Nos. 3,845,770; 3,916,899; 4,063,064; 4,088,864; and 4,816,263. Passageways formed by leaching are disclosed in U.S. Patents Nos. 4,200,098 and 4,285,987.

Regardless of the specific form of sustained release oral dosage form used, compounds of Formula (I) can be released from the dosage form over a period of at least about 4 hours, for example, over a period of at least about 8 hours or at least about 12 hours. Further, in certain embodiments, the dosage form can release from about 0% to about 30% of the prodrug in from 0 to about 2 hours, from about 20% to about 50% of the prodrug in from 2 to about 12 hours, from about 50% to about 85% of the prodrug in from about 3 to about 20 hours and greater than about 75% of the prodrug in from about 5 to about 18 hours. In certain embodiments, a sustained release oral dosage form can provide a concentration of tranexamic acid in the blood plasma of a patient over time, which curve has an area under the curve (C_{max}) that is proportional to the dose of the prodrug of tranexamic acid administered, and a maximum concentration C_{max}.

In certain embodiments, dosage forms are administered once or twice per day, and in certain embodiments, once per day.

Therapeutic Uses of Compounds, Dosages and Dosage Forms

In some embodiments, a therapeutically effective amount of one or more compounds of Formula (I) can be administered to a patient, such as a human, suffering from excessive bleeding, including heavy bleeding associated with cardiac surgery, upper gastrointestinal hemorrhage, blood loss in patients with advanced cancer, excess bleeding that occurs during dental procedures in hemophiliacs, and heavy bleeding during menstruation, i.e., menorrhagia. In certain embodiments, bleeding associated with these and other indications, can be considered heavy or excessive when the bleeding is greater than normal and will depend, at least in part, on the particular pathology and the judgment of the treating physician.

In certain embodiments, a therapeutically effective amount of one or more compounds of Formula (I) can be administered to a patient, such as a human, suffering from skin diseases or disorders such as wound healing, epidermal hyperplasia, skin roughening and unwanted skin pigmentation. In certain embodiments, a therapeutically effective amount of one or more compounds of Formula (I) can be administered to a patient, such as a human, suffering from cancer to treat or prevent tumor metastasis. In some of the above embodiments, sustained release oral dosage forms can be administered to the patient. In certain embodiments, topical formulations of one or more compounds of Formula (I) can be administered to the patient.

Further, in certain embodiments, a therapeutically effective amount of one or more compounds of Formula (I) can be administered to a patient, such as a human, as a preventative measure against various diseases or disorders. Thus, the therapeutically effective amount of one or more compounds of Formula (I) can be administered as a preventative measure to a patient having a predisposition for excessive bleeding, including, but not limited to, excessive bleeding associated with cardiac surgery, upper gastrointestinal hemorrhage, blood loss in patients with advanced cancer, excessive bleeding that occurs during dental procedures, for example in hemophiliacs, and excessive bleeding during menstruation, i.e., menorrhagia. In certain embodiments, the therapeutically effective amount of one or more compounds of Formula (I) can be administered as a preventative measure to a patient having a predisposition for skin disease and disorder including, but not limited to, wound healing, epidermal hyperplasia, skin roughening, and unwanted skin pigmentation. In certain embodiments, the therapeutically effective amount of one or more compounds of Formula (I) can be administered as a preventative measure to a patient having a predisposition for tumor metastasis.

When used to treat or prevent the above diseases or disorders a therapeutically effective amount of one or more compounds of Formula (I) can be administered or applied singly, or in combination with other agents. The therapeutically effective amount of one or more compounds of Formula (I) can also deliver a compound of Formula (I) in combination with another pharmaceutically active agent, including another compound of Formula (I). For example, in the treatment of a patient suffering from cancer, a dosage form comprising a compound of Formula (I) can be administered in conjunction with an anti-cancer agent, such as adriamycin, Alkeran, Aredia, Arimidex, Avastin, BiCNU, Bleomycin, Blenoxane, Camptosar, carboplatin, Casodex, Celestone, Cerubidine, cisplatin, Cosmegan, Cytosar U, Cytoxan, daunorubicin, DaunoXome, Didronel, diethylstilbestrol, Diflucan, Doxil, doxorubicin, Elspar, Emcyt, Epogen, ergamisol, Ethylol, Etopophos, Etoposide, Eulexin, Femara, Fludara, Fluorouracil, Gemzar, Gleevec, Glia, Herceptin, Hexalen, Hycamtin, Hydrea, hydroxyurea, idamycin, Iflex, Intron A, Kytril, Leucovorin calcium, Leukeran, Leukine, Leustatin, Lupron, Lysodren, Marinol, Matulane, Mesnex, methotrexate, Mithracin, Mitoxantrone, Mustargen, Mutamycin, Myleran, Navelbine, Neupogen, Nilandron, Nipent, Novantrone, Oncaspars, Oncovin, oxalplatin, Paraplatin, Photofrin, Platiniol, Procrit, Proleukin, Purinethol, Rituxan, Roferon A, Rubex, Salagen, Sandostatin, squalamine, Tarcvea, Taxol, Taxotere, thioguanine, Thioplex, Tice BCG, TNP 470, Velban, Vesanosid, VePesid, Vitaxin, Vumon, Zanosar, Zinecard, Zofran, Zoladex, and Zyloprim.

In certain embodiments, in the treatment of a patient suffering from excessive bleeding, such as for example
menorrhagia, a dosage form comprising a compound of Formula (I) can be administered in conjunction with an agent
known or believed to be effective in treating excessive bleeding, including oral synthetic progestins such as medroxy-
progesterone, norethindrone acetate, and norgestrel; natural progestins such as progesterone; gonadatrophin inhibitors
such as danazol; or nonsteroidal anti-inflammatory agent such as aspirin, salsalate, diflunisal, ibuprofen, ketoprofen,
nabumetone, piroxicam, mefenamic acid, naproxen, diclofenac, indomethacin, sulindac, tolfenamic, etodolac, ketorolac,
oxaprozin, and COX-2 inhibitors such as celecoxib, meloxicam, and rofecoxib.

[0190] In certain embodiments, a compound of Formula (I) can be administered to a patient in combination with another
antifibrinolytic agent such as desmopressin, aprotinin, ε-aminocaproic acid, a plasmin inhibitor, or another compound
used to treat patients having excessive bleeding such as aluminum hydroxide, ranitidine, or goserelin.

[0191] In certain embodiments, compounds of Formula (I) are prodrugs of both tranexamic acid and a second thera-
peutic agent. The moiety having the structure:

\[
\begin{align*}
R^1 & \quad \text{O} \\
& \quad \text{OH}
\end{align*}
\]

can comprise a second therapeutic agent having a -COOH group. In certain embodiments, the second therapeutic agent
can be a compound effective treating a symptom associated with excessive bleeding. For example, in certain embodi-
ments such as for treating menorrhagia, the second therapeutic agent can be a non-steroidal anti-inflammatory agent
having a -COOH group such as aspirin, salsalate, diflunisal, ibuprofen, ketoprofen, mefenamic acid, naproxen, diclofenac,
indomethacin, sulindac, tolmetin, etodolac, ketorolac, or oxaprozin. In certain embodiments, a compound of Formula (I)
is a prodrug of tranexamic acid and a non-steroidal anti-inflammatory agent such as ibuprofen or naproxen.

[0192] Dosage forms, upon releasing a tranexamic acid prodrug of Formula (I), can provide tranexamic acid upon in
vivo administration to a patient. The promoieties or promoieties of the prodrug of Formula (I) can be cleaved either
chemically and/or enzymatically. One or more enzymes present in the stomach, intestinal lumen, intestinal tissue, blood,
liver, brain or any other suitable tissue of a mammal can enzymatically cleave the promoieties or promoieties of the prodrug.
If the promoieties or promoieties are cleaved after absorption by the gastrointestinal tract, tranexamic acid prodrugs of
Formula (I) can be absorbed into the systemic circulation from the large intestine. In certain embodiments, the promoieties
or promoieties are cleaved after absorption by the gastrointestinal tract. In certain embodiments, the promoieties or
promoieties are cleaved in the gastrointestinal tract and tranexamic acid is absorbed into the systemic circulation form
the large intestine. In certain embodiments, the tranexamic acid prodrug is absorbed into the systemic circulation from
the gastrointestinal tract, and the promoieties or promoieties are cleaved in the systemic circulation, after absorption of
the tranexamic acid prodrug from the gastrointestinal tract.

[0193] In certain embodiments, a tranexamic acid prodrug of Formula (I) can be provided to a patient by topical adminis-
tration. For example, a pharmaceutical composition comprising at least one compound of Formula (I) and at least one
pharmacologically acceptable topical vehicle can be formulated in the form of a cream, lotion, ointment, solution, aerosol,
spray and the like. The topical formulation can be applied to a surface area of a patient to be treated, for example, by
spreading or spraying. The topical formulation may be applied to a surface area of a patient to be treated, for example, by
spreading or spraying. The surface area of a patient to be treated can be an area exhibiting excessive or heavy bleeding
such as a wound, oral mucosa, buccal mucosa, rectal mucosa, vaginal mucosa, nasal mucosa, surfaces exposed during
surgery, or an area of the skin exhibiting a skin disease or disorder. In prophylactic applications, the surface area of a
patient to be treated can be, for example, an area of a mucosa or the skin having a predisposition for a skin disease or
disorder including, but not limited to, bleeding, epidermal hyperplasia, skin roughening, and unwanted skin pigmentation.

**Doses**

[0194] The amount of tranexamic acid prodrug that will be effective in the treatment of a particular disorder or condition
disclosed herein can depend on the nature of the disorder or condition, and can be determined by standard clinical
techniques known in the art. In addition, in vitro or in vivo assays can optionally be employed to help identify optimal
dosage ranges. The amount of a compound administered can depend on, among other factors, the subject being treated,
the weight of the subject, the severity of the affliction, the manner of administration, and the judgment of the prescribing
physician.

[0195] In certain embodiments, a dosage form are adapted to be administered to a patient no more than twice per
day, and in certain embodiments, only once per day. Dosing can be provided alone or in combination with other drugs
and can continue as long as required for effective treatment of the disease state or disorder. When used to treat or
prevent menorrhagia, a therapeutically effective amount of one or more compounds of Formula (I) can be administered
concurrently with menstruation (typically for 4 to 7 days).
EP 1 919 859 B1

[0196] Suitable daily dosage ranges for oral administration can range from about 2 mg to about 50 mg of tranexamic acid equivalents per kilogram body weight. Suitable drug concentrations in formulations for topical administration can range from about 1% to about 10% (on a weight basis). Appropriate dosage ranges can be readily determined by methods known to the skilled artisan.

Examples

[0197] The following examples describe in detail preparation of compounds and compositions disclosed herein and assays for using compounds and compositions disclosed herein.

[0198] In the examples below, the following abbreviations have the following meanings. If an abbreviation is not defined, it has its generally accepted meaning.

DMSO = dimethylsulfoxide

g = gram

h = hour

HPLC = high pressure liquid chromatography

LC/MS = liquid chromatography/mass spectroscopy

M = molar

mg = milligram

min = minute

mL = milliliter

mmol = millimoles

MTBE = methyl tert-butyl ether

NMM = N-methylmorpholine

nM = nanomolar

μL = microliter

μm = micrometer

μM = micromolar

v/v = volume to volume

w/v = weight to volume

General Experimental Protocols

[0199] trans-4-(Aminomethyl)-cyclohexanecarboxylic acid (tranexamic acid) was purchased from Sigma-Aldrich, Inc. and was used without further manipulation. O-(1-Acylxoyalkyl) S-alkylthiocarbonates were previously synthesized according to the procedures disclosed in Gallop et al., U.S. Application Publication No. 2005/0222431 and converted to the corresponding acyloxyalkyl N-hydroxysuccinimide carbonic acid esters as described therein, or according to the general procedure given below. All other reagents and solvents were purchased from commercial suppliers and used without further purification or manipulation.

[0200] Proton NMR spectra (400 MHz) were recorded on a Varian AS 400 NMR spectrometer equipped with an autosampler and data processing computation. DMSO-d⁶ (99.9% D) or CDCl₃ (99.8 % D) were used as solvents unless
otherwise noted. The DMSO or chloroform solvent signal was used for calibration of the individual spectra (H. E. Gottlieb et al., J. Org. Chem., 1997, 62, 7512). Analytical LC/MS was performed on a Waters 2790 separation module equipped with a Waters Micromass QZ mass spectrometer, a Waters 996 photodiode detector, and a Merck Chromolith UM2072-027 or Phenomenex Luna C-18 analytical column. Mass-guided preparative HPLC purification of final compounds was performed on an instrument equipped with a Waters 600 controller, ZMD Micromass spectrometer, a Waters 2996 photodiode array detector, and a Waters 2700 Sample Manager. Acetonitrile/water gradients containing 0.05% formic acid were used as eluents in both analytical and preparative HPLC experiments.

General Procedure for the Synthesis of Acyloxyalkyl N-hydroxysuccinimide Carbonic Acid Esters

[0201] A 250 mL round-bottomed flask equipped with a magnetic stir bar and a pressure-equilibrating dropping funnel was charged with the 1-acyloxyalkyl alkylthiocarbonate (10 mmol) and N-hydroxysuccinimide (20-40 mmol). Dichloromethane (20-40 mL) was added and the reaction mixture cooled to ca. 0 °C in an ice-bath. Peracetic acid (32 wt.%) in a 40-45% aqueous acetic acid solution (30 mmol) was added dropwise with stirring over a period of ca. one hour to the cooled solution. After addition was complete, stirring was continued for additional three to five hours at this temperature, the reaction being monitored by 1H NMR spectroscopy. After complete consumption of the starting material, the reaction mixture was diluted with additional dichloromethane, and the organic solution was washed successively with water (three times) and once with a 10% aqueous solution of sodium metabisulfite or sodium thiosulfate to quench any remaining oxidant. The combined organic extracts were dried over MgSO4, filtered, and the solvent removed under reduced pressure with a rotary evaporator. Compound identity, integrity, and purity were checked by 1H NMR spectroscopy. The crude material was used directly in the next step, or could be further purified by commonly employed techniques well-known to those skilled in the art.

Example 1: 1-[(2,5-Dioxopyrrolidinyl)oxycarbonyloxy]-propyl 2-methylpropanoate (2)

[0202] Following the above general procedure, 1-(ethylthiocarbonyloxy)-propyl 2-methylpropanoate (2.3 g, 9.82 mmol) and N-hydroxysuccinimide (4.6 g, 40 mmol) were reacted in dichloromethane (20 mL) with peracetic acid (32 wt.%, 6.13 mL). After aqueous workup, isolation and removal of residual solvents in vacuo, the crude product 2 (1.76 g, 61%) was obtained as a yellow oil. The material was used in the next step without further purification. 1H NMR (400 MHz, CDCl3): δ =1.02 (t, J = 7.6 Hz, 3H), 1.20 (d, J = 6.8 Hz, 3H), 1.21 (d, J = 7.2 Hz, 3H), 1.88-2.00 (m, 2H), 2.61 (hept., J = 7.2 Hz, 1H), 2.84 (s, 4H), 6.71 (t, J = 5.2 Hz, 1H).

Example 2: 1-[(2,5-Dioxopyrrolidinyl)oxycarbonyloxy]-2-methylpropyl 2-methylpropanoate (3)

[0203] Following the above general procedure, 2-methyl-1-(ethylthiocarbonyloxy)-2-methylpropylpropanoate (2.34 g, 10.0 mmol) and N-hydroxysuccinimide (5.76 g, 50 mmol) were reacted in dichloromethane (30 mL) with peracetic acid (32 wt.% , 8.17 mL). After aqueous workup, isolation and removal of residual solvents in vacuo, the crude product 3 (2.12 g, 70%) was obtained as a pale yellow oil. The material was used in the next step without further purification. 1H NMR (400 MHz, CDCl3): δ =1.04 (d, J = 7.2 Hz, 6H), 1.21 (d, J = 6.8 Hz, 3H), 1.22 (d, J = 6.8 Hz, 3H), 2.15-2.21 (m, 1H), 2.63 (hept., J = 7.2 Hz, 1H), 2.84 (s, 4H), 6.59 (d, J = 5.2 Hz, 1H). MS (ESI) m/z 324.10 (M+Na)+.

General Nucleophilic Carbamoylation Procedure for Synthesis of Acyloxyalkyl Carbamates of Tranexamic Acid

[0204] A screw-capped 40 mL glass vial equipped with a magnetic stir bar was charged with trans-4-(aminomethyl)cyclohexanecarboxylic (tranexamic) acid (472 mg, 3.0 mmol). The appropriate acyloxyalkyl N-hydroxysuccinimide carbamic acid ester (2.0 mmol) was added either as a solid or was dissolved in a small volume of solvent (for oily materials). A mixture of methyl tert-butyl ether (MTBE), acetone, and water (v/v/v = 4:3:1) (15-20 mL) was added, and the reaction mixture stirred for ca. 12 hours at room temperature. Upon completion of the reaction, the mixture was diluted with ethyl acetate and 1 N aqueous hydrochloric acid (ca. 10 mL) was added. After vigorous mixing followed by phase separation, the aqueous layer was extracted once more with EtOAc, and the combined organic extracts were washed with brine. The solvents were evaporated under reduced pressure, the dry residue was dissolved in a mixture of 60% (v/v) acetonitrile/water, and the solution filtered through a 0.2 µm nylon syringe filter. Final purification was achieved by mass-guided preparative HPLC. After lyophilization of the solvents, the pure compounds were obtained as white powders.

General Procedure for One Pot Synthesis of Acyloxyalkyl Carbamates of Tranexamic Acid

[0205] Under an atmosphere of nitrogen, a dry 100 mL round-bottomed flask equipped with a magnetic stir bar and a rubber septum was charged with trans-4-(aminomethyl)cyclohexanecarboxylic (tranexamic) acid (786.1 mg, 5.0 mmol).
Anhydrous dichloromethane (10-15 mL) was added, and the reaction mixture was cooled to ca. 0 °C with an ice bath. Chlorotrimethylsilane (1.396 mL, 1.195 g, 11.0 mmol) was added neat at this temperature, followed by slow addition of N-methylmorpholine (1.374 mL, 1.264 g, 12.5 mmol). The reaction mixture was stirred at this temperature for ca. 30 min, when an appropriately substituted chloroalkylchloroformate (7.5 mmol) was added dropwise and in neat form. The reaction mixture was stirred at this temperature for an additional 30 min when a premixed mixture of NMM (2.75 mL, 2.53 g, 25 mmol) and an appropriately substituted carboxylic acid (50 mmol) was added at ca. 0 °C. The reaction mixture was stirred overnight with warming to room temperature. The dichloromethane was removed in vacuo using a rotary evaporator. The crude reaction product was diluted with methyl tert-butyl ether (MTBE), and the filtrate evaporated in vacuo using a rotary evaporator. The crude dry residue was dissolved in a small amount of a mixture of 60% (v/v) acetonitrile/water (ca. 5 mL), and the solution filtered through a 0.2 μm nylon syringe filter. Final purification was achieved by mass-guided preparative HPLC. After lyophilization of the solvents, the pure compounds were generally obtained as white powders.

