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(19) **United States**(12) **Patent Application Publication**
Kroth et al.(10) **Pub. No.: US 2010/0009961 A1**(43) **Pub. Date: Jan. 14, 2010**(54) **DIPEPTIDYL PEPTIDASE-IV INHIBITORS**(22) Filed: **Jun. 26, 2009**(75) Inventors: **Heiko Kroth**, Leimen (DE); **Tim Feuerstein**, Neckargemuend (DE); **Frank Richter**, HD-Handschuhsheim (DE); **Jurgen Boer**, Wiesbaden (DE); **Michael Essers**, Schoenau (DE); **Bert Nolte**, Schoenau (DE); **Matthias Schneider**, Dossenheim (DE); **Matthias Hochguertel**, Schriesheim (DE); **Fritz-Frieder Frickel**, Deidesheim (DE); **Arthur Taveras**, Southborough, MA (US); **Christoph Steeneck**, Dossenheim (DE)**Related U.S. Application Data**

(63) Continuation of application No. 11/409,481, filed on Apr. 21, 2006, now Pat. No. 7,553,861.

Publication Classification(51) **Int. Cl.****A61K 31/397** (2006.01)**A61K 31/5377** (2006.01)**A61K 31/41** (2006.01)**A61K 31/40** (2006.01)**C07D 413/14** (2006.01)**C07D 403/02** (2006.01)**C07D 207/00** (2006.01)(52) **U.S. Cl.** **514/210.18**; 514/232.2; 514/381; 514/423; 544/107; 548/253; 548/528(57) **ABSTRACT**

The present invention relates generally to pyrrolidine and thiazolidine DPP-IV inhibitor compounds. The present invention also provides synthetic methods for preparation of such compounds, methods of inhibiting DPP-IV using such compounds and pharmaceutical formulations containing them for treatment of DPP-IV mediated diseases, in particular, Type-2 diabetes.

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DIPEPTIDYL PEPTIDASE-IV INHIBITORS**CROSS-REFERENCE TO RELATED APPLICATION**

[0001] This application is a continuation of U.S. application Ser. No. 11/409,481, filed Apr. 21, 2006, now U.S. Pat. No. 7,553,861, the entire contents of which are incorporated herein by reference.

FIELD OF THE INVENTION

[0002] The present invention relates to pyrrolidine and thiazolidine-based inhibitors of dipeptidyl peptidase-IV (DPP-IV) and to methods for treating diabetes, particularly Type-2 diabetes as well as impaired glucose tolerance, impaired glucose homeostasis and complications associated with diabetes by inhibiting DPP-IV with such cyclic amido and cyclic ureido pyrrolidine and thiazolidine inhibitors.

BACKGROUND OF THE INVENTION

[0003] Diabetes results from the occurrence of one or more of several causative factors, and is characterized by an abnormal elevation in levels of plasma glucose (hyperglycemia). Persistent or uncontrolled hyperglycemia results in an increased probability of premature morbidity and mortality. Abnormal glucose homeostasis is usually associated with changes in the lipid, lipoprotein and apolipoprotein metabolism, or due to other metabolic and hemodynamic diseases.

[0004] Patients afflicted with Type-2 diabetes mellitus or noninsulin dependent diabetes mellitus (NIDDM), are especially at increased risk of suffering from macrovascular and microvascular complications, including coronary heart disease, stroke, peripheral vascular disease, hypertension, nephropathy, neuropathy and retinopathy. Therapeutic control of glucose homeostasis, lipid metabolism and hypertension are critical in the clinical management and treatment of Type-2 diabetes mellitus.

[0005] The currently available therapeutics for treating available Type-2 diabetes, although effective, have recognized limitations. Compounds based on sulfonylureas (e.g. tolbutamide, glipizide, etc.), which stimulate the pancreatic beta-cells to secrete more insulin, are limited by the development of inhibitor resistant tissues, causing them to become inefficient or ineffective, even at high doses. Biguanide compounds, on the other hand, increase insulin sensitivity so as to cause correction of hyperglycemia to some extent. However, clinically used biguanides such as phenformin and metformin can induce side-effects such as lactic acidosis, nausea and diarrhea.

[0006] The more recent glitazone-type compounds (i.e. 5-benzylthiazolidine-2,4-diones) substantially increase insulin sensitivity in muscle, liver and adipose tissue resulting in either partial or complete correction of the elevated plasma levels of glucose without occurrence of hypoglycemia. Currently used glitazones are agonists of the peroxisome proliferator activated receptor (PPAR), which is attributed to be responsible for their improved insulin sensitization. However, serious side effects (e.g. liver toxicity) have been known to occur with some glitazones such as, for example, troglitazone. Compounds that are inhibitors of the dipeptidyl peptidase-IV ("DPP-IV", "DPP-4" or "DP-IV") enzyme are also under investigation as drugs that may be useful in the treat-

ment of diabetes, and particularly Type-2 diabetes. See for example, WO 97/40832, WO 98/19998, and U.S. Pat. No. 5,939,560.

[0007] DPP-IV is a membrane bound non-classical serine aminodipeptidase which is located in a variety of tissues (intestine, liver, lung, kidney) as well as on circulating T-lymphocytes (where the enzyme is known as CD-26). It is responsible for the metabolic cleavage of certain endogenous peptides (GLP-1(7-36), glucagon) in vivo and has demonstrated proteolytic activity against a variety of other peptides (e.g. GHRH, NPY, GLP-2, VIP) in vitro.

[0008] The usefulness of DPP-IV inhibitors in the treatment of Type-2 diabetes is based on the fact that DPP-IV in vivo readily inactivates glucagon like peptide-1 (GLP-1) and gastric inhibitory peptide (GIP). GLP-1 (7-36) is a 29 amino-acid peptide derived by post-translational processing of proglucagon in the small intestine. GLP-1(7-36) has multiple actions in vivo including the stimulation of insulin secretion, inhibition of glucagon secretion, the promotion of satiety, and the slowing of gastric emptying. Based on its physiological profile, the actions of GLP-1(7-36) are expected to be beneficial in the prevention and treatment of Type-2 diabetes, and potentially obesity. To support this claim, exogenous administration of GLP-1(7-36) (continuous infusion) in diabetic patients has demonstrated efficacy in this patient population. GLP-1(7-36) is degraded rapidly in vivo and has been shown to have a short half-life in vivo (t_{1/2} of about 1.5 min). Based on a study of genetically bred DPP-IV KO mice and on in vivo/in vitro studies with selective DPP-IV inhibitors, DPP-IV has been shown to be the primary degrading enzyme of GLP-1(7-36) in vivo. GLP-1(7-36) is degraded by DPP-IV efficiently to GLP-1(9-36), which has been speculated to act as a physiological antagonist to GLP-1(7-36). Inhibition of DPP-IV in vivo should, therefore, potentiate endogenous levels of GLP-1(7-36) and attenuate formation of its antagonist GLP-1(9-36) and serve to ameliorate the diabetic condition.

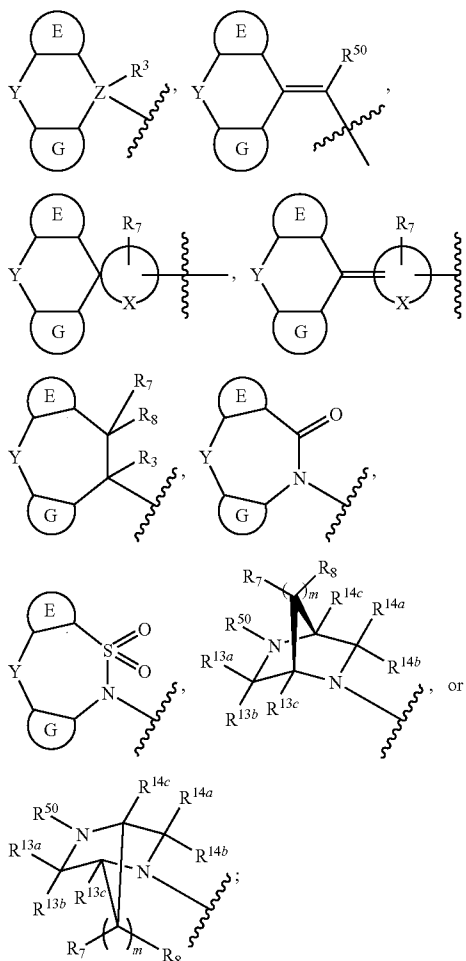
[0009] GLP-1 and GIP are incretins that are produced upon ingestion of food, and which stimulate production of insulin. Inhibition of DPP-IV causes decreased inactivation of the incretins, which in turn, results in an increase in their effectiveness in stimulating pancreatic production of insulin. DPP-IV inhibition therefore, results in an increase in the level of serum insulin. Since the incretins are produced upon consumption of food only, DPP-IV inhibition is not expected to increase insulin levels when not required, thereby precluding excessive lowering of blood sugar (hypoglycemia). Inhibition of DPP-IV, is therefore, is expected to increase insulin levels without increasing the risk of hypoglycemia, thereby lowering deleterious side effects associated with currently used insulin secretagogues. Although DPP-IV inhibitors have not been studied extensively as therapeutics for diseases other than diabetes, they are expected to have other potential therapeutic utilities.

SUMMARY OF THE INVENTION

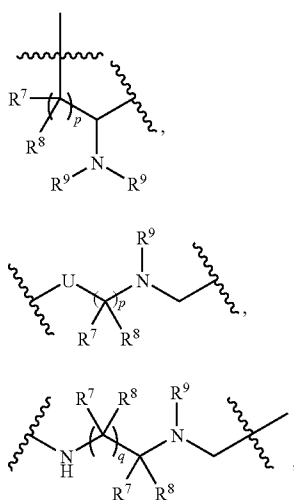
[0010] The present invention relates to a class of pyrrolidine-based inhibitors of dipeptidyl peptidase-IV (DPP-IV). In particular, the present invention provides a new class of pyrrolidine and thiazolidine DPP-IV inhibiting compounds ("DPP-IV inhibitors").

[0011] One aspect of the present invention includes a compound of formula (I):

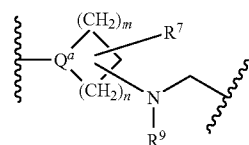
[0012] and all stereoisomers, diastereomers, racemic mixtures and pharmaceutically acceptable salts thereof and all polymorphs; wherein A is:



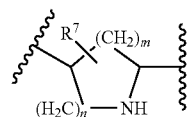
B is:



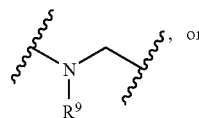
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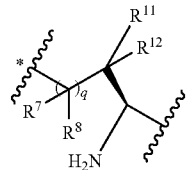
(d)



(e)

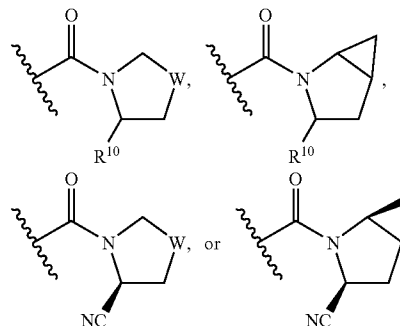


(f)



(g)

and D is:



wherein

[0013] E and G are independently 6-membered aryl, or 5-membered heteroaryl or 6-membered heteroaryl;

(a) [0014] E may be substituted with one or more R¹ groups;

[0015] G may be substituted with one or more R² groups;

[0016] X and Y are divalent and are each independently: a bond, CR⁴R⁵, O, NR⁴, S, S=O, S(=O)₂, C(=O), (C=O)N(R⁴), S(=O)₂N(R⁴), C=N-OR⁴, -C(R⁴R⁵)C(R⁴R⁵)-, -C(R⁴R⁵)C(R⁴R⁵)C(R⁴R⁵)-, -C(R⁴R⁵)C(R⁴R⁵)C(R⁴R⁵)C(R⁴R⁵)-, -C(R⁴)=C(R⁵)-, -C(R⁴R⁵)NR⁴-, -C(R⁴R⁵)O-, -C(R⁴R⁵)S(=O)₂-, -(C=O)O-, -(C=NR⁴)N(R⁴)-, -(C=NR⁴)-, N(C=O)NR⁴R⁵, N(C=O)R⁴, N(C=O)OR⁴, NS(=O)₂NR⁴NR⁵, NS(=O)₂R⁴; or aryl, heteroaryl, cycloalkyl or heterocyclic ring, all of which may be optionally substituted;

(c) [0017] R¹ and R² are each independently: halogen, CF₃, COR⁴, OR⁴, NR⁴R⁵, NO₂, CN, SO₂OR⁴, CO₂R⁴, CONR⁴R⁵, CO₂H, SO₂NR⁴R⁵, S(O)₂R⁴, SO₃H, OC(O)R⁴, OC(O)NR⁴R⁵, NR⁴C(O)R⁵, NR⁴CO₂R⁵, (C₀-C₆)-alkyl-C(=NR⁴)NHR⁴, (C₀-C₆)-alkyl-C(=NR⁴)NR⁴R⁵, (C₀-C₆)-alkyl-C(O)OR⁴, (C₀-C₆)-alkyl-C(O)NR⁴R⁵, (C₀-C₆)-alkyl-C(O)-NH-CN, O-(C₀-C₆)-alkyl-C(O)NR⁴R⁵, S(O)₂-(C₀-C₆)-alkyl-C(O)OR⁴, S(O)₂-

(C₀-C₆)-alkyl-C(O)NR⁴R⁵, (C₀-C₆)-alkyl-C(O)NR⁴—(C₀-C₆)-alkyl-NR⁴R⁵, (C₀-C₆)-alkyl-NR⁴R⁵, (C₀-C₆)-alkyl-NR⁴—C(O)R⁵, (C₀-C₆)-alkyl-NR⁴—C(O)OR⁴, (C₀-C₆)-alkyl-NR⁴—C(O)—NR⁴R⁵, (C₀-C₆)-alkyl-NR⁴—SO₂NR⁴R⁵, (C₀-C₆)-alkyl-NR⁴—SO₂R⁴, hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, haloalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, alkoxyalkyl or aminoalkyl, wherein alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, haloalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, alkoxyalkyl and aminoalkyl all of which may be optionally substituted;

[0018] R³ is absent or is halogen, CF₃, COR⁴, OR⁴, NR⁴R⁵, NO₂, CN, SO₂OR⁴, CO₂R⁴, CONR⁴R⁵, CO₂H, SO₂NR⁴R⁵, S(O)₂R⁴, SO₃H, OC(O)R⁴, OC(O)NR⁴R⁵, NR⁴C(O)R⁵, NR⁴CO₂R⁵, (C₀-C₆)-alkyl-C(=NR⁴)NHR⁴, (C₀-C₆)-alkyl-C(=NR⁴)NHR⁴, (C₀-C₆)-alkyl-C(=NR⁴)NR⁴R⁵, (C₀-C₆)-alkyl-C(O)OR⁴, (C₀-C₆)-alkyl-C(O)NR⁴R⁵, (C₀-C₆)-alkyl-C(O)—NH—CN, O—(C₀-C₆)-alkyl-C(O)NR⁴R⁵, S(O)₂—(C₀-C₆)-alkyl-C(O)OR⁴, S(O)₂—(C₀-C₆)-alkyl-C(O)NR⁴R⁵, (C₀-C₆)-alkyl-C(O)NR⁴—(C₀-C₆)-alkyl-NR⁴R⁵, (C₀-C₆)-alkyl-NR⁴—C(O)R⁵, (C₀-C₆)-alkyl-NR⁴—C(O)OR⁴, (C₀-C₆)-alkyl-NR⁴—C(O)—NR⁴R⁵, (C₀-C₆)-alkyl-NR⁴—SO₂NR⁴R⁵, (C₀-C₆)-alkyl-NR⁴—SO₂R⁴, hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, haloalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, alkoxyalkyl or aminoalkyl, wherein alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, haloalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, alkoxyalkyl and aminoalkyl all of which may be optionally substituted;

[0019] R^a is hydrogen, CN, NO₂, alkyl, haloalkyl, S(O)₂NR⁴R⁵, S(O)₂R⁴, C(O)OR⁴, C(O)R⁴, or C(O)NR⁴R⁵; each occurrence of R⁴, R⁵, R²⁰ and R²¹ are each independently: hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl or aminoalkyl, wherein alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl are all optionally substituted, or R⁴ and R⁵ when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and may optionally contain a heteroatom selected from O, S, or NR⁵⁰ and the 3- to 8-membered ring may be optionally substituted;

[0020] R⁵⁰ is, in each occurrence, R²⁰, CN, NO₂, S(O)₂NR²⁰R²¹, S(O)₂R²⁰, C(O)OR²⁰, C(O)R²⁰C(=NR^a)NR²⁰R²¹, C(=NR²⁰)NR²¹R^a, C(=NOR²⁰)R²¹ or C(O)NR²⁰R²¹;