General Procedure for the Synthesis of Sodium Salts of Acyloxyalkyl Carbamates of Tranexamic Acid

A screw-capped 40 mL vial equipped with a magnetic stir bar was charged with an appropriately substituted acyloxyalkyl carbamate of tranexamic acid (5.0 mmol). The material was dissolved in ca. 10 mL of acetonitrile. A solution of sodium bicarbonate (NaHCO3) (420.1 mg, 5.0 mmol) in ca. 20 mL of water was added at room temperature and the mixture was stirred one hour after the evolution of carbon dioxide subsided. The clear solution was frozen at -78 °C and the solvents were lyophilized. After lyophilization of the solvents, the pure compounds were obtained as white powders.

Example 3: trans-4-[[2-Methylpropanoyloxy]methoxycarbonyl]aminomethyl]-Cyclohexanecarboxylic Acid (4)

Following the general nucleophilic carbamoylation procedure, tranexamic acid (472 mg, 3.0 mmol) and 1-[[2,5-dioxopyrrolidinyl]oxycarbonyloxy]methyl 2-methylpropanoate (518 mg, 2.0 mmol) were reacted in the MTBE/acetone/water mixture (16 mL) to yield the title compound 4 (397 mg, 66% yield) as a white powder after work-up and mass-guided preparative HPLC purification. 1H NMR (400 MHz, DMSO-d6): δ = 0.82-0.95 (br. m, 2H), 1.08 (d, J= 7.2 Hz, 6H), 1.17-1.39 (br. m, 3H), 1.64-1.73 (br. m, 2H), 1.82-1.91 (br. m, 2H), 2.10 (tt, J=11.8, 3.8 Hz, 1H), 2.55 (hept., J=7.2 Hz, 1H), 2.78-2.88 (br. m, 2H), 5.61 (s, 2H), 7.55 (t, J= 5.6 Hz, 1H), 11.98 (br. s, 1H). MS (ESI) m/z 302.09 (M+H)+; 299.99 (M-H)-.

Example 4: trans-4-[[3-Methylbutanoyloxy]methoxycarbonyl]aminomethyl]-Cyclohexanecarboxylic Acid (5)

Following the general nucleophilic carbamoylation procedure, tranexamic acid (472 mg, 3.0 mmol) and 1-[[2,5-dioxopyrrolidinyl]oxycarbonyloxy]methyl 3-methylbutanoate (547 mg, 2.0 mmol) were reacted in the MTBE/acetone/water mixture (16 mL) to yield the title compound 5 (310 mg, 49% yield) as a white powder after work-up and mass-guided preparative HPLC purification. 1H NMR (400 MHz, DMSO-d6): δ = 0.86-0.94 (br. m, 8H), 1.17-1.38 (br. m, 3H), 1.64-1.72 (br. m, 2H), 1.83-1.91 (br. m, 2H), 1.96 (hept., J= 7.2 Hz, 1H), 2.09 (tt, J= 12.4, 3.6 Hz, 1H), 2.21 (d, J= 6.8 Hz, 2H), 2.78-2.86 (br. m, 2H), 5.61 (s, 2H), 7.55 (t, J= 5.6 Hz, 1H), 11.99 (br. s, 1H). MS (ESI) m/z 316.11 (M+H)+; 314.07 (M-H)-.

Example 5: trans-4-[[2,2-Dimethylpropanoyloxy]methoxycarbonyl]-aminomethyl]-Cyclohexanecarboxylic Acid (6)

Following the general nucleophilic carbamoylation procedure, tranexamic acid (472 mg, 3.0 mmol) and 1-[[2,5-dioxopyrrolidinyl]oxycarbonyloxy]methyl 2,2-dimethylpropanoate (547 mg, 2.0 mmol) were reacted in the MTBE/acetone/water mixture (16 mL) to yield the title compound 6 (476 mg, 76% yield) as a white powder after work-up and mass-guided preparative HPLC purification. 1H NMR (400 MHz, DMSO-d6): δ = 0.82-0.94 (br. m, 2H), 1.13 (s, 9H), 1.17-1.38 (br. m, 3H), 1.64-1.72 (br. m, 2H), 1.82-1.91 (br. m, 2H), 2.09 (tt, J= 12.0, 3.6 Hz, 1H), 2.78-2.87 (br. m, 2H), 5.61 (s, 2H), 7.54 (t, J= 5.6 Hz, 1H), 11.98 (br. s, 1H). MS (ESI) m/z 316.11 (M+H)+; 314.01 (M-H)-.

Example 6: trans-4-[[Benzoyloxy]methoxycarbonyl]aminomethyl]-Cyclohexanecarboxylic Acid (7)

Following the general nucleophilic carbamoylation procedure, tranexamic acid (472 mg, 3.0 mmol) and 1-[[2,5-dioxopyrrolidinyl]oxycarbonyloxy]methyl benzoate (587 mg, 2.0 mmol) were reacted in the MTBE/acetone/water mixture (16 mL) to yield the title compound 7 (445 mg, 66% yield) as a white powder after work-up and mass-guided preparative HPLC purification. 1H NMR (400 MHz, DMSO-d6): δ = 0.83-0.95 (br. m, 2H), 1.16-1.39 (br. m, 3H), 1.65-1.72 (br. M,
10. 1.82-1.91 (br. m, 2H), 2.09 (tt, J= 12.4, 3.6 Hz, 1H), 2.81-2.88 (br. m, 2H), 5.88 (s, 2H), 7.50-7.57 (m, 2H), 7.61 (t, J= 6.0 Hz, 1H), 7.65-7.70 (m, 1H), 7.93-7.97 (m, 2H), 11.96 (br. s, 1H). MS (ESI) m/z 336.01 (M+H)+; 333.98 (M-H)-.

Example 7: trans-4-[(1-Acetoxy)ethoxycarbonyl]aminomethyl]-Cyclohexanecarboxylic Acid (8)

[0211] Following the general procedure for the one pot synthesis, tranexamic acid (786 mg, 5.0 mmol) was reacted with chlorotrimethylsilane (1.396 mL, 1.195 g, 11.0 mmol) in anhydrous dichloromethane (10 mL) and in the presence of N-methylmorpholine (1.374 mL, 1.264 g, 12.5 mmol). Subsequent reaction of the intermediate with chlorotrimethylsilane (1.396 mL, 1.195 g, 11.0 mmol) in anhydrous dichloromethane (10 mL) and in the presence of N-methylmorpholine (1.374 mL, 1.264 g, 12.5 mmol). Subsequent reaction of the intermediate with 1-chloroethylchloroformate (0.82 mL, 1.07 g, 7.5 mmol) followed by a mixture of NMM (2.75 mL, 2.53 g, 25 mmol) and acetic acid (2.86 mL, 3.00 g, 50 mmol) yielded the title compound 8 (320 mg, 22% yield) as a very slightly orange-colored oil after aqueous work-up and mass-guided preparative HPLC purification. \( ^1 \text{H NMR} (400 \text{MHz}, \text{DMSO-d}_6): \delta = 0.82-0.94 \text{ (br. m, 2H), 1.17-1.35 (br. m, 3H), 1.38 (d, J= 5.6 Hz, 1H), 1.66-1.73 (br. m, 2H), 1.84-1.91 (br. m, 2H), 1.99 (s, 3H), 2.10 (tt, J= 12.0, 3.6 Hz, 1H), 2.74-2.88 (m, 2H), 6.62 (q, J= 5.2 Hz, 1H), 7.44 (t, J= 6.0 Hz, 1H), 11.97 (br. s, 1H). MS (ESI) m/z 310.12 (M+Na)+; 286.08 (M-H)-.

Example 8: trans-4-[(1-Propanoyloxy)ethoxycarbonyl]aminomethyl]-Cyclohexanecarboxylic Acid (9)

[0212] Following the general procedure for the one pot synthesis, tranexamic acid (786 mg, 5.0 mmol) was reacted with chlorotrimethylsilane (1.396 mL, 1.195 g, 11.0 mmol) in anhydrous dichloromethane (10 mL) and in the presence of 1-chloroethylchloroformate (0.82 mL, 1.07 g, 7.5 mmol) followed by a mixture of NMM (2.75 mL, 2.53 g, 25 mmol) and propionic acid (3.73 mL, 3.70 g, 50 mmol) to yield the title compound 10 (338 mg, 22% yield) as a colorless, very viscous oil after aqueous work-up and two mass-guided preparative HPLC purifications. \( ^1 \text{H NMR} (400 \text{MHz}, \text{DMSO-d}_6): \delta = 0.89-0.97 \text{ (m, 5H), 1.22-1.36 (br. m, 3H), 1.42 (d, J= 5.6 Hz, 3H), 1.51-1.60 (m, 2H), 1.72-1.73 (br. m, 2H), 1.90-1.93 (m, 2H), 2.13 (tt, J=12, 3.6 Hz, 1H), 2.29 (t, J= 6.8 Hz, 2H), 2.85 (t, J= 6.4 Hz, 2H), 6.69 (q, J= 5.6 Hz, 1H), 7.48 (t, J= 6.0 Hz, 1H), 12.03 (br. s, 1H). MS (ESI) m/z 324.14 (M+Na)+; 300.10 (M-H)-.

Example 9: trans-4-[(1-Butanoyloxy)ethoxycarbonyl]aminomethyl]-Cyclohexanecarboxylic Acid (10)

[0213] Following the general nucleophilic carbamoylation procedure, tranexamic acid (800 mg, 5.0 mmol) and 1-[(2,5-dioxopyrrolidinyl)oxycarbonyl]ethyl butanoate (700 mg, 2.6 mmol) were reacted in the MTBE/acetone/water mixture (16 mL) to yield the title compound 10 (200 mg, 28% yield) as a white powder after work-up and mass-guided preparative HPLC purification. \( ^1 \text{H NMR} (400 \text{MHz}, \text{DMSO-d}_6): \delta = 0.89-0.97 \text{ (m, 5H), 1.22-1.36 (br. m, 3H), 1.42 (d, J= 5.6 Hz, 3H), 1.51-1.60 (m, 2H), 1.72-1.73 (br. m, 2H), 1.90-1.93 (m, 2H), 2.13 (tt, J=12, 3.6 Hz, 1H), 2.29 (t, J= 6.8 Hz, 2H), 2.85 (t, J= 6.4 Hz, 2H), 6.69 (q, J= 5.6 Hz, 1H), 7.48 (t, J= 6.0 Hz, 1H), 12.03 (br. s, 1H). MS (ESI) m/z 318.15 (M+Na)+; 314.12 (M-H)-.

Example 10: Sodium trans-4-[(1-Butanoyloxy)ethoxycarbonyl]aminomethyl]-Cyclohexanecarboxylate (11)

[0214] Following the general procedure for the formation of the corresponding sodium carboxylates of acyloxyalkyl carbanates of tranexamic acid, 946 mg (3.0 mmol) of trans-4-[(1-butanoyloxy)ethoxycarbonyl]aminomethyl]-cyclohexanecarboxylic acid 10 was reacted with 252 mg (3.0 mmol) of sodium bicarbonate (NaHCO₃) in 20 mL of a mixture of acetone(tri) and water (1:1) to yield 1.02 g (quant.) of the title compound 11 as a colorless powder. \( ^1 \text{H NMR} (400 \text{MHz}, \text{DMSO-d}_6): \delta = 0.73-0.84 \text{ (m, 2H), 0.87 (t, J= 6.8 Hz, 3H), 1.08-1.20 (m, 2H), 1.20-1.32 (m, 1H), 1.38 (d, J= 5.2 Hz, 3H), 1.46-1.56 (m, 2H), 1.60-1.74 (br. m, 3H), 1.76-1.83 (br. m, 2H), 2.25 (tt, J= 7.2 Hz, 2H), 2.78 (t, J= 6.0 Hz, 2H), 6.65 (q, J= 5.2 Hz, 1H), 7.41 (t, J= 5.6 Hz, 1H) MS (ESI) m/z 338.16 (M+Na)+; 314.18 (M-H)-.

Example 11: trans-4-[(1-Pentanoyl oxy)ethoxycarbonyl]aminomethyl]-Cyclohexanecarboxylic Acid (12)

[0215] Following the general nucleophilic carbamoylation procedure, tranexamic acid (1.1 g, 7.0 mmol) and 1-[(2,5-dioxopyrrolidinyl)oxycarbonyl]ethyl pentanoate (800 mg, 2.8 mmol) were reacted in the MTBE/acetone/water mixture (16 mL) to yield the title compound 12 (150 mg, 16% yield) as a white powder after work-up and mass-guided preparative HPLC purification. \( ^1 \text{H NMR} (400 \text{MHz}, \text{DMSO-d}_6): \delta = 0.88-0.97 \text{ (m, 5H), 1.22-1.38 (br. m, 5H), 1.42 (d, J= 5.2 Hz, 3H), 1.44-1.56 (m, 2H), 1.72-1.74 (m, 2H), 1.92-1.93 (m, 2H), 2.13 (tt, J= 12, 3.6 Hz, 1H), 2.30 (t, J= 7.2 Hz, 2H), 2.85 (t, J= 6.4 Hz, 2H), 6.68 (q, J= 5.6 Hz, 1H), 7.47 (t, J=6.0 Hz, 1H), 12.01 (br. s, 1H). MS (ESI) m/z 352.18 (M+Na)+; 328.14 (M-H)-.
Example 12: trans-4-[[1-(2-Methylpropanoyloxy)ethoxy]carbonyl]-aminomethyl]-Cyclohexanecarboxylic Acid (13)

[0216] Following the general nucleophilic carbamoylation procedure, tranexamic acid (472 mg, 3.0 mmol) and 1-[[2,5-dioxopyrrolidinyl]oxycarbonyl]ethyl 2-methylpropanoate (518 mg, 2.0 mmol) were reacted in the MTBE/acetone/water mixture (16 mL) to yield the title compound (333 mg, 53% yield) as a colorless powder after work-up and mass-guided preparative HPLC purification. 1H NMR (400 MHz, DMSO-d6): δ = 0.82-0.94 (br. m, 2H), 1.058 (d, J = 6.4 Hz, 3H), 1.062 (d, J = 6.8 Hz, 3H), 1.17-1.36 (br. m, 3H), 1.38 (d, J = 5.6 Hz, 3H), 1.65-1.73 (br. m, 2H), 1.83-1.91 (br. m, 2H), 2.10 (tt, J = 12.0, 3.6 Hz, 1H), 2.49 (hept., J = 6.8 Hz, 1H), 2.77-2.85 (br. m, 2H), 6.62 (q, J = 5.2 Hz, 1H), 7.45 (t, J = 6.0 Hz, 1H), 11.97 (br. s, 1H). MS (ESI) m/z 338.08 (M+Na)+; 314.12 (M-H)-.

Example 13: Sodium trans-4-[[1-(2-Methylpropanoyloxy)ethoxy]carbonyl]-aminomethyl]-Cyclohexanecarboxylate (14)

[0217] Following the general procedure for the formation of the corresponding sodium carboxylates of acyloxyalkyl-cyclohexanecarboxylic acid 13 was reacted with 1.34 g (15.94 mmol) of sodium bicarbonate (NaHCO3) in 40 mL of a mixture of acetonitrile and water (1:1) to yield 3.38 g (quant.) of the title compound 14 as a colorless powder. 1H NMR (400 MHz, DMSO-d6): δ = 0.72-0.84 (br. m, 2H), 1.057 (d, J = 6.4 Hz, 3H), 1.059 (d, J = 6.8 Hz, 3H), 1.20-1.32 (br. m, 3H), 1.38 (d, J = 5.2 Hz, 3H), 1.59-1.73 (br. m, 2H), 2.43-2.53 (m, 1H), 2.72-2.84 (br. m, 2H), 6.62 (q, J = 5.6 Hz, 1H), 7.43 (t, J = 5.6 Hz, 1H). MS (ESI) m/z 338.16 (M+Na)+; 314.12 (M-H)-.

Example 14: (+)-trans-4-[[1S]-1-(2-Methylpropanoyloxy)ethoxy]carbonylamino]methyl]-Cyclohexanecarboxylic Acid (15)

[0218] The enantiomers of trans-4-[[1-(2-methylpropanoyloxy)ethoxy]carbonyl]-aminomethyl]-cyclohexanecarboxylic acid 13 were resolved by means of a Waters mass-guided preparative HPLC using a ChiralPak AD-RH 250 x 20 mm column, an isocratic eluent consisting of 30% acetonitrile/70% water/0.05% formic acid, and a flowrate of 15 mL/min (Rf= 12.1 min; e.e. = 98.5%). 1H NMR (400 MHz, DMSO-d6): δ = 0.72-0.84 (br. m, 2H), 1.057 (d, J = 6.4 Hz, 3H), 1.061 (d, J = 6.8 Hz, 3H), 1.17-1.36 (br. m, 3H), 1.38 (d, J = 5.6 Hz, 3H), 1.65-1.73 (br. m, 2H), 1.83-1.91 (br. m, 2H), 2.10 (tt, J = 12.0, 3.6 Hz, 1H), 2.49 (hept., J = 6.8 Hz, 1H), 2.77-2.85 (br. m, 2H), 6.62 (q, J = 5.2 Hz, 1H), 7.45 (t, J = 6.0 Hz, 1H), 11.97 (br. s, 1H). MS (ESI) m/z 338.16 (M+Na)+; 314.12 (M-H)-.

Example 15: Sodium trans-4-[[1S]-1-(2-Methylpropanoyloxy)ethoxy]carbonylamino]methyl]-Cyclohexanecarboxylate (16)

[0219] Following the general procedure for the formation of the corresponding sodium carboxylates of acyloxyalkyl-cyclohexanecarboxylic acid 13 was resolved by means of a Waters mass-guided preparative HPLC using a ChiralPak AD-RH column, an isocratic eluent consisting of 30% acetonitrile/70% water/0.05% formic acid, and a flowrate of 15 mL/min (Rf= 12.2 min; e.e. = 98.3%; [α]D25.8 = +18.64, c (19.97, MeOH)). The assignment of the absolute configuration was accomplished by comparison with material obtained from an independent synthesis. 1H NMR (400 MHz, DMSO-d6): δ = 0.82-0.94 (br. m, 2H), 1.057 (d, J = 6.8 Hz, 3H), 1.061 (d, J = 6.8 Hz, 3H), 1.17-1.36 (br. m, 3H), 1.38 (d, J = 5.6 Hz, 3H), 1.65-1.73 (br. m, 2H), 1.83-1.91 (br. m, 2H), 2.10 (tt, J = 12.0, 3.6 Hz, 1H), 2.49 (hept., J = 6.8 Hz, 1H), 2.77-2.85 (br. m, 2H), 6.62 (q, J = 5.2 Hz, 1H), 7.45 (t, J = 6.0 Hz, 1H), 11.97 (br. s, 1H). MS (ESI) m/z 338.16 (M+Na)+; 314.12 (M-H)-.