[0021] each occurrence of R⁷ and R⁸ are each independently: halogen, CF₃, COR⁴, OR⁴, NR⁴R⁵, NO₂, CN, SO₂OR⁴, CO₂R⁴, CONR⁴R⁵, CO₂H, SO₂NR⁴R⁵, S(O)₂R⁴, SO₃H, OC(O)R⁴, OC(O)NR⁴R⁵, NR⁴C(O)R⁵, NR⁴CO₂R⁵, (C₀-C₆)-alkyl-C(=NR^a)NHR⁴, (C₀-C₆)-alkyl-C(=NR^a)NHR⁴, (C₀-C₆)-alkyl-NR⁴C(=NR^a)NR⁴R⁵, (C₀-C₆)-alkyl-C(O)OR⁴, (C₀-C₆)-alkyl-C(O)NR⁴R⁵, (C₀-C₆)-alkyl-C(O)—NH—CN, O—(C₀-C₆)-alkyl-C(O)NR⁴R⁵, S(O)₂—(C₀-C₆)-alkyl-C(O)OR⁴, S(O)₂—(C₀-C₆)-alkyl-C(O)NR⁴R⁵, (C₀-C₆)-alkyl-C(O)NR⁴—(C₀-C₆)-alkyl-NR⁴R⁵, (C₀-C₆)-alkyl-NR⁴—C(O)R⁵, (C₀-C₆)-alkyl-NR⁴—C(O)OR⁴, (C₀-C₆)-alkyl-NR⁴—C(O)—NR⁴R⁵, (C₀-C₆)-alkyl-NR⁴—SO₂NR⁴R⁵, (C₀-C₆)-alkyl-NR⁴—SO₂R⁴, hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, haloalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, alkoxyalkyl or aminoalkyl, wherein alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, haloalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, alkoxyalkyl and aminoalkyl are all optionally substituted;

NR⁴R⁵, (C₀-C₆)-alkyl-NR⁴—SO₂NR⁴R⁵, (C₀-C₆)-alkyl-NR⁴—SO₂R⁴, hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, haloalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, alkoxyalkyl or aminoalkyl, wherein alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, alkoxyalkyl and aminoalkyl are all optionally substituted;

[0022] R⁹ is H or C₁₋₆ alkyl;

[0023] R¹⁰ is halogen, CF₃, COR⁴, OR⁴, NR⁴R⁵, NO₂, CN, SO₂OR⁴, CO₂R⁴, CONR⁴R⁵, CO₂H, SO₂NR⁴R⁵, S(O)₂R⁴, SO₃H, OC(O)R⁴, OC(O)NR⁴R⁵, NR⁴C(O)R⁵, NR⁴CO₂R⁵, (C₀-C₆)-alkyl-C(=NR^a)NHR⁴, (C₀-C₆)-alkyl-C(=NR^a)NHR⁴, (C₀-C₆)-alkyl-NR⁴C(=NR^a)NR⁴R⁵, (C₀-C₆)-alkyl-C(O)OR⁴, (C₀-C₆)-alkyl-C(O)NR⁴R⁵, (C₀-C₆)-alkyl-C(O)—NH—CN, O—(C₀-C₆)-alkyl-C(O)NR⁴R⁵, S(O)₂—(C₀-C₆)-alkyl-C(O)OR⁴, S(O)₂—(C₀-C₆)-alkyl-C(O)NR⁴R⁵, (C₀-C₆)-alkyl-C(O)NR⁴—(C₀-C₆)-alkyl-NR⁴R⁵, (C₀-C₆)-alkyl-NR⁴—C(O)R⁵, (C₀-C₆)-alkyl-NR⁴—C(O)OR⁴, (C₀-C₆)-alkyl-NR⁴—C(O)—NR⁴R⁵, (C₀-C₆)-alkyl-NR⁴—SO₂NR⁴R⁵, (C₀-C₆)-alkyl-NR⁴—SO₂R⁴, hydrogen, B(OH)₂, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, haloalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, alkoxyalkyl or aminoalkyl, wherein alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, alkoxyalkyl and aminoalkyl are all optionally substituted;

[0024] R¹¹ and R¹² are each independently: halogen, CF₃, COR⁴, OR⁴, NR⁴R⁵, NO₂, CN, SO₂OR⁴, CO₂R⁴, CONR⁴R⁵, CO₂H, SO₂NR⁴R⁵, S(O)₂R⁴, SO₃H, OC(O)R⁴, OC(O)NR⁴R⁵, NR⁴C(O)R⁵, NR⁴CO₂R⁵, (C₀-C₆)-alkyl-C(=NR^a)NHR⁴, (C₀-C₆)-alkyl-C(=NR^a)NHR⁴, (C₀-C₆)-alkyl-NR⁴C(=NR^a)NR⁴R⁵, (C₀-C₆)-alkyl-C(O)OR⁴, (C₀-C₆)-alkyl-C(O)NR⁴R⁵, (C₀-C₆)-alkyl-C(O)—NH—CN, O—(C₀-C₆)-alkyl-C(O)NR⁴R⁵, S(O)₂—(C₀-C₆)-alkyl-C(O)OR⁴, S(O)₂—(C₀-C₆)-alkyl-C(O)NR⁴R⁵, (C₀-C₆)-alkyl-C(O)NR⁴—(C₀-C₆)-alkyl-NR⁴R⁵, (C₀-C₆)-alkyl-NR⁴—C(O)R⁵, (C₀-C₆)-alkyl-NR⁴—C(O)OR⁴, (C₀-C₆)-alkyl-NR⁴—C(O)—NR⁴R⁵, (C₀-C₆)-alkyl-NR⁴—SO₂NR⁴R⁵, (C₀-C₆)-alkyl-NR⁴—SO₂R⁴, hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, haloalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, alkoxyalkyl or aminoalkyl, wherein alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, alkoxyalkyl and aminoalkyl are all optionally substituted;

[0025] R^{13a} and R^{13b} are each independently R⁵ or together are =O;

[0026] R^{14a} and R^{14b} are each independently R⁵ or together are =O;

[0027] R^{13c} and R^{14c} are each independently R⁵;

[0028] Q^a is CH or N;

[0029] U is —C(O)—, —C(=NR⁴)—, —(CR⁴R⁵)_p, NR⁵⁰, S(O)₂, C(=O), (C=O)N(R⁴), N(R⁴)(C=O), S(=O)₂N(R⁴), N(R⁴)S(=O)₂, C=N—OR⁴, —C(R⁴)=C(R⁵)—, —C(R⁴R⁵)_pNR⁵⁰, N(R⁵⁰)C(R⁴R⁵)_p, —O—C(R⁴R⁵)—, —C(R⁴R⁵)S(=O)—, —(C=O)O—, —(C=NR^a)N(R⁴)—, —(C=NR^a)—, N(C=O)NR⁵, N(C=O)R⁴, N(C=O)OR^a, NS(=O)₂NR⁴NR⁴, NS(=O)

$_2R^4$, or an optionally substituted aryl, heteroaryl, cycloalkyl or heterocyclic ring, all of which may be optionally substituted;

[0030] W is $-\text{CH}_2-$, $-\text{S}-$, $-\text{CHF}-$ or $-\text{CF}_2-$;

[0031] Z is C or N;

[0032] m is 1, or 2;

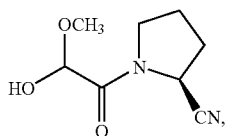
[0033] n is 0, 1, or 2;

[0034] p is 0 to 6;

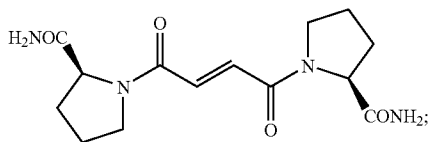
[0035] q is 0 to 6; and

[0036] t is 0, 1, or 2.

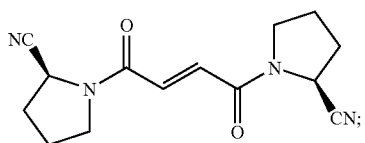
[0037] Another aspect of the present invention includes a method of preparing a compound of the following formula:



comprising (a) coupling prolinamide with fumarylchloride to provide a compound of the following formula:

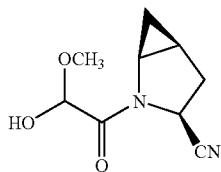


[0038] (b) dehydrating the carboxamides of the compound from step (a) to cyano to provide a compound of formula:

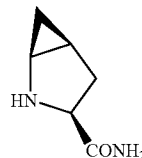


and (c) cleaving the $\text{C}=\text{C}$ bond with an oxidizing agent either: (1) in the presence of methanol, and then adding a reducing agent to the reaction mixture, or (2) and reacting the cleavage products with a reducing agent and subsequently adding methanol to the cleavage product mixture.