Example 16: (-)-trans-4-[[1R]-1-(2-Methylpropanoyloxy)ethoxy]carbonylamino]methyl]-Cyclohexanecarboxylic Acid (17)

[0220] The enantiomers of trans-4-[[1-(2-methylpropanoyloxy)ethoxy]carbonyl]-aminomethyl]-cyclohexanecarboxylic acid 13 were resolved by means of a Waters mass-guided preparative HPLC using a ChiralPak AD-RH column, an isocratic eluent consisting of 30% acetonitrile/70% water/0.05% formic acid, and a flowrate of 15 mL/min. The enantiomeric excesses were determined with an analytical Waters 2690/Q LC/MS apparatus using a ChiralPak AD-RH column, an isocratic eluent of 30% acetonitrile/70% water/0.05% formic acid, and a flowrate of 15 mL/min. The enantiomeric excesses were determined with an analytical Waters 2690/Q LC/MS apparatus using a ChiralPak AD-RH column, an isocratic eluent consisting of 30% acetonitrile/70% water/0.05% formic acid, and a flowrate of 15 mL/min (Rf= 12.2 min; e.e. = 98.3%; [α]D25.8 = +18.64, c (19.97, MeOH)). The assignment of the absolute configuration was accomplished by comparison with material obtained from an independent synthesis. 1H NMR (400 MHz, DMSO-d6): δ = 0.82-0.94 (br. m, 2H), 1.057 (d, J = 6.8 Hz, 3H), 1.061 (d, J = 6.8 Hz, 3H), 1.17-1.36 (br. m, 3H), 1.38 (d, J = 5.6 Hz, 3H), 1.65-1.73 (br. m, 2H), 1.83-1.91 (br. m, 2H), 2.10 (tt, J = 12.0, 3.6 Hz, 1H), 2.49 (hept., J = 6.8 Hz, 1H), 2.77-2.85 (br. m, 2H), 6.62 (q, J = 5.2 Hz, 1H), 7.42 (t, J = 5.6 Hz, 1H). MS (ESI) m/z 338.16 (M+Na)+; 314.12 (M-H)-.
Example 17: Sodium \textit{trans}-4-\{\[(1R)-1-(2-Methylpropanoyloxy)ethoxy\]carbonylamino\}methyl\}-Cyclohexanecarboxylate (18)

Following the general procedure for the formation of the corresponding sodium carboxylates of acyloxyalkyl carbamates of tranexamic acid, 1.976 g (6.0 mmol) of \textit{trans}-4-\{\{(1R)-1-(2-methylpropanoyloxy)ethoxy\}carbonylamino\}methyl\}-cyclohexanecarboxylic acid 17 was reacted with 24.0 mg (0.2854 mmol) of sodium bicarbonate (NaHCO3) in 4 mL of a mixture of acetonitrile and water (1:1) to yield 2.11 g (quant.) of the title compound 18 as a colorless powder. The enantiomeric excesses were determined with an analytical Waters 2690/ZQ LC/MS apparatus using a ChiralPak AD-RH column, an isocratic eluent consisting of 30% acetonitrile/70% water/0.05% formic acid, and a flowrate of 60 μL/min (Rf=15.0 min; e.e. = 97.7 %). $^{1}$H NMR (400 MHz, DMSO-d6): $\delta$ = 0.72-0.84 (br. m, 2H), 1.22-1.32 (br. m, 3H), 1.38 (d, J= 5.2 Hz, 3H), 2.43-2.53 (m, 1H), 2.72-2.84 (br. m, 2H), 6.62 (q, J= 5.6 Hz, 1H), 7.42 (t, J= 5.6 Hz, 1H). MS (ESI) m/z 338.16 (M+Na)+; 314.12 (M-H)-.

Example 18: \textit{trans}-4-\{\{(1R)-1-(3-Methylbutanoyloxy)ethoxy\]carbonyl\}aminomethyl\}-Cyclohexanecarboxylic Acid (19)

Following the general procedure for the formation of the corresponding sodium carboxylates of acyloxyalkyl carbamates of tranexamic acid, 1.976 g (6.0 mmol) of trans-4-\{\{(1R)-1-(3-methylbutanoyloxy)ethoxy\}carbonylamino\}methyl\}-cyclohexanecarboxylic acid 17 was reacted with 24.0 mg (0.2854 mmol) of sodium bicarbonate (NaHCO3) in 4 mL of a mixture of acetonitrile and water (1:1) to yield 96.3 mg (quant.) of the title compound 19 as a colorless powder after lyophilization [Rf= 15.1 min; e.e. = 97.6 %; $[\alpha]_{D}^{25.5} = -14.94$, c (24.30, MeOH)]. The assignment of the absolute configuration was accomplished by comparison with material obtained from an independent synthesis. $^{1}$H NMR (400 MHz, DMSO-d6): $\delta$ = 0.82-0.94 (br. m, 2H), 1.057 (d, J= 6.8 Hz, 3H), 1.061 (d, J= 6.8 Hz, 3H), 1.17-1.36 (br. m, 3H), 1.38 (d, J = 5.6 Hz, 3H), 1.65-1.73 (br. m, 2H), 1.83-1.91 (br. m, 2H), 2.10 (tt, J= 12.0, 3.6 Hz, 1H), 2.49 (hept., J= 6.8 Hz, 1H), 2.77-2.85 (br. m, 2H), 6.62 (q, J= 5.2 Hz, 1H), 7.45 (t, J= 6.0 Hz, 1H), 11.97 (br. s, 1H). MS (ESI) m/z 338.16 (M+Na)+; 314.12 (M-H)-.

Example 19: Sodium \textit{trans}-4-\{\{(1R)-1-(2,5-Dioxopyrrolidinyl)oxycarbonyloxy\]ethyl cyclohexanecarboxylate (700 mg, 2.2 mmol) were reacted in the MTBE/acetone/water mixture (16 mL) to yield the title compound 19 (200 mg, 21 % yield) as a white powder after work-up and mass-guided preparative HPLC purification. $^{1}$H NMR (400 MHz, DMSO-d6): $\delta$ = 0.88-0.97 (m, 8H), 1.22-1.38 (m, 2H), 1.38 (d, J= 5.2 Hz, 3H), 1.59-1.73 (br. m, 3H), 1.75-1.83 (m, 2H), 1.94-2.14 (m, 2H), 2.43-2.53 (m, 1H), 2.72-2.84 (br. m, 2H), 6.69 (q, J= 5.6 Hz, 1H), 7.48 (t, J= 6.0 Hz, 1H), 12.01 (br. s, 1H). MS (ESI) m/z 352.15 (M+Na)+; 328.14 (M-H)-.

Example 20: \textit{trans}-4-\{\{(1R)-1-(2,5-Dioxopyrrolidinyl)oxycarbonyloxy\]ethyl 2,2-dimethylpropanoate (1.1 g, 3.8 mmol) were reacted in the MTBE/acetone/water mixture (16 mL) to yield the title compound 20 (200 mg, 16 % yield) as a white powder after work-up and mass-guided preparative HPLC purification. $^{1}$H NMR (400 MHz, DMSO-d6): $\delta$ = 0.86-0.99 (m, 2H), 1.14 (s, 9H), 1.21-1.39 (br. m, 3H), 1.42 (d, J= 5.2 Hz, 3H), 1.71-1.74 (m, 2H), 1.89-1.91 (m, 2H), 2.13 (tt, J=12, 3.6 Hz, 1H), 2.81-2.89 (m, 2H), 6.64 (q, J= 5.6 Hz, 1H), 7.49 (t, J= 6.0 Hz, 1H), 12.01 (br. s, 1H). MS (ESI) m/z 352.16 (M+Na)+; 328.14 (M-H)-.

Example 21: \textit{trans}-4-\{\{(1R)-1-(2,5-Dioxopyrrolidinyl)oxycarbonyloxy\]ethyl cyclohexanecarboxylate (700 mg, 2.2 mmol) were reacted in the MTBE/acetone/
water mixture (16 mL) to yield the title compound 22 (200 mg, 26% yield) as a white powder after work-up and mass-guided preparative HPLC purification. 1H NMR (400 MHz, DMSO-d6): δ = 0.87-0.99 (m, 2H), 1.20-1.44 (br. m, 11H), 1.58-1.81 (m, 7H), 1.89-1.92 (m, 2H), 2.13 (t, J= 12, 3.6 Hz, 1H), 2.27-2.35 (m, 1H), 2.79-2.90 (m, 2H), 6.66 (q, J= 5.6 Hz, 1H), 7.48 (t, J= 6.0 Hz, 1H), 12.05 (br. s, 1H). MS (ESI) m/z 378.13 (M+Na)+; 354.15 (M-H)-.

Example 22: trans-4-[(1-Benzoyloxy)ethoxycarbonyl]aminomethyl]-Cyclohexanecarboxylic Acid (23)

Following the general nucleophilic carbamoylation procedure, tranexamic acid (1.1 g, 7.0 mmol) and 1-[(2,5-dioxopyrrolidinyl)oxycarbonyloxy]ethyl benzoate (800 mg, 2.6 mmol) were reacted in the MTBE/acetone/water mixture (16 mL) to yield the title compound 23 (160 mg, 18% yield) as a white powder after work-up and mass-guided preparative HPLC purification. 1H NMR (400 MHz, DMSO-d6): δ = 0.72-0.86 (m, 2H), 1.08-1.21 (m, 2H), 1.22-1.32 (m, 1H), 1.53 (d, J= 5.6 Hz, 3H), 1.59-1.84 (br. m, 5H), 2.38-2.44 (m, 4H), 2.68 (q, J= 5.6 Hz, 1H), 6.87-7.00 (m, 2H), 7.00 (m, 1H), 7.94-7.96 (m, 2H), 12.05 (br. s, 1H). MS (ESI) m/z 372.10 (M+Na)+; 348.05 (M-H)-.

Example 23: Sodium trans-4-[(1-Benzoyloxy)ethoxycarbonyl]aminomethyl]-Cyclohexanecarboxylate (24)

Following the general nucleophilic carbamoylation procedure for the formation of the corresponding sodium carboxylates of acyloxyalkyl carbamates of tranexamic acid, 2.096 g (6.0 mmol) of trans-4-[(1-benzoyloxy)ethoxycarbonyl]aminomethyl]-cyclohexanecarboxylic acid 23 was reacted with 504.1 mg (6.0 mmol) of sodium bicarbonate (NaHCO₃) in 20 mL of a mixture of acetonitrile and water (1:1) to yield 2.23 g (quant.) of the title compound 24 as a colorless powder. 1H NMR (400 MHz, DMSO-d6): δ = 0.79-0.99 (m, 2H), 1.20-1.44 (br. m, 11H), 1.57 (d, J= 5.6 Hz, 3H), 1.60-1.92 (m, 5H), 2.02-2.15 (m, 1H), 2.38-2.44 (m, 2H), 2.70-2.86 (m, 2H), 3.68-3.76 (m, 1H), 6.62-6.72 (m, 1H), 7.04-7.18 (m, 4H), 7.32-7.50 (m, 1H), 11.98 (br. s, 1H). MS (ESI) m/z 386.12 (M+Na)+; 362.07 (M-H)-.

Example 24: trans-4-[(2-Methylbenzyloxy)ethoxycarbonyl]aminomethyl]-Cyclohexanecarboxylic Acid (25)

Following the general nucleophilic carbamoylation procedure, tranexamic acid (780 mg, 5.0 mmol) and 1-[(2,5-dioxopyrrolidinyl)oxycarbonyloxy]ethyl 2-methylbenzoate (700 mg, 2.2 mmol) were reacted in the MTBE/acetone/water mixture (16 mL) to yield the title compound 25 (290 mg, 36% yield) as a white powder after work-up and mass-guided preparative HPLC purification. 1H NMR (400 MHz, DMSO-d6): δ = 0.88-0.97 (m, 2H), 1.22-1.38 (br. m, 3H), 1.57 (d, J= 5.6 Hz, 3H), 1.72-1.76 (m, 2H), 1.89-1.92 (m, 2H), 2.13 (t, J= 12, 3.6 Hz, 1H), 2.50 (s, 3H), 2.87 (t, J= 2.8 Hz, 2H), 6.80 (q, J= 5.6 Hz, 1H), 7.32-7.37 (m, 2H), 7.50-7.59 (m, 2H), 7.77 (dd, J= 7.2, 1.2 Hz, 1H), 12.00 (s, 1H). MS (ESI) m/z 386.12 (M+Na)+; 362.07 (M-H)-.


Following the general nucleophilic carbamoylation procedure, tranexamic acid (629 mg, 4.0 mmol) and 1-[(2,5-dioxopyrrolidinyl)oxycarbonyloxy]ethyl 2-[4-(2-methylpropyl)phenyl]propanoate (665 mg, 1.7 mmol) were reacted in the MTBE/acetone/water mixture (32 mL) to yield the title compound 26 (344 mg, 47% yield) as a colorless powder after work-up and mass-guided preparative HPLC purification. 1H NMR (400 MHz, DMSO-d6): δ = 0.79-0.95 (m, 8H), 1.61-1.39 (m, 9H), 1.60-1.92 (m, 5H), 2.02-2.15 (m, 1H), 2.38-2.44 (m, 2H), 2.70-2.86 (m, 2H), 3.68-3.76 (m, 1H), 6.62-6.72 (m, 1H), 7.04-7.18 (m, 4H), 7.32-7.50 (m, 1H), 11.98 (br. s, 1H). MS (ESI) m/z 456.24 (M+Na)+; 432.19 (M-H)-.


Following the general nucleophilic carbamoylation procedure, tranexamic acid (6.9 g, 43.9 mmol) and 1-[(2,5-dioxopyrrolidinyl)oxycarbonyloxy]ethyl (2S)-2-[6-methoxy[2-naphthyl])propanoate (ca. 6.2 g, 14.9 mmol) were reacted in the MTBE/acetone/water mixture (160 mL) to yield the title compound 27 (579 mg, 9% yield) as a colorless powder after work-up, purification by silica gel column chromatography using ethyl acetate/hexane mixtures from 2:1 to 4:1 as eluent, and subsequent mass-guided preparative HPLC. 1H NMR (400 MHz, DMSO-d6): δ = 0.76-0.94 (m, 2H), 1.10-1.92 (m, 13H), 1.98-2.14 (m, 1H), 2.66-2.86 (m, 2H), 3.82-3.95 (m, 4H), 6.64-6.76 (m, 1H), 7.10-7.17 (m, 1H), 7.24-7.50 (m, 3H), 7.63-7.80 (m, 3H), 11.99 (br.s, 1H). MS (ESI) m/z 480.16 (M+Na)+; 456.18 (M-H)-.

Example 27: trans-4-[1-(Propanoyloxy)propoxy]carbonyl]aminomethyl]-Cyclohexanecarboxylic Acid (28)

Following the general nucleophilic carbamoylation procedure, tranexamic acid (472 mg, 3.0 mmol) and 1-[(2,5-
dioxopyrrolidinyl]oxycarbonyloxy]propyl propanoate (281 mg, 1.03 mmol) were reacted in the MTBE/acetone/water mixture (16 mL) to yield the title compound 28 (173 mg, 53% yield) as a white powder after work-up and mass-guided preparative HPLC purification. 1H NMR (400 MHz, DMSO-d6): δ = 0.82-0.94 (br. m, 5H), 1.01 (t, J= 7.2 Hz, 3H), 1.17-1.37 (br. m, 3H), 1.64-1.75 (m, 4H), 1.83-1.91 (br. m, 2H), 2.10 (tt, J=12.0, 3.6 Hz, 1H), 2.26-2.38 (m, 2H), 2.76-2.87 (br. m, 2H), 6.54 (t, J= 6.0 Hz, 1H), 7.42 (t, J= 6.0 Hz, 1H), 11.97 (br. s, 1H). MS (ESI) m/z 338.16 (M+Na)+; 314.12 (M-H)-.

Example 28: trans-4-[[1-(Butanoyloxy)propoxycarbonyl]aminomethyl]-Cyclohexanecarboxylic Acid (29)

Following the general nucleophilic carbamoylation procedure, tranexamic acid (472 mg, 3.0 mmol) and 1-[(2,5-dioxopyrrolidinyl)oxycarbonyloxy]propyl butanoate (575 mg, 2.0 mmol) were reacted in the MTBE/acetone/water mixture (16 mL) to yield the title compound 29 (408 mg, 62% yield) as a white powder after work-up and mass-guided preparative HPLC purification. 1H NMR (400 MHz, DMSO-d6): δ = 0.81-0.94 (br. m, 8H), 1.17-1.38 (br. m, 3H), 1.47-1.58 (m, 2H), 1.64-1.75 (m, 4H), 1.83-1.92 (br. m, 2H), 2.10 (tt, J=12.0, 3.6 Hz, 1H), 2.26 (t, J= 7.2 Hz, 2H), 2.75-2.88 (m, 2H), 6.55 (t, J= 5.2 Hz, 1H), 7.42 (t, J= 5.6 Hz, 1H), 11.97 (br. s, 1H). MS (ESI) m/z 352.18 (M+Na)+; 328.14 (M-H)-.

Example 29: trans-4-[[1-(2-Methylpropanoyloxy)propoxycarbonyl]aminomethyl]-Cyclohexanecarboxylic Acid (30)

Following the general nucleophilic carbamoylation procedure, tranexamic acid (472 mg, 3.0 mmol) and 1-[(2,5-dioxopyrrolidinyl)oxycarbonyloxy]propyl 2-methylpropanoate (281 mg, 1.03 mmol) were reacted in the MTBE/acetone/water mixture (16 mL) to yield the title compound 30 (651 mg, 99% yield) as a white powder after work-up and mass-guided preparative HPLC purification. 1H NMR (400 MHz, DMSO-d6): δ = 0.82-0.94 (br. m, 5H), 1.06 (d, J= 6.8 Hz, 3H), 1.07 (d, J= 6.8 Hz, 3H), 1.17-1.39 (br. m, 3H), 1.64-1.76 (br. m, 4H), 1.83-1.91 (br. m, 2H), 2.09 (tt, J=12.4, 3.6 Hz, 1H), 2.50 (hept., J= 6.8 Hz, 1H), 2.77-2.84 (br. m, 2H), 6.52 (1, J= 5.6 Hz, 1H), 7.43 (t, J= 6.0 Hz, 1H), 11.98 (br. s, 1H). MS (ESI) m/z 352.06 (M+Na)+; 328.02 (M-H)-.

Example 30: trans-4-[[1-(2,2-Dimethylpropanoyloxy)propoxycarbonyl]aminomethyl]-Cyclohexanecarboxylic Acid (31)

Following the general nucleophilic carbamoylation procedure, tranexamic acid (472 mg, 3.0 mmol) and 1-[(2,5-dioxopyrrolidinyl)oxycarbonyloxy]propyl 2,2-dimethylpropanoate (290 mg, 0.96 mmol) were reacted in the MTBE/acetone/water mixture (16 mL) to yield the title compound 31 (147 mg, 45% yield) as a white powder after work-up and mass-guided preparative HPLC purification. 1H NMR (400 MHz, DMSO-d6): δ = 0.82-0.94 (br. m, 5H), 1.12 (s, 9H), 1.16-1.38 (m, 3H), 1.64-1.76 (m, 4H), 1.82-1.91 (br. m, 2H), 2.09 (tt, J=12.0, 3.2 Hz, 1H), 2.72-2.90 (m, 2H), 6.51 (t, J= 5.6 Hz, 1H), 7.44 (t, J= 6.0 Hz, 1H), 11.97 (br. s, 1H). MS (ESI) m/z 366.21 (M+Na)+; 342.16 (M-H)-.

Example 31: trans-4-[[1-(Benzoyloxy)propoxycarbonyl]aminomethyl]-Cyclohexanecarboxylic Acid (32)

Following the general nucleophilic carbamoylation procedure, tranexamic acid (472 mg, 3.0 mmol) and 1-[(2,5-dioxopyrrolidinyl)oxycarbonyloxy]propyl benzoate (602 mg, 2.0 mmol) were reacted in the MTBE/acetone/water mixture (16 mL) to yield the title compound 32 (679 mg, 93% yield) as a white powder after work-up and mass-guided preparative HPLC purification. 1H NMR (400 MHz, DMSO-d6): δ = 0.80-0.95 (br. m, 2H), 0.96 (t, J= 7.6 Hz, 3H), 1.15-1.38 (br. m, 3H), 1.60-1.74 (m, 2H), 1.82-1.91 (m, 4H), 2.08 (tt, J= 12.0, 3.2 Hz, 1H), 2.76-2.87 (br. m, 2H), 6.78 (t, J= 5.6 Hz, 1H), 7.48-7.56 (br. m, 3H), 7.67 (tt, J= 7.6, 1.2 Hz, 1H), 7.90-7.95 (m, 2H), 11.96 (br. s, 1H). MS (ESI) m/z 386.12 (M+Na)+; 362.14 (M-H)-.

Example 32: trans-4-[[1-(Acetoxy)butoxycarbonyl]aminomethyl]-Cyclohexanecarboxylic Acid (33)

Following the general nucleophilic carbamoylation procedure, tranexamic acid (472 mg, 3.0 mmol) and 1-[(2,5-dioxopyrrolidinyl)oxycarbonyloxy]butyl acetate (620 mg, 2.27 mmol) were reacted in the MTBE/acetone/water mixture (16 mL) to yield the title compound 33 (174 mg, 24% yield) as a waxy white solid after work-up and mass-guided preparative HPLC purification. 1H NMR (400 MHz, DMSO-d6): δ = 0.82-0.94 (br. m, 5H), 1.17-1.38 (br. m, 5H), 1.63-1.73 (br. m, 4H), 1.83-1.91 (br. m, 2H), 2.05 (s, 3H), 2.10 (tt, J= 11.6, 3.6 Hz, 1H), 2.74-2.88 (m, 2H), 6.58 (t, J= 5.6 Hz, 1H), 7.42 (t, J= 6.0 Hz, 1H), 11.97 (br. s, 1H). MS (ESI) m/z 338.16 (M+Na)+; 314.12 (M-H)-.

Example 33: trans-4-[[1-(Pronanoyloxy)butoxycarbonyl]aminomethyl]-Cyclohexanecarboxylic Acid (34)

Following the general nucleophilic carbamoylation procedure, tranexamic acid (472 mg, 3.0 mmol) and 1-[(2,5-
dioxopyrrolidinyl)oxycarbonyloxy]-2-methylpropyl acetate (306 mg, 1.12 mmol) were reacted in the MTBE/acetone/water mixture (16 mL) to yield the title compound 34 (144 mg, 18% yield) as a brittle off-white solid after work-up and mass-guided preparative HPLC purification. 1H NMR (400 MHz, DMSO-d6): δ = 0.82-0.94 (br. m, 5H), 1.01 (t, J= 7.2 Hz, 3H), 1.17-1.38 (br. m, 5H), 1.63-1.73 (br. m, 4H), 1.84-1.92 (br. m, 2H), 2.10 (tt, J=12.0, 3.6 Hz, 1H), 2.22-2.38 (m, 2H), 2.75-2.87 (m, 2H), 6.60 (t, J= 6.0 Hz, 1H), 7.42 (t, J= 6.0 Hz, 1H), 11.97 (br.s, 1H). MS (ESI) m/z 352.18 (M+Na)+; 328.14 (M-H)-.

Example 34: trans-4-[(1-(Butanoyloxy)butoxy)carbonyl]aminomethyl]-Cyclohexanecarboxylic Acid (35)

Following the general nucleophilic carbamoylation procedure, tranexamic acid (800 mg, 5 mmol) and 1-[(2,5-dioxopyrrolidinyl)oxycarbonyloxy]butyl 2-methylpropanoate (700 mg, 2.2 mmol) were reacted in the MTBE/acetone/water mixture (16 mL) to yield the title compound 35 (210 mg, 27% yield) as a white powder after work-up and mass-guided preparative HPLC purification. 1H NMR (400 MHz, DMSO-d6): δ = 0.87-0.95 (br. m, 8H), 1.22-1.41 (br. m, 5H), 1.56 (m, 2H), 1.68-1.73 (m, 4H), 1.89-1.92 (m, 2H), 2.13 (tt, J= 12, 3.2 Hz, 1H), 2.30 (t, J= 7.2 Hz, 2H), 6.65 (t, J= 5.6 Hz, 1H), 7.45 (t, J= 6.0 Hz, 1H), 12.04 (s, 1H). MS (ESI) m/z 366.21 (M+Na)+; 342.16 (M-H)-.

Example 35: trans-4-[(1-(2-Methylpropanoyloxy)butoxy)carbonyl]aminomethyl]-Cyclohexanecarboxylic Acid (36)

Following the general nucleophilic carbamoylation procedure, tranexamic acid (800 mg, 5 mmol) and 1-[(2,5-dioxopyrrolidinyl)oxycarbonyloxy]butyl 3-methylbutanoate (700 mg, 2.3 mmol) were reacted in the MTBE/acetone/water mixture (16 mL) to yield the title compound 36 (100 mg, 13% yield) as a white powder after work-up and mass-guided preparative HPLC purification. 1H NMR (400 MHz, DMSO-d6): δ = 0.87-0.95 (m, 8H), 1.08 (d, J= 4.0 Hz, 3H), 1.10 (d, J= 4.0 Hz, 3H), 1.21-1.41 (br. m, 5H), 1.68-1.73 (m, 4H), 1.89-1.91 (m, 2H), 2.13 (tt, J= 12.3 Hz, 1H), 2.79-2.88 (m, 3H), 6.65 (t, J= 5.6 Hz, 1H), 7.45 (t, J= 6.0 Hz, 1H), 12.04 (s, 1H). MS (ESI) m/z 380.22 (M+Na)+; 356.18 (M-H)-.

Example 36: trans-4-[(1-(3-Methylbutanoyloxy)butoxy)carbonyl]aminomethyl]-Cyclohexanecarboxylic Acid (37)

Following the general nucleophilic carbamoylation procedure, tranexamic acid (800 mg, 5 mmol) and 1-[(2,5-dioxopyrrolidinyl)oxycarbonyloxy]butyl 2-methylpropanoate (700 mg, 2.3 mmol) were reacted in the MTBE/acetone/water mixture (16 mL) to yield the title compound 37 (120 mg, 15% yield) as a white powder after work-up and mass-guided preparative HPLC purification. 1H NMR (400 MHz, DMSO-d6): δ = 0.87-0.95 (m, 11H), 1.21-1.41 (br. m, 5H), 1.68-1.73 (m, 4H), 1.89-2.02 (m, 3H), 2.10-2.22 (m, 3H), 2.80-2.89 (m, 2H), 6.65 (t, J= 5.6 Hz, 1H), 7.45 (t, J= 6.0 Hz, 1H), 12.04 (s, 1H). MS (ESI) m/z 392.30 (M+Na)+; 368.16 (M-H)-.

Example 37: trans-4-[(1-(2,2-Dimethylpropanoyloxy)butoxy)carbonyl]aminomethyl]-Cyclohexanecarboxylic Acid (38)

Following the general nucleophilic carbamoylation procedure, tranexamic acid (800 mg, 5 mmol) and 1-[(2,5-dioxopyrrolidinyl)oxycarbonyloxy]butyl 2,2-dimethylpropanoate (700 mg, 2.2 mmol) were reacted in the MTBE/acetone/water mixture (16 mL) to yield the title compound 38 (90 mg, 12% yield) as a white powder after work-up and mass-guided preparative HPLC purification. 1H NMR (400 MHz, DMSO-d6): δ = 0.82-0.89 (m, 9H), 1.12-1.38 (br. m, 14H), 1.69-1.74 (m, 4H), 1.89-1.92 (m, 2H), 2.13 (tt, J= 12, 3.2 Hz, 1H), 2.78-2.91 (m, 2H), 6.61 (t, J= 5.6 Hz, 1H), 7.47 (t, J= 6.0 Hz, 1H), 12.04 (s, 1H). MS (ESI) m/z 380.22 (M+Na)+; 356.18 (M-H)-.

Example 38: trans-4-[(1-(Benzooyloxy)butoxy)carbonyl]aminomethyl]-Cyclohexanecarboxylic Acid (39)

Following the general nucleophilic carbamoylation procedure, tranexamic acid (800 mg, 5 mmol) and 1-[(2,5-dioxopyrrolidinyl)oxycarbonyloxy]butyl benzoate (700 mg, 2.1 mmol) were reacted in the MTBE/acetone/water mixture (16 mL) to yield the title compound 39 (150 mg, 19% yield) as a white powder after work-up and mass-guided preparative HPLC purification. 1H NMR (400 MHz, DMSO-d6): δ = 0.84-0.99 (m, 5H), 1.20-1.38 (br. m, 3H), 1.41-1.51 (m, 2H), 1.70-1.73 (m, 2H), 1.84-1.89 (m, 4H), 2.11 (tt, J= 12.3 Hz, 1H), 2.82-2.91 (m, 2H), 6.61 (t, J= 5.6 Hz, 1H), 7.52-7.58 (m, 3H), 7.47 (t, J= 6.0 Hz, 1H), 7.95-7.97 (m, 2H), 12.04 (s, 1H). MS (ESI) m/z 400.15 (M+Na)+; 376.16 (M-H)-.

Example 39: trans-4-[(1-(Acetoxy)-2-methylpropoxy)carbonyl]aminomethyl]-Cyclohexanecarboxylic Acid (40)

Following the general nucleophilic carbamoylation procedure, tranexamic acid (472 mg, 3.0 mmol) and 1-[(2,5-dioxopyrrolidinyl)oxycarbonyloxy]-2-methyl(propyl) acetate (306 mg, 1.12 mmol) were reacted in the MTBE/acetone/water mixture (16 mL) to yield the title compound 40 (144 mg, 18% yield) as a brittle off-white solid after work-up and mass-guided preparative HPLC purification. 1H NMR (400 MHz, DMSO-d6): δ = 0.82-0.94 (br. m, 5H), 1.01 (t, J= 7.2 Hz, 3H), 1.17-1.38 (br. m, 5H), 1.63-1.73 (br. m, 4H), 1.84-1.92 (br. m, 2H), 2.10 (tt, J=12.0, 3.6 Hz, 1H), 2.22-2.38 (m, 2H), 2.75-2.87 (m, 2H), 6.60 (t, J= 6.0 Hz, 1H), 7.42 (t, J= 6.0 Hz, 1H), 11.97 (br.s, 1H). MS (ESI) m/z 380.22 (M+Na)+; 356.18 (M-H)-.
EP 1 919 859 B1

mixture (16 mL) to yield the title compound 40 (89 mg, 28% yield) as an oily solid after work-up and mass-guided preparative HPLC purification. $^1$H NMR (400 MHz, DMSO-d$_6$): $\delta$ = 0.83-0.95 (br. m, 8H), 1.18-1.37 (m, 3H), 1.65-1.73 (br. m, 2H), 1.84-1.97 (br. m, 3H), 2.02 (s, 3H), 2.10 (tt, J = 12.0, 3.6 Hz, 1H), 2.78-2.84 (m, 2H), 6.41 (d, J = 5.2 Hz, 1H), 7.39 (t, J = 6.0 Hz, 1H), 11.97 (br. s, 1H). MS (ESI) m/z 338.16 (M+Na)$^+$; 314.12 (M-H)$^-$.  

Example 40: trans-4-[[1-(Propanoyloxy)-2-methylpropoxycarbonyl]aminomethyl]-Cyclohexanecarboxylic Acid (41)

Following the general nucleophilic carbamoylation procedure, tranexamic acid (250 mg, 1.6 mmol) and 1-[[2,5-dioxopyrrolidinyl]oxycarbonyloxy]-2-methylpropyl propanoate (230 mg, 0.80 mmol) were reacted in the MTBE/acetone/water mixture (16 mL) to yield the title compound 41 (150 mg, 21% yield) as a white powder after work-up and mass-guided preparative HPLC purification. $^1$H NMR (400 MHz, DMSO-d$_6$): $\delta$ = 0.85-0.92 (m, 8H), 1.08 (t, J = 7.2 Hz, 3H), 1.17-1.32 (br. m, 3H), 1.68 (d, J = 12 Hz, 2H), 1.85-1.96 (br. m, 3H), 2.05-2.12 (m, 1H), 2.25-2.36 (br. m, 2H), 2.80 (t, J = 6.4 Hz, 2H), 6.42 (d, J = 5.2 Hz, 1H), 7.38 (t, J = 6.0 Hz, 1H), 11.97 (br. s, 1H). MS (ESI) m/z 352.12 (M+Na)$^+$; 328.14 (M-H)$^-$.  

Example 41: trans-4-[[1-(Pentanoyloxy)-2-methylpropoxycarbonyl]aminomethyl]-Cyclohexanecarboxylic Acid (42)

Following the general nucleophilic carbamoylation procedure, tranexamic acid (700 mg, 4.5 mmol) and 1-[[2,5-dioxopyrrolidinyl]oxycarbonyloxy]-2-methylpropyl pentanoate (500 mg, 1.6 mmol) were reacted in the MTBE/acetone/water mixture (16 mL) to yield the title compound 42 (150 mg, 27% yield) as a white powder after work-up and mass-guided preparative HPLC purification. $^1$H NMR (400 MHz, DMSO-d$_6$): $\delta$ = 0.83-0.92 (br. m, 11H), 1.17-1.32 (br. m, 5H), 1.45-1.52 (m, 2H), 1.68 (d, J = 12 Hz, 2H), 1.85-1.94 (br. m, 3H), 2.04-2.12 (m, 1H), 2.27-2.32 (br. m, 1H), 2.83 (td, J = 7.2, 1.6 Hz, 2H), 2.78-2.82 (m, 2H), 6.42 (d, J = 5.2 Hz, 1H), 7.38 (t, J = 6.0 Hz, 1H), 11.97 (br. s, 1H). MS (ESI) m/z 380.16 (M+Na)$^+$; 356.17 (M-H)$^-$.  

Example 42: trans-4-[[1-(Butanoyloxy)-2-methylpropoxycarbonyl]aminomethyl]-Cyclohexanecarboxylic Acid (43)

Following the general nucleophilic carbamoylation procedure, tranexamic acid (472 mg, 3.0 mmol) and 1-[[2,5-dioxopyrrolidinyl]oxycarbonyloxy]-2-methylpropyl butanoate (602 mg, 2.0 mmol) were reacted in the MTBE/acetone/water mixture (16 mL) to yield the title compound 43 (513 mg, 75% yield) as a white powder after work-up and mass-guided preparative HPLC purification. $^1$H NMR (400 MHz, DMSO-d$_6$): $\delta$ = 0.83-0.95 (br. m, 11H), 1.17-1.38 (m, 3H), 1.48-1.58 (m, 2H), 1.65-1.73 (br. m, 2H), 1.83-1.98 (br. m, 3H), 2.10 (tt, J = 12.0, 3.2 Hz, 1H), 2.21-2.32 (br. m, 2H), 2.75-2.87 (br. m, 2H), 6.44 (d, J = 5.6 Hz, 1H), 7.40 (t, J = 6.0 Hz, 1H), 11.97 (br. s, 1H). MS (ESI) m/z 366.21 (M+Na)$^+$; 342.16 (M-H)$^-$.  

Example 43: trans-4-[[1-(2-Methylpropanoyloxy)-2-methylpropoxycarbonyl]aminomethyl]-Cyclohexanecarboxylic Acid (44)

Following the general nucleophilic carbamoylation procedure, tranexamic acid (472 mg, 3.0 mmol) and 1-[[2,5-dioxopyrrolidinyl]oxycarbonyloxy]-2-methylpropyl 2-methylpropanoate (603 mg, 2.0 mmol) were reacted in the MTBE/acetone/water mixture (16 mL) to yield the title compound 44 (486 mg, 71% yield) as a white powder after work-up and mass-guided preparative HPLC purification. $^1$H NMR (400 MHz, DMSO-d$_6$): $\delta$ = 0.82-0.94 (br. m, 8H), 1.06 (d, J = 6.8 Hz, 3H), 1.08 (d, J = 7.2 Hz, 3H), 1.16-1.38 (br. m, 3H), 1.64-1.73 (br. m, 2H), 1.82-1.92 (br. m, 3H), 2.10 (tt, J = 12.0, 3.6 Hz, 1H), 2.52 (hept., J = 6.8 Hz, 1H), 2.74-2.87 (br. m, 2H), 6.42 (d, J = 5.2 Hz, 1H), 7.40 (t, J = 6.0 Hz, 1H), 11.97 (br. s, 1H). MS (ESI) m/z 366.08 (M+Na)$^+$; 342.04 (M-H)$^-$.  