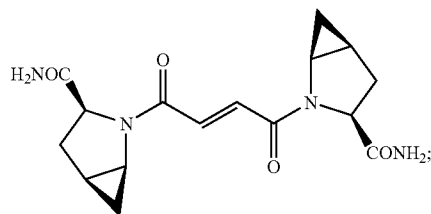
[0039] A further aspect of the present invention provides a method of preparing a compound of the following formula:



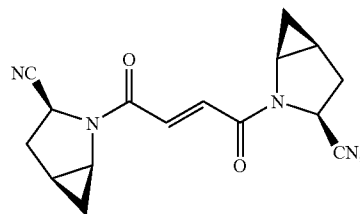
comprising: (a) coupling a compound of formula:



with fumaryl chloride to provide a compound of formula



[0040] (b) dehydrating the carboxamide in the compound from step (a) to provide a compound of formula:

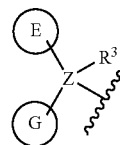


and (c) cleaving the $\text{C}=\text{C}$ bond with an oxidizing agent either: (1) in the presence of methanol, and then adding a reducing agent to the reaction mixture, or (2) and reacting the cleavage products with a reducing agent and subsequently adding methanol to the cleavage product mixture.

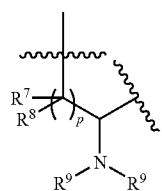
[0041] Another aspect of the present invention provides a compound of formula A compound of formula (I):



wherein A is:

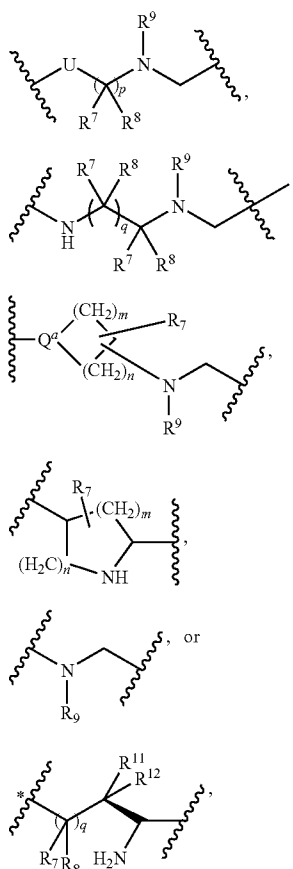


[0042] B is:

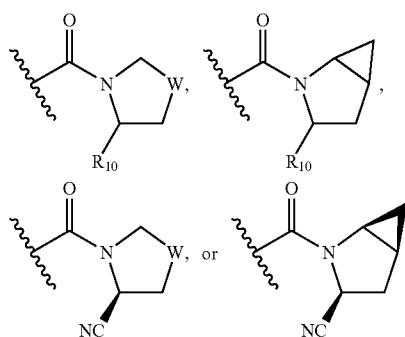


(a)

-continued



[0043] and
[0044] D is:



wherein

[0045] E and G are independently selected from 6-membered aryl, 5-membered heteroaryl, 6-membered heteroaryl, and 5-6-membered saturated or partially saturated carbocyclic or heterocyclic rings;

[0046] E may be substituted with one or more R¹ groups;

[0048] R^1 and R^2 are independently: halogen, CF_3 , COR^4 , OR^4 , NR^4R^5 , NO_2 , CN , SO_2OR^4 , CO_2R^4 , $CONR^4R^5$, CO_2H , $SO_2NR^4R^5$, $S(O)R^4$, SO_2H , $OC(O)R^4$, $OC(O)NR^4R^5$, NR^4C

- (b) $(\text{O})\text{R}^5$, $\text{NR}^4\text{CO}_2\text{R}^5$, $(\text{C}_0\text{--C}_6)\text{-alkyl-C(=NR}^4\text{)NHR}^4$, $(\text{C}_0\text{--C}_6)\text{-alkyl-C(=NR}^4\text{)NHR}^4$, $(\text{C}_0\text{--C}_6)\text{-alkyl-C(=NR}^4\text{)C(=NR}^4\text{)NR}^4\text{R}^5$, $(\text{C}_0\text{--C}_6)\text{-alkyl-C(O)OR}^4$, $(\text{C}_0\text{--C}_6)\text{-alkyl-C(O)NR}^4\text{R}^5$, $(\text{C}_0\text{--C}_6)\text{-alkyl-C(O)NH-CN}$, $\text{O}-(\text{C}_0\text{--C}_6)\text{-alkyl-C(O)NR}^4\text{R}^5$, $\text{S(O)}_i-(\text{C}_0\text{--C}_6)\text{-alkyl-C(O)OR}^4$, $\text{S(O)}_i-(\text{C}_0\text{--C}_6)\text{-alkyl-C(O)NR}^4\text{R}^5$, $(\text{C}_0\text{--C}_6)\text{-alkyl-C(O)NR}^4-(\text{C}_0\text{--C}_6)\text{-alkyl-NR}^4\text{R}^5$, $(\text{C}_0\text{--C}_6)\text{-alkyl-NR}^4\text{R}^5$, $(\text{C}_0\text{--C}_6)\text{-alkyl-NR}^4-(\text{O})\text{R}^5$, $(\text{C}_0\text{--C}_6)\text{-alkyl-NR}^4-\text{C(O)OR}^4$, $(\text{C}_0\text{--C}_6)\text{-alkyl-NR}^4-\text{C(O)-NR}^4\text{R}^5$, $(\text{C}_0\text{--C}_6)\text{-alkyl-NR}^4-\text{SO}_2\text{NR}^4\text{R}^5$, $(\text{C}_0\text{--C}_6)\text{-alkyl-NR}^4-\text{SO}_2\text{R}^4$, hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, haloalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, alkoxyalkyl or aminoalkyl, wherein alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, alkoxyalkyl and aminoalkyl are all optionally substituted;
- [0049]** R^3 is absent or is halogen, CF_3 , COR^4 , OR^4 , NR^4R^5 , NO_2 , CN , SO_2OR^4 , CO_2R^4 , CONR^4R^5 , CO_2H , $\text{SO}_2\text{NR}^4\text{R}^5$, $\text{S(O)}_i\text{R}^4$, SO_3H , OC(O)R^4 , $\text{OC(O)NR}^4\text{R}^5$, $\text{NR}^4\text{C(O)R}^5$, $\text{NR}^4\text{CO}_2\text{R}^5$, $(\text{C}_0\text{--C}_6)\text{-alkyl-C(=NR}^4\text{)NHR}^4$, $(\text{C}_0\text{--C}_6)\text{-alkyl-C(=NR}^4\text{)NHR}^4$, $(\text{C}_0\text{--C}_6)\text{-alkyl-NR}^4\text{C(=NR}^4\text{)NR}^4\text{R}^5$, $(\text{C}_0\text{--C}_6)\text{-alkyl-C(O)OR}^4$, $(\text{C}_0\text{--C}_6)\text{-alkyl-C(O)NR}^4\text{R}^5$, $(\text{C}_0\text{--C}_6)\text{-alkyl-C(O)NH-CN}$, $\text{O}-(\text{C}_0\text{--C}_6)\text{-alkyl-C(O)NR}^4\text{R}^5$, $\text{S(O)}_i-(\text{C}_0\text{--C}_6)\text{-alkyl-C(O)OR}^4$, $\text{S(O)}_i-(\text{C}_0\text{--C}_6)\text{-alkyl-C(O)NR}^4\text{R}^5$, $(\text{C}_0\text{--C}_6)\text{-alkyl-C(O)NR}^4-(\text{C}_0\text{--C}_6)\text{-alkyl-NR}^4\text{R}^5$, $(\text{C}_0\text{--C}_6)\text{-alkyl-NR}^4\text{R}^5$, $(\text{C}_0\text{--C}_6)\text{-alkyl-NR}^4-\text{C(O)OR}^4$, $(\text{C}_0\text{--C}_6)\text{-alkyl-NR}^4-\text{C(O)-NR}^4\text{R}^5$, $(\text{C}_0\text{--C}_6)\text{-alkyl-NR}^4-\text{SO}_2\text{NR}^4\text{R}^5$, $(\text{C}_0\text{--C}_6)\text{-alkyl-NR}^4-\text{SO}_2\text{R}^4$, hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, haloalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, alkoxyalkyl or aminoalkyl, wherein alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, alkoxyalkyl and aminoalkyl are all optionally substituted;

[0050] R^a is hydrogen, CN, NO₂, alkyl, haloalkyl, S(O)NR⁴R⁵, S(O)R⁴, C(O)OR⁴, C(O)R⁴, or C(O)NR⁴R⁵;

[0051] each occurrence of R⁴, R⁵, R²⁰ and R²¹ are each independently: hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl or aminoalkyl, wherein alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl are all optionally substituted, or R⁴ and R⁵ when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and may be optionally containing a heteroatom selected from O, S, or NR⁵⁰ and the 3- to 8-membered ring may be optionally substituted;

[0052] R^{50} is, in each occurrence, R^{20} , CN, NO_2 , $S(O)NR^{20}R^{21}$, $S(O)R^{20}$, $C(O)OR^{20}$, $C(O)R^{20}C(=NR^a)$, $NR^{20}R^{21}$, $C(=NR^{20})NR^{21}R^a$, $C(=NOR^{20})R^{21}$ or $C(O)NR^{20}R^{21}$.

[0053] each occurrence of R^7 and R^8 are each independently: halogen, CF_3 , COR^4 , OR^4 , NR^4R^5 , NO_2 , CN , SO_2OR^4 , CO_2R^4 , $CNRR^5$, CO_2H , SO_2NR^5 , $S(O)_iR^4$, SO_3H , $OC(O)R^4$, $OC(O)NR^5$, $\dot{N}R^4C(O)R^5$, $NR^4CO_2R^5$, $(C_0-C_6)\text{-alkyl-C(=NR}^4)NHR^4$, $(C_0-C_6)\text{-alkyl-C(=NR}^4)NHR^4$, $(C_0-C_6)\text{-alkyl-}NR^4C(=NR^4)NR^5$, $(C_0-C_6)\text{-alkyl-}NR^4R^5$, $(C_0-C_6)\text{-alkyl-C(O)OR}^4$, $(C_0-C_6)\text{-alkyl-C(O)NR}^4R^5$, $(C_0-C_6)\text{-alkyl-C(O)-NH-CN}$, $O-(C_0-C_6)\text{-alkyl-C(O)NR}^4R^5$, $S(O)_i-(C_1-C_6)\text{-alkyl-C(O)OR}^4$, $S(O)_i-(C_0-C_6)\text{-alkyl-C(O)NR}^4R^5$, $(C_0-C_6)\text{-alkyl-C(O)NR}^4-(C_0-C_6)\text{-alkyl-}NR^4R^5$, $(C_0-C_6)\text{-alkyl-}NR^4R^5$, $(C_0-C_6)\text{-alkyl-}NR^4-C(O)R^5$, $(C_0-$

C_6)-alkyl-NR⁴-C(O)OR⁴, (C_6-C_6) -alkyl-NR⁴-C(O)-NR⁴R⁵, (C_6-C_6) -alkyl-NR⁴-SO₂NR⁴R⁵, (C_6-C_6) -alkyl-NR⁴-SO₂R⁴, hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, haloalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, alkoxyalkyl or aminoalkyl, wherein alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, alkoxyalkyl and aminoalkyl all may be optionally substituted;

[0054] R⁹ is H or C₁₋₆alkyl;

[0055] R¹⁰ is halogen, CF₃, COR⁴, OR⁴, NR⁴R⁵, NO₂, CN, SO₂OR⁴, CO₂R⁴, CONR⁴R⁵, CO₂H, SO₂NR⁴R⁵, S(O)₂R⁴, SO₃H, OC(O)R⁴, OC(O)NR⁴R⁵, NR⁴C(O)R⁵, NR⁴CO₂R⁵, (C_6-C_6) -alkyl-C(=NR⁴)NHR⁴, (C_6-C_6) -alkyl-C(=NR⁴)NHR⁴, (C_6-C_6) -alkyl-NR⁴C(=NR⁴)NR⁴R⁵, (C_6-C_6) -alkyl-C(O)OR⁴, (C_6-C_6) -alkyl-C(O)NR⁴R⁵, (C_6-C_6) -alkyl-C(O)-NH-CN, O- (C_6-C_6) -alkyl-C(O)NR⁴R⁵, S(O)₂- (C_6-C_6) -alkyl-C(O)OR⁴, S(O)₂- (C_6-C_6) -alkyl-C(O)NR⁴R⁵, (C_6-C_6) -alkyl-C(O)NR⁴R⁵, (C_6-C_6) -alkyl-C(O)NR⁴R⁵, (C_6-C_6) -alkyl-NR⁴-C(O)R⁵, (C_6-C_6) -alkyl-NR⁴-C(O)OR⁴, (C_6-C_6) -alkyl-NR⁴-C(O)-NR⁴R⁵, (C_6-C_6) -alkyl-NR⁴-SO₂NR⁴R⁵, (C_6-C_6) -alkyl-NR⁴-SO₂R⁴, hydrogen, B(OH)₂, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, haloalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, alkoxyalkyl or aminoalkyl, wherein alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, alkoxyalkyl and aminoalkyl all may be optionally substituted;

[0056] R¹¹ and R¹² are each independently: halogen, CF₃, COR⁴, OR⁴, NR⁴R⁵, NO₂, CN, SO₂OR⁴, CO₂R⁴, CONR⁴R⁵, CO₂H, SO₂NR⁴R⁵, S(O)₂R⁴, SO₃H, OC(O)R⁴, OC(O)NR⁴R⁵, NR⁴C(O)R⁵, NR⁴CO₂R⁵, (C_6-C_6) -alkyl-C(=NR⁴)NHR⁴, (C_6-C_6) -alkyl-C(=NR⁴)NHR⁴, (C_6-C_6) -alkyl-NR⁴C(=NR⁴)NR⁴R⁵, (C_6-C_6) -alkyl-C(O)OR⁴, (C_6-C_6) -alkyl-C(O)NR⁴R⁵, (C_6-C_6) -alkyl-C(O)-NH-CN, O- (C_6-C_6) -alkyl-C(O)NR⁴R⁵, S(O)₂- (C_6-C_6) -alkyl-C(O)OR⁴, S(O)₂- (C_6-C_6) -alkyl-C(O)NR⁴R⁵, (C_6-C_6) -alkyl-C(O)NR⁴R⁵, (C_6-C_6) -alkyl-NR⁴-C(O)R⁵, (C_6-C_6) -alkyl-NR⁴-C(O)OR⁴, (C_6-C_6) -alkyl-NR⁴-C(O)-NR⁴R⁵, (C_6-C_6) -alkyl-NR⁴-SO₂NR⁴R⁵, (C_6-C_6) -alkyl-NR⁴-SO₂R⁴, hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, haloalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, alkoxyalkyl or aminoalkyl, wherein alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, alkoxyalkyl and aminoalkyl all may be optionally substituted;

[0057] R^{13a} and R^{13b} are each independently R⁵ or together are =O;

[0058] R^{14a} and R^{14b} are each independently R⁵ or together are =O;

[0059] R^{13c} and R^{14c} are each independently R⁵;

[0060] Q^a is CH or N;

[0061] U is -C(O)-, -C(=NR⁴)-, -(CR⁴R⁵)-, NR⁵⁰, S(=O)₂, C(=O), (C=O)N(R⁴), N(R⁴)(C=O), S(=O)₂N(R⁴), N(R⁴)S(=O)₂, C=N-OR⁴, -C(R⁴)=C(R⁵)-, -C(R⁴R⁵)NR⁵⁰-, N(R⁵⁰)C(R⁴R⁵)-, -O-C(R⁴R⁵)-, -C(R⁴R⁵)S(=O)-, -(C=O)O-, -(C=NR⁴)N(R⁴)-, -(C=NR⁴)-, N(C=O)NR⁴NR⁵, N(C=O)R⁴, N(C=O)OR⁴, NS(=O)₂NR⁴NR⁵, NS(=O)

₂R⁴, or an optionally substituted aryl, heteroaryl, cycloalkyl or heterocyclic ring, all of which may be optionally substituted;

[0062] W is -CH₂-, -S-, -CHF- or -CF₂-;

[0063] Z is C or N;

[0064] m is 1, or 2;

[0065] n is 0, 1, or 2;

[0066] p is 0 to 6;

[0067] q is 0 to 6; and

[0068] t is 0, 1, or 2

wherein: when E and G are both phenyl either:

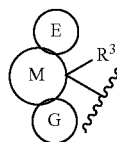
[0069] (1) at least one of R¹ or R² is present and is:

[0070] CF₃, COR⁴, OR⁴, NR⁴R⁵, NO₂, CN, SO₂OR⁴, CO₂R⁴, CONR⁴R⁵, CO₂H, SO₂NR⁴R⁵, S(O)₂R⁴, SO₃H, OC(O)R⁴, OC(O)NR⁴R⁵, NR⁴C(O)R⁵, NR⁴CO₂R⁵, (C_6-C_6) -alkyl-C(=NR⁴)NHR⁴, (C_6-C_6) -alkyl-C(=NR⁴)NHR⁴, (C_6-C_6) -alkyl-NR⁴C(=NR⁴)NR⁴R⁵, (C_6-C_6) -alkyl-C(O)OR⁴, (C_6-C_6) -alkyl-C(O)NR⁴R⁵, (C_6-C_6) -alkyl-C(O)-NH-CN, O- (C_6-C_6) -alkyl-C(O)NR⁴R⁵, S(O)₂- (C_6-C_6) -alkyl-C(O)OR⁴, S(O)₂- (C_6-C_6) -alkyl-C(O)NR⁴R⁵, (C_6-C_6) -alkyl-C(O)NR⁴R⁵, (C_6-C_6) -alkyl-NR⁴-C(O)R⁵, (C_6-C_6) -alkyl-NR⁴-C(O)OR⁴, (C_6-C_6) -alkyl-NR⁴-C(O)-NR⁴R⁵, (C_6-C_6) -alkyl-NR⁴-SO₂NR⁴R⁵, (C_6-C_6) -alkyl-NR⁴-SO₂R⁴, hydrogen, (C₅₋₂₀) alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, haloalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, alkoxyalkyl or aminoalkyl, wherein alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, alkoxyalkyl and aminoalkyl are all optionally substituted; and wherein OR⁴ is alkoxy, OR⁴ is (C₅₋₂₀) alkoxy; or (2) and when B is (b) R⁷ and R⁸ are not selected from hydrogen, hydroxy, hydroxymethyl, and phenyl; or (3) and when B is (b) or (f), R⁹ is: C₁₋₆ alkyl.