Example 44: Sodium trans-4-[[1-(2-Methylpropanoyloxy)-2-methylpropoxycarbonyl]aminomethyl]-Cyclohexanecarboxylate (45)

Following the general nucleophilic carbamoylation procedure for the formation of the corresponding sodium carboxylates of acyloxyalkyl carbamates of tranexamic acid, 4.343 g (10.0 mmol) of trans-4-[[1-(2-methylpropanoyloxy)-2-methylpropoxycarbonyl]aminomethyl]-cyclohexanecarboxylic acid 44 was reacted with 840.1 mg (10.0 mmol) of sodium bicarbonate (NaHCO$_3$) in 60 mL of a mixture of acetoneitrile and water (1:2) to yield 3.654 g (quant.) of the title compound 45 as a colorless powder. $^1$H NMR (400 MHz, DMSO-d$_6$): $\delta$ = 0.72-0.84 (m, 2H), 0.87-0.92 (m, 6H), 1.04-1.20 (m, 8H), 1.20-1.32 (m, 1H), 1.59-1.73 (m, 3H), 1.74-1.83 (m, 2H), 1.88-1.98 (m, 1H), 2.46-2.56 (m, 1H), 2.72-2.84 (br.
Example 45: trans-4-{[1-(3-Methylbutanoyloxy)-2-methylpropoxycarbonyl]aminomethyl}-Cyclohexanecarboxylic Acid (46)

[0249] Following the general nucleophilic carbamoylation procedure, tranexamic acid (472 mg, 3.0 mmol) and 1-[(2,5-dioxopyrrolidinyl)oxycarbonyloxy]-2-methylpropyl 3-methylbutanoate (558 mg, 1.77 mmol) were reacted in the MTBE/acetone/water mixture (16 mL) to yield the title compound 46 (75 mg, 12% yield) as a white powder after work-up and mass-guided preparative HPLC purification. 1H NMR (400 MHz, DMSO-d6): δ = 0.82-0.94 (br. m, 14H), 1.17-1.37 (m, 3H), 1.65-1.73 (br. m, 2H), 1.83-2.12 (br. m, 4H), 2.09 (tt, J=12.4, 3.6 Hz, 1H), 2.72-2.87 (br. m, 2H), 6.45 (d, J= 4.8 Hz, 1H), 7.40 (t, J= 6.0 Hz, 1H), 11.97 (br. s, 1H). MS (ESI) m/z 380.23 (M+Na)+; 356.18 (M-H)-.

Example 46: trans-4-{[1-(2,2-Dimethylpropanoyloxy)-2-methylpropoxycarbonyl]aminomethyl}-Cyclohexane-carboxylic Acid (47)

[0250] Following the general nucleophilic carbamoylation procedure, tranexamic acid (472 mg, 3.0 mmol) and 1-[(2,5-dioxopyrrolidinyl)oxycarbonyloxy]-2-methylpropyl 2,2-dimethylpropanoate (631 mg, 2.0 mmol) were reacted in the MTBE/acetone/water mixture (16 mL) to yield the title compound 47 (23 mg, 3% yield) as an off-white powder after work-up and mass-guided preparative HPLC purification. 1H NMR (400 MHz, DMSO-d6): δ = 0.81-0.94 (br. m, 8H), 1.12 (s, 9H), 1.17-1.38 (m, 3H), 1.64-1.72 (br. m, 2H), 1.82-2.00 (br. m, 3H), 2.09 (tt, J=12.4, 3.2 Hz, 1H), 2.72-2.89 (br. m, 2H), 6.40 (d, J= 4.8 Hz, 1H), 7.41 (t, J= 5.6 Hz, 1H), 11.98 (br. s, 1H). MS (ESI) m/z 380.23 (M+Na)+; 356.18 (M-H)-.

Example 47: trans-4-{[1-(Cyclohexylcarbonyloxy)-2-methylpropoxycarbonyl]aminomethyl}-Cyclohexanecarboxylic Acid (48)

[0251] Following the general nucleophilic carbamoylation procedure, tranexamic acid (1.4 g, 8.0 mmol) and 1-[(2,5-dioxopyrrolidinyl)oxycarbonyloxy]-2-methylpropyl cyclohexanecarboxylate (1.0 g, 2.9 mmol) were reacted in the MTBE/acetone/water mixture (16 mL) to yield the title compound 48 (300 mg, 27% yield) as a white powder after work-up and mass-guided preparative HPLC purification. 1H NMR (400 MHz, DMSO-d6): δ = 0.83-0.92 (br. m, 8H), 1.15-1.35 (br. m, 8H), 1.54-1.95 (br. m, 10H), 2.08 (tt, J=12.0, 3.6 Hz, 1H), 2.74-2.83 (br. m, 2H), 6.41 (d, J= 5.2 Hz, 1H), 7.39 (t, J= 6.0 Hz, 1H), 11.97 (br. s, 1H). MS (ESI) m/z 406.14 (M+Na)+; 382.17 (M-H)-.

Example 48: trans-4-{[1-(Benzoyloxy)-2-methylpropoxycarbonyl]aminomethyl}-Cyclohexanecarboxylic Acid (49)

[0252] Following the general nucleophilic carbamoylation procedure, tranexamic acid (630 mg, 4.0 mmol) and 1-[(2,5-dioxopyrrolidinyl)oxycarbonyloxy]-2-methylpropyl benzoate (500 mg, 1.5 mmol) were reacted in the MTBE/acetone/water mixture (16 mL) to yield the title compound 49 (200 mg, 35% yield) as a white powder after work-up and mass-guided preparative HPLC purification. 1H NMR (400 MHz, DMSO-d6): δ = 0.84-0.91 (br. m, 2H), 0.99 (d, J= 6.8 Hz , 6H), 1.16-1.31 (br. m, 3H), 1.66-1.68 (br. m, 2H), 1.82-1.85 (m, 2H), 2.03-2.12 (br. m, 2H), 2.80 (tt, J= 6.4 Hz, 2H), 6.11 (d, J= 4.4 Hz, 1H), 7.51 (t, J= 6.0 Hz, 1H), 7.57 (t, J= 6.0 Hz, 2H), 7.71 (t, J= 7.2 Hz, 1H), 7.96 (dd, J= 8.4, 1.6 Hz, 2H), 11.97 (br. s, 1H). MS (ESI) m/z 400.08 (M+Na)+; 376.10 (M-H)-.

Example 49: trans-4-{[1-(Butanoyloxy)-1-cyclohexylmethoxycarbonyl]aminomethyl}-Cyclohexanecarboxylic Acid (50)

[0253] Following the general nucleophilic carbamoylation procedure, tranexamic acid (472 mg, 3.0 mmol) and 1-[(2,5-dioxopyrrolidinyl)oxycarbonyloxy]cyclohexylmethyl butanoate (683 mg, 2.0 mmol) were reacted in the MTBE/acetone/water mixture (16 mL) to yield the title compound 50 (329 mg, 43% yield) as a white powder after work-up and mass-guided preparative HPLC purification. 1H NMR (400 MHz, DMSO-d6): δ = 0.83-0.95 (br. m, 5H), 0.96-1.37 (br. m, 8H), 1.47-1.57 (m, 2H), 1.58-1.74 (br. m, 8H), 1.83-1.92 (br. m, 2H), 2.09 (tt, J=12.0, 3.6 Hz, 1H), 2.26 (td, J= 7.6,0.8 Hz, 2H), 2.74-2.86 (m, 2H), 6.44 (d, J= 5.6 Hz, 1H), 7.39 (t, J= 6.0 Hz, 1H), 11.97 (br. s, 1H). MS (ESI) m/z 406.24 (M+Na)+; 382.23 (M-H)-.
dioxopyrrolidinyl[oxycarbonyloxy]cyclohexylmethyl 2-methylpropanoate (683 mg, 2.0 mmol) were reacted in the MTBE/acetone/water mixture (16 mL) to yield the title compound 51 (327 mg, 43% yield) as a white powder after work-up and mass-guided preparative HPLC purification. $^1$H NMR (400 MHz, DMSO-d$_6$): $\delta$ = 0.81-0.94 (br. m, 2H), 1.00-1.36 (br. m, 14H), 1.58-1.74 (br. m, 8H), 1.83-1.91 (br. m, 2H), 2.09 (tt, $J$ = 12.0,3.6 Hz, 1H), 2.51 (hept., $J$= 6.8 Hz, 1H), 2.74-2.86 (m, 2H), 6.41 (d, $J$=5.2 Hz, 1H), 7.40 (br. t, $J$=5.6 Hz, 1H), 11.97 (br. s, 1H). MS (ESI) m/z 406.18 (M+Na$^+$); 382.19 (M-H$^-$).

Example 51: Standard Methods for Determination of Enzymatic Cleavage of Prodrugs in Vitro

[0255] The stabilities of prodrugs were evaluated in one or more in vitro systems using a variety of tissue preparations following methods known in the art. The chemical stability of prodrugs in aqueous buffers at a pH of 2.0, 7.4, and 8.0 were also measured. Tissues were obtained from commercial sources (e.g., Pel-Freez Biologicals, Rogers, AR, or GenTest Corporation, Woburn, MA). Experimental conditions used for the in vitro studies are described in Table 1. Each preparation was incubated with test compound at 37°C for one hour. Aliquots (50 μL) were removed at 0, 30, and 60 min and quenched with 0.1 % trifluoroacetic acid in acetonitrile. Samples were then centrifuged and analyzed by LC/MS/MS. Stability of prodrugs towards specific enzymes (e.g., peptidases, etc.) was also assessed in vitro by incubation with the purified enzyme.

[0256] Pancreatin Stability: Stability studies were conducted by incubating prodrug (5 μM) with 1% (w/v) pancreatin (Sigma, P-1625, from porcine pancreas) in 0.025 M Tris buffer containing 0.5 M NaCl (pH 7.5) at 37°C for 60 min. The reaction was stopped by addition of 2 volumes of methanol. After centrifugation at 14,000 rpm for 10 min, the supernatant was removed and analyzed by LC/MS/MS.

[0257] Caco-2 Homogenate S9 Stability: Caco-2 cells were grown for 21 days prior to harvesting. Culture medium was removed and cell monolayers were rinsed and scraped off into ice-cold 10 mM sodium phosphate/0.15 M potassium chloride, pH 7.4. Cells were lysed by sonication at 4 °C using a probe sonicator. Lysed cells were then transferred into 1.5 mL centrifuge vials and centrifuged at 9,000 g for 20 min at 4°C. The resulting supernatant (Caco-2 cell homogenate S9 fraction) was aliquoted into 0.5 mL vials and stored at -80 °C until used.

[0258] For stability studies, prodrug (5 μM) was incubated in Caco-2 homogenate S9 fraction (0.5 mg protein per mL) for 60 min at 37°C. Concentrations of intact prodrug and released tranexamic acid were determined at zero time and 60 min using LC/MS/MS.

[0259] pH-Dependent Stability: The long-term pH-dependent stability of tranexamic acid prodrug at 37 °C was measured by LC/MS/MS at five different representative pH values from pH 2.0 to pH 8.0 was determined. The test concentration was 5 μM. The amount of remaining prodrug and the amount of tranexamic acid released from the prodrug was determined at 0 hour and after 24 hours.

[0260] Compounds 13, 15-19, 32-34, 44, 46, 48-49, and 51, for example, showed good stability from pH 2 to pH 8, are stable in the presence of pancreatin and colonic wash (> 40% intact prodrug remaining after 60 min incubation) and are extensively hydrolyzed to liberate tranexamic acid in the presence of human liver S9(< 15% prodrug remaining after 60 min incubation).

| Table 1. Standard Conditions for Prodrug In Vitro Metabolism Studies |
|----------------------|---------------------|-----------------|
| Preparation          | Substrate Concentration | Cofactors       |
| Rat Plasma           | 2.0 pM               | None            |
| Human Plasma         | 2.0 μM               | None            |
| Rat Liver S9 (0.5 mg/mL) | 2.0 μM         | NADPH*          |
| Human Liver S9       | 2.0 μM (0.5 mg/mL)   | NADPH*          |
| Human Intestine S9 (0.5 mg/mL) | 2.0 μM       | NADPH*          |
| CarboxypeptidaseA (10 units/mL) | 2.0 μM    | None            |
| Caco-2 Homogenate    | 5.0 μM               | None            |
| Pancreatin           | 5.0 μM               | None            |

* NADPH generating system, e.g., 1.3 mM NADP*, 3.3 mM glucose-6-phosphate, 0.4 U/mL glucose-6-phosphate dehydrogenase, 3.3 mM magnesium chloride and 0.95 mg/mL potassium phosphate, pH 7.4.
**Example 52: In Vitro Determination of Caco-2 Cellular Permeability of Prodrugs**

[0261] The passive permeability of the prodrugs of the present disclosure can be assessed in vitro using standard methods well known in the art (see, e.g., Stewart, et al., Pharm. Res., 1995, 12, 693). For example, passive permeability can be evaluated by examining the flux of a prodrug across a cultured polarized cell monolayer (e.g., Caco-2 cells).

[0262] Caco-2 cells obtained from continuous culture (passage less than 28) were seeded at high density onto Transwell polycarbonate filters. Cells were maintained with DMEM/10% fetal bovine serum, 1 mM nonessential amino acids, and 6 mM L-Gln, 5% CO2 / 95% O2, at 37 °C until the day of the experiment. Permeability studies were conducted at pH 6.5 apically (in 50 mM MES buffer containing 1 mM CaCl2, 1mM MgCl2, 150 mM NaCl, 3 mM KCl, 1mM NaH2PO4, 5 mM glucose) and pH 7.4 basolaterally (in Hanks’ balanced salt solution containing 10 mM HEPES) in the presence of efflux pump inhibitors (250 μM MK-571 and 250 μM Verapamil). Inserts were placed in 12 or 24 well plates containing buffer and incubated for 30 min at 37°C. Prodrug (200 μM) was added to the apical or basolateral compartment (donor) and concentrations of prodrug and/or released parent drug in the opposite compartment (receiver) were determined at intervals over 1 hour using LC/MS/MS. Values of apparent permeability (Papp) were calculated using the equation:

\[
P_{\text{app}} = \frac{V_r (dC/dt)}{(A)(C_0)}
\]

where \(V_r\) is the volume of the receiver compartment in mL; \(dC/dt\) is the total flux of prodrug and parent drug (μM/sec), determined from the slope of the plot of concentration in the receiver compartment versus time; \(C_0\) is the initial concentration of prodrug in μM; and \(A\) is the surface area of the membrane in cm². Prodrugs with significant transcellular permeability may demonstrate a value of \(P_{\text{app}}\) of \(\geq 1 \times 10^{-6}\) cm/sec, for example, a value of \(P_{\text{app}}\) of \(\geq 1 \times 10^{-5}\) cm/sec, or even a value of \(P_{\text{app}}\) of \(\geq 5 \times 10^{-5}\) cm/sec. Typical values of \(P_{\text{app}}\) obtained for prodrugs of the present disclosure are shown in Table 2.

<table>
<thead>
<tr>
<th>Compound</th>
<th>(P_{\text{app}}) (apical to basolateral) ((\times 10^{-5}) cm/sec)</th>
<th>(P_{\text{app}}) (basolateral to apical) ((\times 10^{-5}) cm/sec)</th>
<th>Ratio (A-B/B-A)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.04</td>
<td>0.03</td>
<td>1.3</td>
</tr>
<tr>
<td>4</td>
<td>4.74</td>
<td>0.62</td>
<td>7.7</td>
</tr>
<tr>
<td>7</td>
<td>4.06</td>
<td>0.97</td>
<td>4.2</td>
</tr>
<tr>
<td>10</td>
<td>6.04</td>
<td>1.22</td>
<td>4.9</td>
</tr>
<tr>
<td>13</td>
<td>5.09</td>
<td>1.07</td>
<td>4.8</td>
</tr>
<tr>
<td>14</td>
<td>4.49</td>
<td>1.34</td>
<td>3.4</td>
</tr>
<tr>
<td>15</td>
<td>7.32</td>
<td>1.20</td>
<td>6.1</td>
</tr>
<tr>
<td>17</td>
<td>4.87</td>
<td>1.22</td>
<td>4.0</td>
</tr>
<tr>
<td>19</td>
<td>7.24</td>
<td>1.39</td>
<td>5.2</td>
</tr>
<tr>
<td>23</td>
<td>7.90</td>
<td>1.77</td>
<td>4.5</td>
</tr>
<tr>
<td>36</td>
<td>3.77</td>
<td>0.84</td>
<td>4.5</td>
</tr>
<tr>
<td>42</td>
<td>4.68</td>
<td>1.59</td>
<td>2.9</td>
</tr>
<tr>
<td>44</td>
<td>6.05</td>
<td>2.70</td>
<td>2.2</td>
</tr>
<tr>
<td>48</td>
<td>5.58</td>
<td>1.79</td>
<td>3.1</td>
</tr>
<tr>
<td>49</td>
<td>4.50</td>
<td>1.54</td>
<td>2.9</td>
</tr>
</tbody>
</table>

[0263] The data in Table 2 shows that the prodrugs disclosed herein have high cellular permeability and should be well absorbed from the intestine. The apical-to-basolateral permeabilities of these prodrugs exceed their basolateral-to-apical permeabilities. This suggests that these compounds are substrates for active transport mechanisms present in the apical membrane of Caco-2 cells (although some component of this transcellular permeability may also be mediated by passive diffusion).
Example 53: Pharmacokinetics of Tranexamic Acid Following Administration of Tranexamic Acid or Tranexamic Acid Prodrug to Rats

[0264] Tranexamic acid or a tranexamic acid prodrug of the present disclosure was administered as an intravenous bolus injection (i.v.), by oral gavage (p.o.), or by intracolonic (i.c.) administration via an indwelling catheter in the ascending colon to groups of four to six adult male Sprague-Dawley rats (weight approximately 250 g). Animals were fasted overnight before the study and for 4 hours post-dosing and were conscious at the time of the experiment. When administered intravenously, tranexamic acid was administered as a solution in water at a dose equivalent to 16 mg (0.1 mmol) of tranexamic acid per kg body weight. Prodrugs were orally or intracolonically administered as a suspension in 0.5 % methyl cellulose in 0.1 % Tween 80 at a dose equivalent to 16 mg (0.1 mmol) of tranexamic acid per kg body weight.

Blood samples (300 μL) were obtained via a jugular vein cannula at intervals over 8 hours after oral dosing. Blood was quenched immediately using methanol and then was frozen at -80°C until analyzed.

The following procedure was used to prepared blood samples for analysis:

1. Rat blood (100 μL) was collected at different times into K2EDTA tubes, 300 μL of methanol, and the mixture was vortexed to mix the ingredients.
2. Blank rat blood (90 μL) was quenched with 300 μL of methanol. Then ten μL of a standard stock solution (0.04, 0.2, 1, 5, 25, and 100 μg/mL) were added to the tube individually. Then 20 μL of p-chlorophenylalanine (5 μg/mL in 50% methanol) was added to each tube to make up a final calibration standard (0.004, 0.02, 0.1, 0.5, 2.5, and 10 μg/mL). The samples were vortexed and centrifuged at 14,000 rpm for 20 min.
3. To the quenched blood samples were added 20 μL of p-chlorophenylalanine (5 μg/mL in 50% methanol), the samples were vortexed and centrifuged at 14,000 rpm for 20 min.
4. The supernatant was analyzed by LC/MS/MS.