[0071] Another aspect of the present invention provides a compound of formula A compound of formula (I):

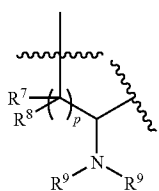


wherein A is:



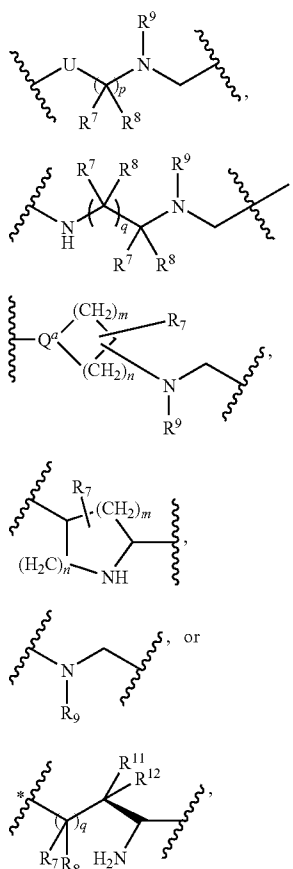
B is:

[0072]



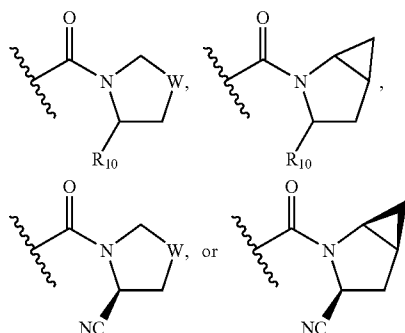
(a)

-continued



[0073] and

[0074] D is:



wherein

[0075] E, G, and M include a three ring system wherein M shares two carbon atoms with each of E and G;

[0076] E, G and M are each independently selected from a 5-7-membered saturated or partially saturated carbocyclic ring, a 5-7 membered saturated or partially saturated heterocyclic ring, a 5-6-membered aromatic ring, and a 5-6-membered heteroaromatic ring;

[0077] E may be substituted with one or more R¹ groups;[0078] G may be substituted with one or more R² groups;

- (b) [0079] R¹ and R² are independently: halogen, CF₃, COR⁴, OR⁴, NR⁴R⁵, NO₂, CN, SO₂OR⁴, CO₂R⁴, CONR⁴R⁵, CO₂H, SO₂NR⁴R⁵, S(O)₂R⁴, SO₃H, OC(O)R⁴, OC(O)NR⁴R⁵, NR⁴C(O)R⁵, NR⁴CO₂R⁵, (C₀-C₆)-alkyl-C(=NR⁴)NHR⁴, (C₀-C₆)-alkyl-C(=NR⁴)NHR⁵, (C₀-C₆)-alkyl-NR⁴C(=NR⁴)NR⁵, (C₀-C₆)-alkyl-C(O)OR⁴, (C₀-C₆)-alkyl-C(O)NR⁴R⁵, (C₀-C₆)-alkyl-C(O)—NH—CN, O—(C₀-C₆)-alkyl-C(O)NR⁴R⁵, S(O)—(C₀-C₆)-alkyl-C(O)OR⁴, S(O)—(C₀-C₆)-alkyl-C(O)NR⁴R⁵, (C₀-C₆)-alkyl-C(O)NR⁴—(C₀-C₆)-alkyl-NR⁴R⁵, (C₀-C₆)-alkyl-NR⁴R⁵, (C₀-C₆)-alkyl-NR⁴—C(O)R⁵, (C₀-C₆)-alkyl-NR⁴—C(O)OR⁴, (C₀-C₆)-alkyl-NR⁴—C(O)—NR⁴R⁵, (C₀-C₆)-alkyl-NR⁴—SO₂NR⁴R⁵, (C₀-C₆)-alkyl-NR⁴—SO₂R⁴, hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, haloalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, alkoxyalkyl or aminoalkyl, wherein alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, alkoxyalkyl and aminoalkyl are all optionally substituted;

- (c) [0080] R³ is absent or is halogen, CF₃, COR⁴, OR⁴, NR⁴R⁵, NO₂, CN, SO₂OR⁴, CO₂R⁴, CONR⁴R⁵, CO₂H, SO₂NR⁴R⁵, S(O)₂R⁴, SO₃H, OC(O)R⁴, OC(O)NR⁴R⁵, NR⁴C(O)R⁵, NR⁴CO₂R⁵, (C₀-C₆)-alkyl-C(=NR⁴)NHR⁴, (C₀-C₆)-alkyl-C(=NR⁴)NHR⁵, (C₀-C₆)-alkyl-NR⁴C(=NR⁴)NR⁵, (C₀-C₆)-alkyl-C(O)OR⁴, (C₀-C₆)-alkyl-C(O)NR⁴R⁵, (C₀-C₆)-alkyl-C(O)—NH—CN, O—(C₀-C₆)-alkyl-C(O)NR⁴R⁵, S(O)—(C₀-C₆)-alkyl-C(O)OR⁴, S(O)—(C₀-C₆)-alkyl-C(O)NR⁴R⁵, (C₀-C₆)-alkyl-C(O)NR⁴—(C₀-C₆)-alkyl-NR⁴R⁵, (C₀-C₆)-alkyl-NR⁴R⁵, (C₀-C₆)-alkyl-NR⁴—C(O)R⁵, (C₀-C₆)-alkyl-NR⁴—C(O)OR⁴, (C₀-C₆)-alkyl-NR⁴—C(O)—NR⁴R⁵, (C₀-C₆)-alkyl-NR⁴—SO₂NR⁴R⁵, (C₀-C₆)-alkyl-NR⁴—SO₂R⁴, hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, haloalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, alkoxyalkyl or aminoalkyl, wherein alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, alkoxyalkyl and aminoalkyl are all optionally substituted;

[0081] R^a is hydrogen, CN, NO₂, alkyl, haloalkyl, S(O)₂NR⁴R⁵, S(O)₂R⁴, C(O)OR⁴, C(O)R⁴, or C(O)NR⁴R⁵;[0082] each occurrence of R⁴, R⁵, R²⁰ and R²¹ are each independently: hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl or aminoalkyl, wherein alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl are all optionally substituted, or R⁴ and R⁵ when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and may be optionally containing a heteroatom selected from O, S, or NR⁵⁰ and the 3- to 8-membered ring may be optionally substituted;[0083] R⁵⁰ is, in each occurrence, R²⁰, CN, NO₂, S(O)₂NR²⁰R²¹, S(O)₂R²⁰, C(O)OR²⁰, C(O)R²⁰, C(O)NR²⁰R²¹, C(=NR²⁰)NR²¹R^a, C(=NR²⁰)R²¹ or C(O)NR²⁰R²¹;[0084] each occurrence of R⁷ and R⁸ are each independently: halogen, CF₃, COR⁴, OR⁴, NR⁴R⁵, NO₂, CN, SO₂OR⁴, CO₂R⁴, CONR⁴R⁵, CO₂H, SO₂NR⁴R⁵, S(O)₂R⁴,

SO₃H, OC(O)R⁴, OC(O)NR⁴R⁵, NR⁴C(O)R⁵, NR⁴CO₂R⁵, (C₀-C₆)-alkyl-C(=NR^a)NHR⁴, (C₀-C₆)-alkyl-C(=NR^a)NHR^a, (C₀-C₆)-alkyl-NR⁴C(=NR^a)NR⁴R⁵, (C₀-C₆)-alkyl-C(O)OR⁴, (C₀-C₆)-alkyl-C(O)NR⁴R⁵, (C₀-C₆)-alkyl-C(O)—NH—CN, O—(C₀-C₆)-alkyl-C(O)NR⁴R⁵, S(O)_t—(C₀-C₆)-alkyl-C(O)OR⁴, S(O)_t—(C₀-C₆)-alkyl-C(O)NR⁴R⁵, (C₀-C₆)-alkyl-C(O)NR⁴—(C₀-C₆)-alkyl-NR⁴R⁵, (C₀-C₆)-alkyl-NR⁴R⁵, (C₀-C₆)-alkyl-NR⁴—C(O)R⁵, (C₀-C₆)-alkyl-NR⁴—C(O)OR⁴, (C₀-C₆)-alkyl-NR⁴—C(O)—NR⁴R⁵, (C₀-C₆)-alkyl-NR⁴—SO₂NR⁴R⁵, (C₀-C₆)-alkyl-NR⁴—SO₂R⁴, hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, haloalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, alkoxyalkyl or aminoalkyl, wherein alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, alkoxyalkyl and aminoalkyl all may be optionally substituted;

[0085] R⁹ is H or C₁₋₆ alkyl;

[0086] R¹⁰ is halogen, CF₃, COR⁴, OR⁴, NR⁴R⁵, NO₂, CN, SO₂OR⁴, CO₂R⁴, CONR⁴R⁵, CO₂H, SO₂NR⁴R⁵, S(O)_tR⁴, SO₃H, OC(O)R⁴, OC(O)NR⁴R⁵, NR⁴C(O)R⁵, NR⁴CO₂R⁵, (C₀-C₆)-alkyl-C(=NR^a)NHR⁴, (C₀-C₆)-alkyl-C(=NR^a)NHR^a, (C₀-C₆)-alkyl-NR⁴C(=NR^a)NR⁴R⁵, (C₀-C₆)-alkyl-C(O)OR⁴, (C₀-C₆)-alkyl-C(O)NR⁴R⁵, (C₀-C₆)-alkyl-C(O)—NH—CN, O—(C₀-C₆)-alkyl-C(O)NR⁴R⁵, S(O)_t—(C₀-C₆)-alkyl-C(O)OR⁴, S(O)_t—(C₀-C₆)-alkyl-C(O)NR⁴R⁵, (C₀-C₆)-alkyl-C(O)NR⁴—(CO—C₆)-alkyl-NR⁴R⁵, (C₀-C₆)-alkyl-NR⁴R⁵, (C₀-C₆)-alkyl-NR⁴—C(O)R⁵, (C₀-C₆)-alkyl-NR⁴—C(O)OR⁴, (C₀-C₆)-alkyl-NR⁴—C(O)—NR⁴R⁵, (C₀-C₆)-alkyl-NR⁴—SO₂NR⁴R⁵, (C₀-C₆)-alkyl-NR⁴—SO₂R⁴, hydrogen, B(OH)₂, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, haloalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, alkoxyalkyl or aminoalkyl, wherein alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, alkoxyalkyl and aminoalkyl all may be optionally substituted;

[0087] R¹¹ and R¹² are each independently: halogen, CF₃, COR⁴, OR⁴, NR⁴R⁵, NO₂, CN, SO₂OR⁴, CO₂R⁴, CONR⁴R⁵, CO₂H, SO₂NR⁴R⁵, S(O)_tR⁴, SO₃H, OC(O)R⁴, OC(O)NR⁴R⁵, NR⁴C(O)R⁵, NR⁴CO₂R⁵, (C₀-C₆)-alkyl-C(=NR^a)NHR⁴, (C₀-C₆)-alkyl-C(=NR^a)NHR^a, (CO—C₆)-alkyl-NR⁴C(=NR^a)NR⁴R⁵, (C₀-C₆)-alkyl-C(O)OR⁴, (C₀-C₆)-alkyl-C(O)NR⁴R⁵, (C₀-C₆)-alkyl-C(O)—NH—CN, O—(C₀-C₆)-alkyl-C(O)NR⁴R⁵, S(O)_t—(C₀-C₆)-alkyl-C(O)OR⁴, S(O)_t—(C₀-C₆)-alkyl-C(O)NR⁴R⁵, (C₀-C₆)-alkyl-C(O)NR⁴—(C₀-C₆)-alkyl-NR⁴R⁵, (C₀-C₆)-alkyl-NR⁴R⁵, (C₀-C₆)-alkyl-NR⁴—C(O)R⁵, (C₀-C₆)-alkyl-NR⁴—C(O)OR⁴, (C₀-C₆)-alkyl-NR⁴—C(O)—NR⁴R⁵, (C₀-C₆)-alkyl-NR⁴—SO₂NR⁴R⁵, (C₀-C₆)-alkyl-NR⁴—SO₂R⁴, hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, haloalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, alkoxyalkyl or aminoalkyl, wherein alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, alkoxyalkyl and aminoalkyl all may be optionally substituted;

[0088] R^{13a} and R^{13b} are each independently R⁵ or together are =O;

[0089] R^{14a} and R^{14b} are each independently R⁵ or together are =O;

[0090] R^{13c} and R^{14c} are each independently R⁵;

[0091] Q^a is CH or N;

[0092] U is —C(O)—, —C(=NR⁴)—, —(CR⁴R⁵)_p, NR⁵⁰, S(=O)₂, C(=O), (C=O)N(R⁴), N(R⁴)(C=O), S(=O)₂N(R⁴), N(R⁴)S(=O)₂, C=N—OR⁴, —C(R⁴)=C(R⁵)—, —C(R⁴R⁵)_pNR⁵⁰, N(R⁵⁰)C(R⁴R⁵)_p, —O—C(R⁴R⁵)—, —C(R⁴R⁵)S(=O)_t—, —(C=O)O—, —(C=NR^a)N(R⁴)—, —(C=NR^a)—, N(C=O)NR⁴NR⁵, N(C=O)R⁴, N(C=O)OR⁴, NS(=O)₂NR⁴NR⁵, NS(=O)₂R⁴, or an optionally substituted aryl, heteroaryl, cycloalkyl or heterocyclic ring, all of which may be optionally substituted;

[0093] W is —CH₂—, —S—, —CHF— or —CF₂—;

[0094] Z is C or N;

[0095] m is 1, or 2;

[0096] n is 0, 1, or 2;

[0097] p is 0 to 6;

[0098] q is 0 to 6; and

[0099] t is 0, 1, or 2

wherein: when E and G are both phenyl either:

[0100] (1) at least one of R¹ or R² is present and is:

[0101] CF₃, COR⁴, OR⁴, NR⁴R⁵, NO₂, CN, SO₂OR⁴, CO₂R⁴, CONR⁴R⁵, CO₂H, SO₂NR⁴R⁵, S(O)_tR⁴, SO₃H, OC(O)R⁴, OC(O)NR⁴R⁵, NR⁴C(O)R⁵, NR⁴CO₂R⁵, (C₀-C₆)-alkyl-C(=NR^a)NHR⁴, (C₀-C₆)-alkyl-C(=NR^a)NHR^a, (C₀-C₆)-alkyl-NR⁴C(=NR^a)NR⁴R⁵, (C₀-C₆)-alkyl-C(O)OR⁴, (CO—C₆)-alkyl-C(O)NR⁴R⁵, (C₀-C₆)-alkyl-C(O)—NH—CN, O—(C₀-C₆)-alkyl-C(O)NR⁴R⁵, S(O)_t—(C₀-C₆)-alkyl-C(O)OR⁴, S(O)_t—(C₀-C₆)-alkyl-C(O)NR⁴R⁵, (C₀-C₆)-alkyl-C(O)NR⁴—(C₀-C₆)-alkyl-NR⁴R⁵, (C₀-C₆)-alkyl-NR⁴R⁵, (C₀-C₆)-alkyl-NR⁴—C(O)R⁵, (C₀-C₆)-alkyl-NR⁴—C(O)OR⁴, (C₀-C₆)-alkyl-NR⁴—C(O)—NR⁴R⁵, (C₀-C₆)-alkyl-NR⁴—SO₂NR⁴R⁵, (C₀-C₆)-alkyl-NR⁴—SO₂R⁴, hydrogen, (C₅₋₂₀)alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, haloalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, alkoxyalkyl or aminoalkyl, wherein alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, alkoxyalkyl and aminoalkyl are all optionally substituted; and wherein OR⁴ is alkoxy, OR⁴ is (C₅₋₂₀) alkoxy; or (2) and when B is (b) R⁷ and R⁸ are not selected from hydrogen, hydroxy, hydroxymethyl, and phenyl; or (3) and when B is (b) or (f), R⁹ is: C₁₋₆ alkyl.

[0102] Compounds of the present invention having one or more optically active carbons can exist as racemates and racemic mixtures, diastomeric mixtures and individual diastereomers, enantiomeric mixtures and single enantiomers, tautomers, atropisomers, and rotamers, with all isomeric forms being included in the present invention. Compounds described in this invention containing olefinic double bonds include both E and Z geometric isomers. Also included in this invention are all salt forms, polymorphs, hydrates and solvates. All of the above mentioned compounds are included within the scope of the invention.