The following method was used for LC/MS/MS Analysis of the prepared blood samples. An API 4000 or 2000 LC/MS/MS spectrometer equipped with Agilent 1100 binary pumps and a CTC HTS-PAL autosampler were used in the analysis. A ThermoHypersil-BetaSil C18, 100 × 4.6 mm, 5 μm column was used during the analysis. The mobile phase for the analysis of tranexamic acid and prodrug was (A) 0.1 % formic acid in water, and (B) 0.1 % formic acid in acetonitrile. The gradient condition was: 2 % eluent-B to 95 % eluent-B for 2.5 min, then to 98 % eluent-B to 4.0 min. At 4.1 min, it was returned to 2 % eluent-B and maintained at 2 % eluent-B till 6.0 min. The flow rate was 1 mL/min. An ESI source was used on the API 4000. The analysis of tranexamic acid was performed in positive ion mode for and negative ion mode was used for analysis of tranexamic acid prodrugs.

The MRN transition for each analyte was optimized using standard solutions. 20 μL of the sample was injected. Non-compartmental analysis was performed using WinNonlin (v.3.1 Professional Version, Pharsight Corporation, Mountain View, California) on individual animal profiles. Summary statistics on major parameter estimates was performed for Cmax (peak observed concentration following dosing), Tmax (time to maximum concentration is the time at which the peak concentration was observed), AUC(0-t) (area under the serum concentration-time curve from time zero to last collection time, estimated using the log-linear trapezoidal method), AUC(0-∞) (area under the serum concentration-time curve from time zero to infinity, estimated using the log-linear trapezoidal method to the last collection time with extrapolation to infinity), and T1/2 (terminal half-life).

The oral or intracolonic bioavailability (F) of tranexamic acid was determined by comparing the area under the tranexamic acid concentration vs. time curve (AUC) following oral or intracolonic administration of tranexamic acid or prodrug with the AUC of the tranexamic acid concentration vs. time curve following intravenous administration of tranexamic acid on a dose normalized basis. An AUCinf of 22.2 hr μg/mL for the intravenously administered tranexamic acid (dosed at 16 mg/kg) was used for the calculations of the bioavailability of tranexamic acid released from prodrugs post absorption. The results for tranexamic acid and tranexamic prodrug 13 are shown in Table 3, Figure 1, and Figure 2. In Table 3, the values represent the mean ± 1SD. When administered intracolonically, each of compounds 13-20, 23-24, and 44-45, for example, showed greater than 8-fold higher bioavailability of tranexamic acid compared to the bioavailability of tranexamic acid when tranexamic acid itself was administered intracolonically.

Table 3. Pharmacokinetic parameters of tranexamic acid and a tranexamic acid prodrug.

<table>
<thead>
<tr>
<th>Route of Administration</th>
<th>Tranexamic Acid</th>
<th>Tranexamic Acid</th>
<th>Compound 13</th>
<th>Compound 13</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>p.o.</td>
<td>i.c.</td>
<td>p.o.</td>
<td>i.c.</td>
</tr>
<tr>
<td>Cmax (μg/mL)</td>
<td>2.06 (0.45)</td>
<td>0.22 (0.22)</td>
<td>5.64 (0.58)</td>
<td>7.82 (5.2)</td>
</tr>
<tr>
<td>Tmax (h)</td>
<td>1.1 (0.5)</td>
<td>3.1 (2.4)</td>
<td>0.8 (0.3)</td>
<td>0.5 (0.1)</td>
</tr>
<tr>
<td>T1/2 (h)</td>
<td>1.9 (0.1)</td>
<td>1.7 (1.6)</td>
<td>2.2 (0.2)</td>
<td>4.2 (0.8)</td>
</tr>
<tr>
<td>AUC(0-t) (hr·μg/mL)</td>
<td>7.3 (1.8)</td>
<td>0.6 (0.7)</td>
<td>15.7 (2.0)</td>
<td>15.7 (2.0)</td>
</tr>
<tr>
<td>AUCinf(hr·μg/mL)</td>
<td>7.8 (1.9)</td>
<td>0.8 (0.8)</td>
<td>17.1 (2.0)</td>
<td>21.5 (2.3)</td>
</tr>
</tbody>
</table>
Claims

1. A compound of Formula (I):

\[
\begin{align*}
\text{R}^1 & \text{ is selected from } \text{C}_{1-6} \text{ alkyl, substituted } \text{C}_{1-6} \text{ alkyl, C}_{6-10} \text{ aryl, substituted } \text{C}_{6-10} \text{ aryl, } \\
\text{C}_{3-7} \text{ cycloalkyl, substituted } \text{C}_{3-7} \text{ cycloalkyl, } \\
\text{C}_{7-16} \text{ arylalkyl, and } \text{C}_{7-16} \text{ substituted arylalkyl;} \\
\text{R}^2 & \text{ and } \text{R}^3 \text{ are independently selected from hydrogen, } \text{C}_{1-6} \text{ alkyl, substituted } \text{C}_{1-6} \text{ alkyl, C}_{6-10} \text{ aryle, substituted } \\
\text{C}_{6-10} \text{ aryl, C}_{3-7} \text{ cycloalkyl, and substituted } \text{C}_{3-7} \text{ cycloalkyl;} \\
\text{R}^4 & \text{ is selected from hydrogen, } \text{C}_{1-6} \text{ alkyl, substituted } \text{C}_{1-6} \text{ alkyl, } \\
\text{C}_{3-7} \text{ cycloalkyl, substituted } \text{C}_{3-7} \text{ cycloalkyl, } \\
\text{C}_{6-10} \text{ aryl, substituted } \text{C}_{6-10} \text{ aryl, substituted } \text{C}_{7-16} \text{ arylalkyl, substituted } \text{C}_{7-16} \text{ arylalkyl, } \\
\text{C}_{3-12} \text{ trialkylsilyl, and } \text{C}_{7-14} \text{ arylalkylsilyl; and } \\
\text{wherein each substituent group is independently selected from at least one of } \text{C}_{1-3} \text{ alkyl, } \\
- \text{OH, -NH}_2, -\text{SH, C}_{1-3} \text{ alkoxy, C}_{1-3} \text{ acyl, C}_{1-3} \text{ thioalkyl, C}_{1-3} \text{ alkoxy carbonyl, C}_{1-3} \text{ alkylamino, and C}_{1-3} \text{ dialkylamino.}
\end{align*}
\]

2. The compound of claim 1, wherein \text{R}^1 is selected from \text{C}_{1-4} \text{ alkyl, substituted } \text{C}_{1-4} \text{ alkyl, phenyl, substituted phenyl, } \\
cyclohexyl, and substituted cyclohexyl.

3. The compound of claim 1, wherein \text{R}^1 is selected from methyl, ethyl, \text{n-propyl, isopropyl, carbonbutyl, } \\
\text{sec-butyl, tert-butyl, phenyl, o-tolyl, and cyclohexyl.}

4. The compound of claim 1, wherein \text{R}^4 is selected from hydrogen, methyl, ethyl, tert-butyl, allyl, benzyl, 4-methoxy- \\
benzyl, diphenylmethyl, triphenylmethyl, triethylylsilyl, triisopropylylsilyl, tert-butyl dimethylylsilyl, and phe- 

5. The compound of claim 1, wherein \text{R}^4 is selected from hydrogen, allyl, benzyl, and trimethylsilyl.

6. The compound of claim 1, wherein \text{R}^4 is hydrogen.

7. The compound of claim 1, wherein \text{R}^2 and \text{R}^3 are independently selected from hydrogen, methyl, ethyl, \text{n-propyl, } \\
isopropyl, phenyl, and cyclohexyl.

8. The compound of claim 1, wherein \text{R}^2 is hydrogen, and \text{R}^3 is selected from methyl, ethyl, \text{n-propyl, isopropyl, phenyl, } \\
and cyclohexyl.

9. The compound of claim 1, wherein \text{R}^1 is selected from methyl, ethyl, \text{n-propyl, isopropyl, carbonbutyl, } \\
\text{sec-butyl, tert-butyl, phenyl, o-tolyl, and cyclohexyl, } \text{R}^2 \text{ is hydrogen, and } \text{R}^3 \text{ is selected from methyl, ethyl, } \\
\text{n-propyl, isopropyl, phenyl, and cyclohexyl.

10. The compound of claim 9, wherein \text{R}^4 is hydrogen.

11. The compound of claim 1, wherein the compound is selected from:
trans-4\\((\text{[2-methylpropanoyloxy]methoxycarbonyl})\text{aminomethyl})-cyclohexanecarboxylic acid;  
trans-4\\((\text{2,2-dimethylpropanoyloxy})\text{methoxycarbonyl})\text{aminomethyl})-cyclohexanecarboxylic acid;  
trans-4\\((\text{3-methylbutanoyloxy})\text{methoxycarbonyl})\text{aminomethyl})-cyclohexanecarboxylic acid;  
trans-4\\((\text{benzoyloxy})\text{methoxycarbonyl})\text{aminomethyl})-cyclohexanecarboxylic acid;  
trans-4\\((\text{[1-(2-methylpropanoyloxy)ethoxycarbonyl]aminomethyl})-cyclohexanecarboxylic acid;  
trans-4\\((\text{[1-(2-methylpropanoyloxy)propoxycarbonyl]aminomethyl})-cyclohexanecarboxylic acid;  
trans-4\\((\text{[1-(2-methylpropanoyloxy)-2-methylpropoxycarbonyl]aminomethyl})-cyclohexanecarboxylic acid;  
trans-4\\((\text{[1-(penantoxyl])-2-methylpropoxycarbonyl]aminomethyl})-cyclohexanecarboxylic acid;  
trans-4\\((\text{[1-(propanoyloxy)-2-methylpropoxycarbonyl]aminomethyl})-cyclohexanecarboxylic acid;  
trans-4\\((\text{[1-(butanoyloxy)ethoxycarbonyl]aminomethyl})-cyclohexanecarboxylic acid;  
trans-4\\((\text{[1-(pentanoyloxy)ethoxycarbonyl]aminomethyl})-cyclohexanecarboxylic acid;  
trans-4\\((\text{[1-(3-methylbutanoyloxy)ethoxycarbonyl]aminomethyl})-cyclohexanecarboxylic acid;  
trans-4\\((\text{[1-(2,2-dimethylpropanoyloxy)ethoxycarbonyl]aminomethyl})-cyclohexanecarboxylic acid;  
trans-4\\((\text{[1-(cyclohexylcarbonyloxy)ethoxycarbonyl]aminomethyl})-cyclohexanecarboxylic acid;  
trans-4\\((\text{[1-(benzoyloxy)ethoxycarbonyl]aminomethyl})-cyclohexanecarboxylic acid;  
trans-4\\((\text{[1-(2-methylbenzoyloxy)ethoxycarbonyl]aminomethyl})-cyclohexanecarboxylic acid;  
trans-4\\((\text{[1-(butanoyloxy)butoxycarbonyl]aminomethyl})-cyclohexanecarboxylic acid;  
trans-4\\((\text{[1-(2-methylpropanoyloxy)butoxycarbonyl]aminomethyl})-cyclohexanecarboxylic acid;  
trans-4\\((\text{[1-(3-methylbutanoyloxy)butoxycarbonyl]aminomethyl})-cyclohexanecarboxylic acid;  
trans-4\\((\text{[1-(2,2-dimethylpropanoyloxy)butoxycarbonyl]aminomethyl})-cyclohexanecarboxylic acid;  
trans-4\\((\text{[1-(benzoyloxy)butoxycarbonyl]aminomethyl})-cyclohexanecarboxylic acid;  
trans-4\\((\text{[1-(propanoyloxy)propoxycarbonyl]aminomethyl})-cyclohexanecarboxylic acid;  
trans-4\\((\text{[1-(butanoyloxy)propoxycarbonyl]aminomethyl})-cyclohexanecarboxylic acid;  
trans-4\\((\text{[1-(2,2-dimethylpropanoyloxy)propoxycarbonyl]aminomethyl})-cyclohexanecarboxylic acid;  
trans-4\\((\text{[1-(benzoyloxy)propoxycarbonyl]aminomethyl})-cyclohexanecarboxylic acid;  
trans-4\\((\text{[1-(butanoyloxy)-2-methylpropoxycarbonyl]aminomethyl})-cyclohexanecarboxylic acid;  
trans-4\\((\text{[1-(butanoyloxy)-1-cyclohexylmethoxycarbonyl]aminomethyl})-cyclohexanecarboxylic acid;  
trans-4\\((\text{[1-(acetoxy)butoxycarbonyl]aminomethyl})-cyclohexanecarboxylic acid;  
trans-4\\((\text{[1-(acetoxy)propoxycarbonyl]aminomethyl})-cyclohexanecarboxylic acid;  
trans-4\\((\text{[1-(acetoxy)-2-methylpropoxycarbonyl]aminomethyl})-cyclohexanecarboxylic acid;  
trans-4\\((\text{[1-(3-methylbutanoyloxy)-2-methylpropoxycarbonyl]aminomethyl})-cyclohexanecarboxylic acid;  
trans-4\\((\text{[1-(2,2-dimethylpropanoyloxy)-2-methylpropoxycarbonyl]aminomethyl})-cyclohexanecarboxylic acid;  
trans-4\\((\text{[1-(acetoxy)ethoxycarbonyl]aminomethyl})-cyclohexanecarboxylic acid;  
trans-4\\((\text{[1-(propanoyloxy)ethoxycarbonyl]aminomethyl})-cyclohexanecarboxylic acid;  
pharmaceutically acceptable salts thereof, and pharmaceutically acceptable solvates of any of the foregoing.

12. The compound of claim 1, wherein the compound is selected from:

trans-4\\((\text{[1-(2-Methylpropanoyloxy)ethoxycarbonyl]}-\text{aminomethyl})-\text{Cyclohexanecarboxylic Acid;}  
Sodium trans-4\\((\text{[2-Methylpropanoyloxy]ethoxycarbonyl]}-\text{aminomethyl})-\text{Cyclohexanecarboxylic Acid;}  
(+)-trans-4\\((\text{[1S]-1-(2-Methylpropanoyloxy)ethoxy carbonylamino) methyl}-\text{Cyclohexanecarboxylic Acid;}  
Sodium trans-4\\((\text{[1S]-1-(2-methylpropanoyloxy)ethoxy carbonylamino) methyl)-\text{Cyclohexanecarboxylic Acid;}  
(-)-trans-4\\((\text{[1R]-1-(2-Methylpropanoyloxy)ethoxy carbonylamino) methyl)-\text{Cyclohexanecarboxylic Acid;}  
Sodium trans-4\\((\text{[1R]-1-(2-Methylpropanoyloxy)ethoxy carbonylamino) methyl)-\text{Cyclohexanecarboxylic Acid;}  
trans-4\\((\text{[1-(3-Methylbutanoyloxy)ethoxycarbonyl]}-\text{aminomethyl})-\text{Cyclohexanecarboxylic Acid;}  
Sodium trans-4\\((\text{[3-Methylbutanoyloxy]ethoxycarbonyl]}-\text{aminomethyl})-\text{Cyclohexanecarboxylic Acid;}  
trans-4\\((\text{[1-(Benzyloxy)ethoxycarbonyl]}-\text{aminomethyl})-\text{Cyclohexanecarboxylic Acid;}  
Sodium trans-4\\((\text{[Benzyloxy]ethoxycarbonyl]}-\text{aminomethyl})-\text{Cyclohexanecarboxylic Acid;}  
trans-4\\((\text{[1-(2-Methylpropanoyloxy)ethoxycarbonyl]}-\text{aminomethyl})-\text{Cyclohexanecarboxylic Acid;}  
and  

Sodium trans-4\\((\text{[1-(2-Methylpropanoyloxy)2-methylpropoxycarbonyl]}-\text{aminomethyl})-\text{Cyclohexanecarboxylic Acid;}  

13. The compound of claim 1, wherein the compound is selected from:

(+)-trans-4\\((\text{[1S]-1-(2-methylpropanoyloxy)ethoxy carbonylamino) methyl)-\text{Cyclohexanecarboxylic acid; and}
(-)-trans-4-{[(1R)-1-(2-methylpropanoyloxy)ethoxy]carbonylamino methyl}-cyclohexanecarboxylic acid.

14. The compound of claim 1, wherein the compound is selected from:

sodium trans-4-{[1-(2-methylpropanoyloxy)ethoxycarbonyl]-aminomethyl}-cyclohexanecarboxylate;
sodium trans-4-{[(1S)-1-(2-methylpropanoyloxy)ethoxy]carbonylamino}methyl)-cyclohexanecarboxylate; and
sodium trans-4-{[(1R)-1-(2-methylpropanoyloxy)ethoxy]carbonylamino] methyl}-cyclohexanecarboxylate

15. A pharmaceutical composition comprising at a therapeutically effective amount of least one compound of Formula (I) according to any one of claims 1 to 14, and a pharmaceutically acceptable vehicle.

16. The pharmaceutical composition of claim 15, wherein the pharmaceutical composition is an ural formulation.

17. The pharmaceutical composition of claim 15, wherein the pharmaceutical composition is a topical formulation.

18. The pharmaceutical composition of any one of claims 15 to 17, wherein the pharmaceutical composition is a sustained release formulation.

19. The pharmaceutical composition of any one of claims 15 to 18, for treating a pathology selected from excessive bleeding, a skin disease or disorder, and tumor metastasis in a patient.

20. The Pharmaceutical composition of any one of claims 15 to 18, for treating excessive bleeding in a patient.

21. The pharmaceutical composition of claim 20, for treating excessive menstrual bleeding in a patient.

22. The pharmaceutical composition of claim 20, for treating excessive bleeding associated with cardiac surgery, upper gastrointestinal hemorrhage, blood loss in patients with advanced cancer, or bleeding that occurs during dental procedures in hemophiliacs.

23. The pharmaceutical composition of any one of claims 15 to 18, for treating a skin disease or disorder selected from wound healing, epidermal hyperplasia, skin roughening, and unwanted skin pigmentation in a patient.

24. The pharmaceutical composition of any one of claims 15 to 18, for treating tumor metastasis in a patient.

25. The pharmaceutical composition of claim 24, further comprising at least one cytotoxic agent.

26. Use of a therapeutically effective amount of at least one compound according to any one of claims 1 to 14 in the manufacture of a medicament for the treatment of excessive bleeding in a patient.

27. The use of claim 26, wherein excessive bleeding is excessive menstrual bleeding.

28. The use of claim 26, wherein excessive bleeding is associated with cardiac surgery, upper gastrointestinal hemorrhage, blood loss in patients with advanced cancer, or bleeding that occurs during dental procedures in hemophiliacs.

29. Use of a therapeutically effective amount of at least one compound according to claim 1 in the manufacture of a medicament for the treatment of a skin disease or disorder in a patient.

30. The use of claim 29, wherein the skin disease or disorder is selected from wound healing, epidermal hyperplasia, skin roughening, and unwanted skin pigmentation.

31. Use of therapeutically effective amount of at least one compound according to claim 1 in the manufacture of a medicament for the treatment of tumor metastasis in a patient.

32. The use of claim 31, wherein the medicament comprises at least one cytotoxic agent.

33. The use of any one of claims 26-32, wherein the medicament is an oral formulation.

34. The use of claim 33, wherein the oral formulation is a sustained release oral formulation.
35. The use of any one of claims 26-32, wherein the medicament is a topical formulation.

36. The use of claim 35, wherein the topical formulation is a sustained release topical formulation.

Patentansprüche

1. Verbindung der Formel (I):

![Chemical Structure Image]

ein pharmazeutisch geeignetes Salz davon oder ein pharmazeutische geeignetes Solvat der Verbindung oder des Salzes, worin
R<sup>1</sup> ausgewählt ist unter C<sub>1-6</sub>-Alkyl, substituiertem C<sub>1-6</sub>-Alkyl, C<sub>6-10</sub>-Aryl, substituiertem C<sub>6-10</sub>-Aryl, C<sub>3-7</sub>-Cycloalkyl, substituiertem C<sub>3-7</sub>-Cycloalkyl, C<sub>7-16</sub>-Arylalkyl und C<sub>7-16</sub> substituiertem Arylalkyl;
R<sup>2</sup> und R<sup>3</sup> unabhängig voneinander ausgewählt sind unter Wasserstoff, C<sub>1-6</sub>-Alkyl, substituiertem C<sub>1-6</sub>-Alkyl, C<sub>6-10</sub>-Aryl, substituiertem C<sub>6-10</sub>-Aryl, C<sub>3-7</sub>-Cycloalkyl und substituiertem C<sub>3-7</sub>-Cycloalkyl;
R<sup>4</sup> ausgewählt ist unter Wasserstoff, C<sub>1-6</sub>-Alkyl, substituiertem C<sub>1-6</sub>-Alkyl, C<sub>3-7</sub>-Cycloalkyl, substituiertem C<sub>3-7</sub>-Cycloalkyl, C<sub>6-10</sub>-Aryl, substituiertem C<sub>6-10</sub>-Aryl, C<sub>7-16</sub>-Arylalkyl substituiertem C<sub>7-16</sub>-Arylalkyl, C<sub>3-12</sub>-Trialkylsilyl und C<sub>7-14</sub> Aryldialkylsilyl; und
worin jede Substituentengruppe unabhängig voneinander ausgewählt ist unter mindestens einer der Gruppen

2. Verbindung nach Anspruch 1, worin R<sup>1</sup> unter C<sub>1-4</sub>-Alkyl, substituiertem C<sub>1-4</sub>-Alkyl, Phenyl, substituiertem Phenyl, Cyclohexyl und substituiertem Cyclohexyl ausgewählt ist.

3. Verbindung nach Anspruch 1, worin R<sup>1</sup> unter Methyl, Ethyl, n-Propyl, Isopropyl, n-Butyl, Isobutyl, sec-Butyl, tert-Butyl, Phenyl, α-Tolyl und Cyclohexyl ausgewählt ist.

4. Verbindung nach Anspruch 1, worin R<sup>4</sup> unter Wasserstoff, Methyl, Ethyl, tert-Butyl, Allyl, Benzyl, 4-Methoxybenzyl, Diphenylmethyl, Triphenylmethyl, Trimethylsilyl, Triethylsilyl, Triisopropylsilyl, tert-Butyldimethylsilyl und Phenylidimethylsilyl ausgewählt ist.

5. Verbindung nach Anspruch 1, worin R<sup>4</sup> unter Wasserstoff, Allyl, Benzyl und Trimethylsilyl ausgewählt ist.

6. Verbindung nach Anspruch 1, worin R<sup>4</sup> Wasserstoff ist.

7. Verbindung nach Anspruch 1, worin R<sup>2</sup> und R<sup>3</sup> unabhängig voneinander unter Wasserstoff, Methyl, Ethyl, n-Propyl, Isopropyl, Phenyl und Cyclohexyl ausgewählt sind.

8. Verbindung nach Anspruch 1, worin R<sup>2</sup> Wasserstoff ist und R<sup>3</sup> unter Methyl, Ethyl, n-Propyl, Isopropyl, Phenyl und Cyclohexyl ausgewählt ist.

9. Verbindung nach Anspruch 1, worin R<sup>1</sup> unter Methyl, Ethyl, n-Propyl, Isopropyl, n-Butyl, Isobutyl, sec-Butyl, tert-Butyl, Phenyl, α-Tolyl und Cyclohexyl ausgewählt ist, R<sup>2</sup> Wasserstoff ist und R<sup>3</sup> unter Methyl, Ethyl, n-Propyl, Isopropyl, Phenyl und Cyclohexyl ausgewählt ist.

10. Verbindung nach Anspruch 9, worin R<sup>5</sup> Wasserstoff ist.
11. Verbindung nach Anspruch 1, wobei die Verbindung ausgewählt ist unter:

- trans-4-[[2-Methylpropanoyloxy]methoxycarbonyl]aminomethyl]-cyclohexancarbonsäure;
- trans-4-[[2,2-Dimethylpropanoyloxy]methoxycarbonyl]aminomethyl]-cyclohexancarbonsäure;
- trans-4-[[3-Methylbutanoyloxy]methoxycarbonyl]aminomethyl]-cyclohexancarbonsäure;
- trans-4-[[Benzoyloxy]methoxycarbonyl]aminomethyl]-cyclohexancarbonsäure;
- trans-4-[[2-(2-Methylpropanoyloxy)ethoxycarbonyl]aminomethyl]-cyclohexancarbonsäure;
- trans-4-[[2-(2-Methylpropanoyloxy)propoxy carbonyl]aminomethyl]-cyclohexancarbonsäure;
- trans-4-[[1-(Benzoyloxy)-2-methylpropoxy carbonyl]aminomethyl]-cyclohexancarbonsäure;
- trans-4-[[1-(Cyclohexylcarbonyloxy)-2-methylpropoxy carbonyl]aminomethyl]-cyclohexancarbonsäure;
- trans-4-[[1-(Pentanoyloxy)-2-methylpropoxy carbonyl]aminomethyl]-cyclohexancarbonsäure;
- trans-4-[[1-(Propanoyloxy)-2-methylpropoxy carbonyl]aminomethyl]-cyclohexancarbonsäure;
- trans-4-[[1-(Butanoyloxy)ethoxy carbonyl]aminomethyl]-cyclohexancarbonsäure;
- trans-4-[[1-(Pentanoyloxy)ethoxy carbonyl]aminomethyl]-cyclohexancarbonsäure;
- trans-4-[[1-(2-Methylpropanoyloxy)ethoxy carbonyl]aminomethyl]-cyclohexancarbonsäure;
- trans-4-[[1-(2-Methylpropanoyloxy)propoxy carbonyl]aminomethyl]-cyclohexancarbonsäure;
- trans-4-[[1-(2-Methylpropanoyloxy)-2-methylpropoxy carbonyl]aminomethyl]-cyclohexancarbonsäure;
- trans-4-[[1-(Benzoyloxy)-2-methylpropoxy carbonyl]aminomethyl]-cyclohexancarbonsäure;
- trans-4-[[1-(Cyclohexylcarbonyloxy)-2-methylpropoxy carbonyl]aminomethyl]-cyclohexancarbonsäure;
- trans-4-[[1-(Benzoyloxy)-2-methylpropoxy carbonyl]aminomethyl]-cyclohexancarbonsäure;
- trans-4-[[1-(Cyclohexylcarbonyloxy)-2-methylpropoxy carbonyl]aminomethyl]-cyclohexancarbonsäure;
- trans-4-[[1-(Benzoyloxy)-2-methylpropoxy carbonyl]aminomethyl]-cyclohexancarbonsäure;
- trans-4-[[1-(Benzoyloxy)ethoxy carbonyl]aminomethyl]-cyclohexancarbonsäure;
- trans-4-[[1-[(1S)-1-(2-Methylpropanoyloxy)ethoxy carbonyl]aminomethyl]-cyclohexancarbonsäure;
- trans-4-[[1-[(1R)-1-(2-Methylpropanoyloxy)ethoxy carbonyl]aminomethyl]-cyclohexancarbonsäure;
- trans-4-[[1-(2-Methylpropanoyloxy)-2-methylpropoxy carbonyl]aminomethyl]-cyclohexancarbonsäure;
- trans-4-[[1-(Benzoyloxy)ethoxy carbonyl]aminomethyl]-cyclohexancarbonsäure;
- trans-4-[[1-[(1S)-1-(2-Methylpropanoyloxy)-1-cyclohexylmethoxycarbonyl]aminomethyl]-cyclohexancarbonsäure;
- trans-4-[[1-[(1R)-1-(2-Methylpropanoyloxy)-1-cyclohexylmethoxycarbonyl]aminomethyl]-cyclohexancarbonsäure;
- trans-4-[[1-(3-Methylbutanoyloxy)ethoxy carbonyl]aminomethyl]-cyclohexancarbonsäure;
- trans-4-[[1-(3-Methylbutanoyloxy)propoxy carbonyl]aminomethyl]-cyclohexancarbonsäure;
- trans-4-[[1-(2,2-Dimethylpropanoyloxy)ethoxy carbonyl]aminomethyl]-cyclohexancarbonsäure;
- trans-4-[[1-(2,2-Dimethylpropanoyloxy)propoxy carbonyl]aminomethyl]-cyclohexancarbonsäure;
- trans-4-[[1-(2,2-Dimethylpropanoyloxy)-2-methylpropoxy carbonyl]aminomethyl]-cyclohexancarbonsäure;
- trans-4-[[1-(Benzoyloxy)propoxy carbonyl]aminomethyl]-cyclohexancarbonsäure;
- trans-4-[[1-(2-Methylbenzoyloxy)ethoxy carbonyl]aminomethyl]-cyclohexancarbonsäure;
- trans-4-[[1-(2-Methylbenzoyloxy)propoxy carbonyl]aminomethyl]-cyclohexancarbonsäure;
- trans-4-[[1-(Butanoyloxy)butoxycarbonyl]aminomethyl]-cyclohexancarbonsäure;
- trans-4-[[1-(2-Methylpropanoyloxy)butoxycarbonyl]aminomethyl]-cyclohexancarbonsäure;
- trans-4-[[1-(3-Methylbutanoyloxy)butoxycarbonyl]aminomethyl]-cyclohexancarbonsäure;
- trans-4-[[1-(2,2-Dimethylpropanoyloxy)butoxycarbonyl]aminomethyl]-cyclohexancarbonsäure;
- trans-4-[[1-(Benzoyloxy)butoxycarbonyl]aminomethyl]-cyclohexancarbonsäure;
- trans-4-[[1-(Propanoyloxy)propoxy carbonyl]aminomethyl]-cyclohexancarbonsäure;
- trans-4-[[1-(Butanoyloxy)propoxy carbonyl]aminomethyl]-cyclohexancarbonsäure;
- trans-4-[[1-(2,2-Dimethylpropanoyloxy)propoxy carbonyl]aminomethyl]-cyclohexancarbonsäure;
- trans-4-[[1-(Benzoyloxy)propoxy carbonyl]aminomethyl]-cyclohexancarbonsäure;
- trans-4-[[1-(2-Methylpropanoyloxy)-2-methylpropoxy carbonyl]aminomethyl]-cyclohexancarbonsäure;
- trans-4-[[1-(2-Methylpropanoyloxy)-2-methylpropoxycarbonyl]aminomethyl]-cyclohexancarbonsäure;
- trans-4-[[1-(Acetoxy)butoxycarbonyl]aminomethyl]-cyclohexancarbonsäure;
- trans-4-[[1-(Propanoyloxy)butoxycarbonyl]aminomethyl]-cyclohexancarbonsäure;
- trans-4-[[1-(Acetoxy)-2-methylpropoxy carbonyl]aminomethyl]-cyclohexancarbonsäure;
- trans-4-[[1-(Acetoxy)-2-methylpropoxycarbonyl]aminomethyl]-cyclohexancarbonsäure;
- trans-4-[[1-(3-Methylbutanoyloxy)-2-methylpropoxy carbonyl]aminomethyl]-cyclohexancarbonsäure;
- trans-4-[[1-(2,2-dimethylpropanoyloxy)-2-methylpropoxy-carbonyl]aminomethyl]-cyclohexancarbonsäure;
- trans-4-[[1-(Benzoyloxy)-2-methylpropoxy carbonyl]aminomethyl]-cyclohexancarbonsäure;
- trans-4-[[1-(Benzoyloxy)-2-methylpropoxycarbonyl]aminomethyl]-cyclohexancarbonsäure;
- trans-4-[[1-(Benzoyloxy)ethoxy carbonyl]aminomethyl]-cyclohexancarbonsäure;

pharmazeutisch geeignete Salze davon und pharmazeutisch geeignete Solvate der Verbindung oder der Salze.

12. Verbindung nach Anspruch 1, wobei die Verbindung ausgewählt ist unter:

- trans-4-[[1-(2-Methylpropanoyloxy)ethoxy carbonyl]aminomethyl]-cyclohexancarbonsäure;
- Natrium-trans-4-[[1-(2-Methylpropanoyloxy)ethoxy carbonyl]aminomethyl]-cyclohexancarbonsäure;
- (+)-trans-4-[[1-(1S)-1-(2-Methylpropanoyloxy)ethoxy carbonyl]aminomethyl]-cyclohexancarbonsäure;
- Natrium-trans-4-[[1-(1S)-1-(2-Methylpropanoyloxy)ethoxy] carbonyl]aminomethyl]-cyclohexancarbonsäure;
- (-)-trans-4-[[1-(1R)-1-(2-Methylpropanoyloxy)ethoxy carbonyl]aminomethyl]-cyclohexancarbonsäure;
- Natrium-trans-4-[[1-(1R)-1-(2-Methylpropanoyloxy)ethoxy] carbonyl]aminomethyl]-cyclohexancarbonsäure;
- trans-4-[[1-(3-Methylbutanoyloxy)ethoxy carbonyl]aminomethyl]-cyclohexancarbonsäure;
- Natrium-trans-4-[[1-(3-Methylbutanoyloxy)ethoxy carbonyl]aminomethyl]-cyclohexancarbonsäure;
- trans-4-[[1-(Benzoyloxy)ethoxy carbonyl]aminomethyl]-cyclohexancarbonsäure;
- Natrium-trans-4-[[1-(Benzoyloxy)ethoxy carbonyl]aminomethyl]-cyclohexancarbonsäure;
- trans-4-[[1-(2-Methylpropionyl)-2-methylpropoxycarbonyl]aminomethyl]-cyclohexancarbonsäure;
- Natrium-trans-4-[[1-(2-Methylpropionyl)-2-methylpropoxycarbonyl]aminomethyl]-cyclohexancarbonsäure;

13. Verbindung nach Anspruch 1, wobei die Verbindung ausgewählt ist unter: (+)-trans-4-[[1-(1S)-1-(2-Methylpropan-
EP 1 919 859 B1

oyloxy)ethoxy][carbonyl-amino)methyl)cyclohexancarbonsäure; und (-)-trans-4-(((1R)-1-(2-Methylpropanoyloxy)ethoxy][carbonyl-amino)methyl)cyclohexancarbonsäure;

14. Verbindung nach Anspruch 1, wobei die Verbindung ausgewählt ist unter:
Natrium-trans-4-(((1R)-1-(2-Methylpropanoyloxy)ethoxycarbonyl]-aminomethyl)cyclohexancarbonsäure;
Natrium-trans-4-(((1S)-1-(2-Methylpropanoyloxy)ethoxy][carbonylamino)methyl)cyclohexancarbonsäure;
Natrium-trans-4-(((1R)-1-(2-Methylpropanoyloxy)ethoxy][carbonylamino)methyl)cyclohexancarbonsäure;

15. Arzneimittelzusammensetzung, die eine therapeutisch wirksame Menge mindestens einer Verbindung der Formel (I) nach einem der Ansprüche 1 bis 14 und einem pharmazeutisch geeigneten Träger enthält.

16. Arzneimittelzusammensetzung nach Anspruch 15, worin die Arzneimittelzusammensetzung eine orale Formulierung ist.

17. Arzneimittelzusammensetzung nach Anspruch 15, wobei die Arzneimittelzusammensetzung eine topische Formulierung ist.

18. Arzneimittelzusammensetzung nach einem der Ansprüche 15 bis 17, wobei die Arzneimittelzusammensetzung eine Langzeitwirkungsformulierung ist.

19. Arzneimittelzusammensetzung nach einem der Ansprüche 15 bis 18 zur Behandlung einer Krankheit, die unter übermäßigem Bluten, einer Hautkrankheit oder -störung und Tumormetastasen in einem Patienten ausgewählt ist.


25. Arzneimittelzusammensetzung nach Anspruch 24, die außerdem mindestens ein cytotoxisches Mittel enthält.


27. Verwendung nach Anspruch 26, wobei das übermäßige Bluten übermäßiges Menstruationsbluten ist.

28. Verwendung nach Anspruch 26, wobei das übermäßige Bluten in Zusammenhang steht mit Herzoperationen, Blutungen des oberen Magen-Darm-Bereichs, Blutverlust in Patienten mit fortgeschrittener Krebserkrankung oder Blutungen, die während Zahnbehandlungen bei Blutern auftreten.


30. Verwendung nach Anspruch 29, wobei die Hautkrankheit oder Störung unter Wundheilen, epidermaler Hyperplasie, Rauheit der Haut und unerwünschter Hautpigmentierung ausgewählt ist.
EP 1 919 859 B1


32. Verwendung nach Anspruch 31, wobei das Arzneimittel mindestens ein cytotoxisches Mittel enthält.

33. Verwendung nach einem der Ansprüche 26 bis 33, wobei das Arzneimittel eine orale Formulierung ist.

34. Verwendung nach Anspruch 33, wobei die orale Formulierung eine orale Langzeitwirkungsformulierung ist.

35. Verwendung nach einem der Ansprüche 26 bis 33, wobei das Arzneimittel eine topische Formulierung ist.

36. Verwendung nach Anspruch 35, wobei die topische Formulierung eine topische Langzeitwirkungsformulierung ist.

Revendications

1. Composé de formule (I):

\[
\begin{align*}
\text{I:} \quad & R^1, R^2, R^3, R^4 \text{ sont choisis indépendamment entre un atome d'hydrogène, des groupes alkyle en C1 à C4, alkyle en C1 à C4 substitué, aryle en C6 à C10, aryle en C6 à C10 substitué, cycloalkyle en C3 à C7, cycloalkyle en C3 à C7 substitué, arylalkyle en C7 à C16 et arylalkyle en C7 à C16 substitué ;} \\
& \text{R2 et R3 sont choisis indépendamment entre un atome d'hydrogène, des groupes alkyle en C1 à C4, alkyle en C1 à C4 substitué, aryle en C6 à C10, aryle en C6 à C10 substitué, cycloalkyle en C3 à C7 et cycloalkyle en C3 à C7 substitué ;} \\
& \text{R4 est choisi entre un atome d'hydrogène, des groupes méthyloxyde en C1 à C3, -OH, -N2, -SH, alkoxy en C1 à C3, acyle en C1 à C3, thioalkyle en C1 à C3, alkoxykarbonyle en C1 à C3, alkylamino en C1 à C3 et di (alkyle en C1 à C3) amino.}
\end{align*}
\]

2. Composé suivant la revendication 1, dans laquelle R1 est choisi entre des groupes alkyle en C1 à C4, alkyle en C1 à C4 substitué, phényle, phényle substitué, cyclohexyle et cyclohexyle substitué.

3. Composé suivant la revendication 1, dans laquelle R1 est choisi entre des groupes méthyle, éthyle, n-propyle, isopropyle, n-butyle, isobutyle, sec.-butyle, tertiobutyle, phényle, o-tolyle et cyclohexyle.

4. Composé suivant la revendication 1, dans laquelle R4 est choisi entre un atome d'hydrogène, des groupes méthyle, éthyle, tertiobutyle, allyle, benzyle, 4-méthoxy-benzyle, diphenylnéthyle, triméthylsilyle, triéthylsilyle, tripropylsilyle, tertiobutylméthylsilyle et phényliméthylsilyle.

5. Composé suivant la revendication 1, dans laquelle R4 est choisi entre un atome d'hydrogène, des groupes allyle, benzyle et triméthylsilyle.

6. Composé suivant la revendication 1, dans laquelle R4 représente un atome d'hydrogène.
7. Composé suivant la revendication 1, dans laquelle R₂ et R³ sont choisis indépendamment entre un atome d'hydrogène, des groupes méthyle, éthyle, n-propyle, isopropyle, phényle et cyclohexyle.

8. Composé suivant la revendication 1, dans laquelle R₂ représente un atome d'hydrogène et R³ est choisi entre des groupes méthyle, éthyle, n-propyle, isopropyle, n-butyle, isobutyle, sec.-butyle, tertiobutyle, phényle, α-tolyle et cyclohexyle.

9. Composé suivant la revendication 1, dans laquelle R₁ est choisi entre des groupes méthyle, éthyle, n-propyle, isopropyle, n-butyle, isobutyle, sec.-butyle, tertiobutyle, phényle, α-tolyle et cyclohexyle, R₂ représente un atome d'hydrogène et R³ est choisi entre des groupes méthyle, éthyle, n-propyle, isopropyle, phényle et cyclohexyle.

10. Composé suivant la revendication 9, dans laquelle R⁴ représente un atome d'hydrogène.

11. Composé suivant la revendication 1, le composé étant choisi entre :

- l’acide trans-4-[(2-méthylpropanoyloxy)méthoxycarbonyl]-aminométhyl]-cyclohexanecarboxylique ;
- l’acide trans-4-[(2,2-diméthylpropanoyloxy)méthoxycarbonyl]-aminométhyl]-cyclohexanecarboxylique ;
- l’acide trans-4-[(3-méthylbutanoyloxy)méthoxycarbonyl]-aminométhyl]-cyclohexanecarboxylique ;
- l’acide trans-4-[(benzyloxy)méthoxycarbonyl]-aminométhyl]-cyclohexanecarboxylique ;
- l’acide trans-4-[(1-(2-méthylpropanoyloxy)éthoxy-carbonyl]aminométhyl]-cyclohexanecarboxylique ;
- l’acide trans-4-[(1-(2-méthylpropanoyloxy)propoxy-carbonyl]-aminométhyl]-cyclohexanecarboxylique ;
- l’acide trans-4-[(1-(2-méthylpropanoyloxy)-2-méthyl-propoxycarbonyl]aminométhyl]-cyclohexanecarboxyli-que ;
- l’acide trans-4-[(1-(2,2-diméthylpropanoyloxy)éthoxycarbonyl]-aminométhyl]-cyclohexanecarboxylique ;
- l’acide trans-4-[(1-(2,2-diméthylpropanoyloxy)butoxycarbonyl]-aminométhyl]-cyclohexanecarboxylique ;
- l’acide trans-4-[(1-(3-méthylbutanoyloxy)butoxycarbonyl]-aminométhyl]-cyclohexanecarboxylique ;
- l’acide trans-4-[(1-(2,2-diméthylpropanoyloxy)butoxycarbonyl]aminométhyl]-cyclohexanecarboxylique ;
- l’acide trans-4-[(1-(2,2-diméthylpropanoyloxy)-1-cyclohexylméthoxycarbonyl]aminométhyl]-cyclohexanecarboxylique ;
- l’acide trans-4-[(1-(2-méthylpropanoyloxy)-1-cyclohexylméthoxycarbonyl]aminométhyl]-cyclohexanecarboxylique ;
- l’acide trans-4-[(1-(2,2-diméthylpropanoyloxy)-2-méthyl-propoxycarbonyl]aminométhyl]-cyclohexanecarboxylique ;
- l’acide trans-4-[(1-(propanoyloxy)éthoxycarbonyl]amino-méthyl]-cyclohexanecarboxylique ;
- l’acide trans-4-[(1-(propanoyloxy)propoxy-carbonyl]-aminométhyl]-cyclohexanecarboxylique ;
- l’acide trans-4-[(1-(propanoyloxy)-2-méthylpropoxy-carbonyl]-aminométhyl]-cyclohexanecarboxylique ;
- l’acide trans-4-[(1-(2-méthylpropoxycarbonyl)]aminométhyl]-cyclohexanecarboxylique ;
- l’acide trans-4-[(1-(3-méthylbutanoyloxy)éthoxycarbonyl]-aminométhyl]-cyclohexanecarboxylique ;
- l’acide trans-4-[(1-(2,2-diméthylpropanoyloxy)éthoxycarbonyl]-aminométhyl]-cyclohexanecarboxylique ;
- l’acide trans-4-[(1-(propanoyloxy)éthoxycarbonyl]amino-méthyl]-cyclohexanecarboxylique ;
- l’acide trans-4-[(1-(propanoyloxy)butoxycarbonyl]-aminométhyl]-cyclohexanecarboxylique ;
- l’acide trans-4-[(1-(2,2-diméthylpropanoyloxy)butoxycarbonyl]aminométhyl]-cyclohexanecarboxylique ;
- l’acide trans-4-[(1-(3-méthylbutanoyloxy)butoxycarbonyl]-aminométhyl]-cyclohexanecarboxylique ;
- l’acide trans-4-[(1-(benzyloxy)éthoxycarbonyl]-aminométhyl]-cyclohexanecarboxylique ;
- l’acide trans-4-[(1-(benzyloxy)butoxycarbonyl]-aminométhyl]-cyclohexanecarboxylique ;
- l’acide trans-4-[(1-(benzyloxy)propoxy-carbonyl]-aminométhyl]-cyclohexanecarboxylique ;
- l’acide trans-4-[(1-(benzyloxy)propoxy-carbonyl]-aminométhyl]-cyclohexanecarboxylique ;
- l’acide trans-4-[(1-(butanoyloxy)-2-méthylpropoxycarbonyl]-aminométhyl]-cyclohexanecarboxylique ;
- l’acide trans-4-[(1-(butanoyloxy)-2-méthylpropoxycarbonyl]-aminométhyl]-cyclohexanecarboxylique ;
- l’acide trans-4-[(1-(butanoyloxy)-2-méthylpropoxycarbonyl]-aminométhyl]-cyclohexanecarboxylique ;
- l’acide trans-4-[(1-(butanoyloxy)-1-cyclohexylméthoxy-carbonyl]aminométhyl]-cyclohexanecarboxylique ;
- l’acide trans-4-[(1-(2-méthylpropoxy-carbonyl)]aminométhyl]-cyclohexanecarboxylique ;
- l’acide trans-4-[(1-(2-méthylpropoxy-carbonyl)]aminométhyl]-cyclohexanecarboxylique ;
- l’acide trans-4-[(1-(2,2-diméthylpropoxy-carbonyl)]aminométhyl]-cyclohexanecarboxylique ;
- l’acide trans-4-[(1-(2,2-diméthylpropoxy-carbonyl)]aminométhyl]-cyclohexanecarboxylique ;
- l’acide trans-4-[(1-(3-méthylbutanoyloxy)-2-méthylpropoxy-carbonyl]aminométhyl]-cyclohexanecarboxylique ;
- l’acide trans-4-[(1-(2,2-diméthylpropoxy-carbonyl)]aminométhyl]-cyclohexanecarboxylique ;
- l’acide trans-4-[(1-(2,2-diméthylpropoxy-carbonyl)]aminométhyl]-cyclohexanecarboxylique ;

leurs sels pharmaceutiquement acceptables, et les produits de solvatation pharmaceutiquement acceptables de n’importe laquelle des entités précitées.
12. Composé suivant la revendication 1, le composé étant choisi entre :

- l’acide trans-4-[[1-(2-méthylpropanoyloxy)éthoxy carbonyl]-aminométhyl]-cyclohexanecarboxylique ;
- le trans-4-[[1-2-méthylpropanoyloxy]-éthoxy carbonyl]-aminométhyl]-cyclohexanecarboxylate de sodium ;
- l’acide (+)-trans-4-[[[1(S)-1-(2-méthylpropanoyloxy)éthoxy]-carbonyl amino]-méthyl]-cyclohexanecarboxylique ;
- le trans-4-[[1(S)-1-(2-méthylpropanoyloxy)éthoxy]-carbonyl amino]-méthyl]-cyclohexanecarboxylate de sodium ;
- l’acide (-)-trans-4-[[1(R)-1-(2-méthylpropanoyloxy)éthoxy]-carbonyl amino]-méthyl]-cyclohexanecarboxylique ;
- le trans-4-[[1(R)-1-(2-méthylpropanoyloxy)éthoxy]-carbonyl amino]-méthyl]-cyclohexanecarboxylate de sodium ;
- l’acide trans-4-[[1-(3-méthylbutanoyloxy)éthoxy carbonyl]-aminométhyl]-cyclohexanecarboxylique ;
- le trans-4-[[1-3-méthylbutanoyloxy]-éthoxy carbonyl]-aminométhyl]-cyclohexanecarboxylate de sodium ;
- l’acide trans-4-[[1-(benzoyloxy)éthoxy carbonyl]-aminométhyl]-cyclohexanecarboxylique ;
- le trans-4-[[1-(benzoyloxy)éthoxy carbonyl]-aminométhyl]-cyclohexanecarboxylate de sodium ;
- l’acide trans-4-[[1-(2-méthylpropanoyloxy)-2-méthyl propoxy carbonyl]-aminométhyl]-cyclohexanecarboxylique ;
- et
- le trans-4-[[1-(2-méthylpropanoyloxy)-2-méthyl propoxy carbonyl]-aminométhyl]-cyclohexanecarboxylate de sodium.

13. Composé suivant la revendication 1, le composé étant choisi entre :

- l’acide (+)-trans-4-[[[1(S)-1-(2-méthylpropanoyloxy)éthoxy]-carbonyl amino]-méthyl]-cyclohexanecarboxylique ; et
- l’acide (-)-trans-4-[[[1(R)-1-(2-méthylpropanoyloxy)éthoxy]-carbonyl amino]-méthyl]-cyclohexanecarboxylique.

14. Composé suivant la revendication 1, le composé étant choisi entre :

- le trans-4-[[1-(2-méthylpropanoyloxy)éthoxy carbonyl]-aminométhyl]-cyclohexanecarboxylate de sodium ;
- le trans-4-[[1(S)-1-(2-méthylpropanoyloxy)éthoxy]-carbonyl amino]-méthyl]-cyclohexanecarboxylate de sodium ; et
- le trans-4-[[1(R)-1-(2-méthylpropanoyloxy)éthoxy]-carbonyl amino]-méthyl]-cyclohexanecarboxylate de sodium ;

15. Composition pharmaceutique comprenant une quantité thérapeutiquement efficace d’au moins un composé de formule (I) suivant l’une quelconque des revendications 1 à 14 et un véhicule pharmaceutiquement acceptable.


17. Composition pharmaceutique suivant la revendication 15, ladite composition pharmaceutique étant une formulation topique.

18. Composition pharmaceutique suivant l’une quelconque des revendications 15 à 17, ladite composition pharmaceutique étant une formulation à libération prolongée.

19. Composition pharmaceutique suivant l’une quelconque des revendications 15 à 18, destinée au traitement d’une pathologie choisie entre un saignement excessif, une maladie cutanée ou un trouble cutané, et une métastase tumorale chez un patient.

20. Composition pharmaceutique suivant l’une quelconque des revendications 15 à 18, destinée au traitement d’un saignement excessif chez un patient.

21. Composition pharmaceutique suivant la revendication 20, destinée au traitement d’un saignement menstruel excessif chez une patiente.

22. Composition pharmaceutique suivant la revendication 20, destinée au traitement d’un saignement excessif associé à une intervention de chirurgie cardiaque, une hémorragie du tractus gastro-intestinal supérieur, une perte chez
des patients présentant un cancer avancé ou le saignement qui se produit au cours d'interventions dentaires chez les sujets hémophiles.

23. Composition pharmaceutique suivant l'une quelconque des revendications 15 à 18, destinée au traitement d'une maladie cutanée ou d'un trouble cutané choisi entre la guérison de plaies, l'hyperplasie épidermique, la rugosité cutanée et une pigmentation cutanée indésirable chez un patient.

24. Composition pharmaceutique suivant l'une quelconque des revendications 15 à 18, destinée au traitement d'une métastase tumorale chez un patient.

25. Composition pharmaceutique suivant la revendication 24, comprenant en outre au moins un agent cytotoxique.

26. Utilisation d'une quantité thérapeutiquement efficace d'au moins un composé suivant l'une quelconque des revendications 1 à 14 dans la production d'un médicament destiné au traitement d'un saignement excessif chez un patient.

27. Utilisation suivant la revendication 26, dans laquelle le saignement excessif est un saignement menstruel excessif.

28. Utilisation suivant la revendication 26, dans laquelle le saignement excessif est associé à une intervention de chirurgie cardiaque, une hémorragie du tractus gastro-intestinal supérieur, une perte de sang chez des patients présentant un cancer avancé, ou un saignement qui se produit au cours d'interventions dentaires chez les sujets hémophiles.

29. Utilisation d'une quantité thérapeutiquement efficace d'au moins un composé suivant la revendication 1 dans la production d'un médicament destiné au traitement d'une maladie cutanée ou d'un trouble cutané chez un patient.

30. Utilisation suivant la revendication 29, dans laquelle la maladie cutanée ou le trouble cutané est choisi entre la guérison de plaies, l'hyperplasie épidermique, la rugosité cutanée et une pigmentation cutanée indésirable.

31. Utilisation d'une quantité thérapeutiquement efficace d'au moins un composé suivant la revendication 1 dans la production d'un médicament destiné au traitement d'une métastase tumorale chez un patient.

32. Utilisation suivant la revendication 31, dans laquelle le médicament comprend au moins un agent cytotoxique.

33. Utilisation suivant l'une quelconque des revendications 26 à 32, dans laquelle le médicament est une formulation orale.

34. Utilisation suivant la revendication 33, dans laquelle la formulation orale est une formulation orale à libération prolongée.

35. Utilisation suivant l'une quelconque des revendications 26 à 32, dans laquelle le médicament est une formulation topique.

36. Utilisation suivant la revendication 35, dans laquelle la formulation topique est une formulation topique à libération prolongée.
REFERENCES CITED IN THE DESCRIPTION

This list of references cited by the applicant is for the reader’s convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

Patent documents cited in the description

- US 5690914 A, Suetsugu [0004]
- JP 2002114673 B [0005]
- US 2005002828 A [0008]
- US 4483867 A, Svaen [0010]
- WO 9415904 A, Jonsson [0010]
- US 4426391 A, Alexander [0114]
- US 4760057 A, Alexander [0114] [0132]
- US 5401868 A, Lund [0114]
- EP 0416889 B1 [0114]
- WO 0105813 A, Chen [0114]
- US 6927036 B, Gallop [0114] [0134]
- US 2004014940 A, Raillard [0114]
- US 20050070715 A, Hiat [0114] [0134]
- US 20050222431 A, Gallop [0114] [0145] [0199]
- US 4916230 A, Alexander [0132]
- US 5466811 A, Alexander [0132]
- US 5684018 A, Alexander [0132]
- US 4036298 A, Ferres [0133]
- US 5698155 A, Grosswald [0154]
- US 4083949 A [0165]
- US 6627223 B [0169]
- US 5229135 A [0169]
- US 6375987 B, Farah [0172]
- US 6379700 B, Joachim [0172]
- US 6171615 B, Roussin [0172]
- US 3402240 A, Cain [0173]
- US 4820523 A, Shlothryn [0173]
- US 4421763 A, Walters [0173]
- US 3845770 A, Theeuwes [0174] [0182]
- US 3916899 A, Theeuwes [0174] [0182]
- US 3811444 A [0176]
- US 3962414 A [0176]
- US 4066747 A [0176]
- US 4070347 A [0176]
- US 4079038 A [0176]
- US 4093709 A [0176]
- US 3992518 A [0177]
- US 4434153 A [0178]
- US 4721613 A [0178]
- US 4853229 A [0178]
- US 2996431 A [0178]
- US 3139383 A [0178]
- US 4752470 A [0178]
- US 4063064 A [0182]
- US 408884 A [0182]
- US 4816263 A [0182]
- US 4200098 A [0182]
- US 4285987 A [0182]

Non-patent literature cited in the description

- Bradlow et al. Patterns of referral. Oxford Health Services Research Unit, 1992 [0006]
- Remington’s Pharmaceutical Sciences. Philadelphia College of Pharmacy and Science, 1995 [0008]
• Butcher. *Synlett*, 1994, 825-6 [0133]
• Kayser et al. *Synlett*, 1999, 153 [0134]
• Cooper et al. *Synlett.*, 1990, 533-535 [0137] [0138]
• Remington's Pharmaceutical Sciences. Philadelphia College of Pharmacy and Science, 1995 [0154]
•Medical Applications of Controlled Release. CRC Press, 1974 [0170]
• Rosoff. *Controlled Release of Drugs*. 1989, 53-95 [0176]
• Roerdink et al. *Drug Carrier Systems*, 1989, vol. 9, 57-10 [0177]