[0103] The present invention also provides methods of inhibiting the DPP-IV enzyme.

[0104] The present invention further provides methods of treatment or prevention of diseases in which the dipeptidyl peptidase-IV enzyme is involved, such as diabetes and particularly Type-2 diabetes.

[0105] The present invention also provides methods for obtaining the DPP-IV inhibiting compounds and pharmaceutical compositions comprising them either singly or in combination with one or more additional therapeutic agents for

the prevention or treatment of DPP-IV enzyme mediated diseases, particularly Type-2 diabetes.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

[0106] The terms “alkyl” or “alk”, as used herein alone or as part of another group, denote optionally substituted, straight and branched chain saturated hydrocarbon groups, preferably having 1 to 10 carbons in the normal chain, most preferably lower alkyl groups. Exemplary unsubstituted such groups include methyl, ethyl, propyl, isopropyl, n-butyl, t-butyl, isobutyl, pentyl, hexyl, isohexyl, heptyl, 4,4-dimethylpentyl, octyl, 2,2,4-trimethylpentyl, nonyl, decyl, undecyl, dodecyl and the like. Exemplary substituents may include, but are not limited to, one or more of the following groups: halo, alkoxy, alkylthio, alkenyl, alkynyl, aryl (e.g., to form a benzyl group), cycloalkyl, cycloalkenyl, hydroxy or protected hydroxy, carboxyl ($-\text{COOH}$), alkylloxycarbonyl, alkylcarbonyloxy, alkylcarbonyl, carbamoyl ($\text{NH}_2-\text{CO}-$), substituted carbamoyl ($(\text{R}^4)(\text{R}^5)\text{N}-\text{CO}-$ wherein R^4 or R^5 are as defined below, except that at least one of R^4 or R^5 is not hydrogen), amino, heterocyclo, mono- or dialkylamino, or thiol ($-\text{SH}$).

[0107] The terms “lower alk” or “lower alkyl” as used herein, denote such optionally substituted groups as described above for alkyl having 1 to 4 carbon atoms in the normal chain.

[0108] The term “alkoxy” denotes an alkyl group as described above bonded through an oxygen linkage ($-\text{O}-$).

[0109] The term “alkenyl”, as used herein alone or as part of another group, denotes optionally substituted, straight and branched chain hydrocarbon groups containing at least one carbon to carbon double bond in the chain, and preferably having 2 to 10 carbons in the normal chain. Exemplary unsubstituted such groups include ethenyl, propenyl, isobutenyl, butenyl, pentenyl, hexenyl, heptenyl, octenyl, nonenyl, decenyl, and the like. Exemplary substituents may include, but are not limited to, one or more of the following groups: halo, alkoxy, alkylthio, alkyl, alkynyl, aryl, cycloalkyl, cycloalkenyl, hydroxy or protected hydroxy, carboxyl ($-\text{COOH}$), alkylloxycarbonyl, alkylcarbonyloxy, alkylcarbonyl, carbamoyl ($\text{NH}_2-\text{CO}-$), substituted carbamoyl ($(\text{R}^4)(\text{R}^5)\text{N}-\text{CO}-$ wherein R^4 or R^5 are as defined below, except that at least one of R^4 or R^5 is not hydrogen), amino, heterocyclo, mono- or dialkylamino, or thiol ($-\text{SH}$).

[0110] The term “alkynyl”, as used herein alone or as part of another group, denotes optionally substituted, straight and branched chain hydrocarbon groups containing at least one carbon to carbon triple bond in the chain, and preferably having 2 to 10 carbons in the normal chain. Exemplary unsubstituted such groups include, but are not limited to, ethynyl, propynyl, butynyl, pentynyl, hexynyl, heptynyl, octynyl, nonynyl, decynyl, and the like. Exemplary substituents may include, but are not limited to, one or more of the following groups: halo, alkoxy, alkylthio, alkyl, alkenyl, aryl, cycloalkyl, cycloalkenyl, hydroxy or protected hydroxy, carboxyl ($-\text{COOH}$), alkylloxycarbonyl, alkylcarbonyloxy, alkylcarbonyl, carbamoyl ($\text{NH}_2-\text{CO}-$), substituted carbamoyl ($(\text{R}^4)(\text{R}^5)\text{N}-\text{CO}-$ wherein R^4 or R^5 are as defined below, except that at least one of R^4 or R^5 is not hydrogen), amino, heterocyclo, mono- or dialkylamino, or thiol ($-\text{SH}$).

[0111] The term “cycloalkyl”, as used herein alone or as part of another group, denotes optionally substituted, saturated cyclic hydrocarbon ring systems, including bridged ring

systems, desirably containing 1 to 3 rings and 3 to 9 carbons per ring. Exemplary unsubstituted such groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclodecyl, cyclododecyl, and adamantyl. Exemplary substituents include, but are not limited to, one or more alkyl groups as described above, or one or more groups described above as alkyl substituents.

[0112] The terms “ar” or “aryl”, as used herein alone or as part of another group, denote optionally substituted, homocyclic aromatic groups, preferably containing 1 or 2 rings and 6 to 12 ring carbons. Exemplary unsubstituted such groups include, but are not limited to, phenyl, biphenyl, and naphthyl. Exemplary substituents include, but are not limited to, one or more nitro groups, alkyl groups as described above or groups described above as alkyl substituents.

[0113] The term “heterocycle” or “heterocyclic system” denotes a heterocyclyl, heterocyclenyl, or heteroaryl group as described herein, which contains carbon atoms and from 1 to 4 heteroatoms independently selected from the group consisting of N, O and S and including any bicyclic or tricyclic group in which any of the above-defined heterocyclic rings is fused to one or more heterocycle, aryl or cycloalkyl groups. The nitrogen and sulfur heteroatoms may optionally be oxidized. The heterocyclic ring may be attached to its pendant group at any heteroatom or carbon atom which results in a stable structure. The heterocyclic rings described herein may be substituted on carbon or on a nitrogen atom.

[0114] Examples of heterocycles include, but are not limited to, 1H-indazole, 2-pyrrolidinyl, 2H,6H-1,5,2-dithiazinyl, 2H-pyrrolyl, 3H-indolyl, 4-piperidinyl, 4aH-carbazole, 4H-quinoliziny, 6H-1,2,5-thiadiazinyl, acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazoliny, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazolonyl, carbazolyl, 4aH-carbazolyl, b-carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinoliny, 2H,6H-1,5,2-dithiazinyl, dihydrofuro[2,3-b] tetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazoliny, imidazolyl, 1H-indazolyl, indolenyl, indoliny, indoliziny, indolyl, isatinoyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindoliny, isoindolyl, isoquinoliny, isothiazolyl, isoxazolyl, morpholiny, naphthyridinyl, octahydroisoquinoliny, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxazolidinylperimidiny, oxindolyl, phenanthridinyl, phenanthrolinyl, phenarsazinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, pteridinyl, piperidinyl, 4-piperidinyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazoliny, pyrazolyl, pyridazinyl, pyridoazole, pyridoimidazole, pyridothiazole, pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrroliny, pyrrolyl, quinazoliny, quinoliny, 4H-quinoliziny, quinoxaliny, quinuclidiny, carbolinyl, tetrahydrofuranyl, tetrahydroisoquinoliny, tetrahydroquinoliny, tetrazolyl, 6H-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, xanthenyl.

[0115] “Heterocyclenyl” denotes a non-aromatic monocyclic or multicyclic hydrocarbon ring system of about 3 to about 10 atoms, desirably about 4 to about 8 atoms, in which one or more of the carbon atoms in the ring system is/are

hetero element(s) other than carbon, for example nitrogen, oxygen or sulfur atoms, and which contains at least one carbon-carbon double bond or carbon-nitrogen double bond. Ring sizes of rings of the ring system may include 5 to 6 ring atoms. The designation of the aza, oxa or thia as a prefix before heterocyclenyl define that at least a nitrogen, oxygen or sulfur atom is present respectively as a ring atom. The heterocyclenyl may be optionally substituted by one or more substituents as defined herein. The nitrogen or sulphur atom of the heterocyclenyl may also be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. "Heterocyclenyl" as used herein includes by way of example and not limitation those described in Paquette, Leo A.; "Principles of Modern Heterocyclic Chemistry" (W. A. Benjamin, New York, 1968), particularly Chapters 1, 3, 4, 6, 7, and 9; "The Chemistry of Heterocyclic Compounds, A series of Monographs" (John Wiley & Sons, New York, 1950 to present), in particular Volumes 13, 14, 16, 19, and 28; and "J. Am. Chem. Soc.", 82:5566 (1960), the contents all of which are incorporated by reference herein. Exemplary monocyclic azaheterocyclenyl groups include, but are not limited to, 1,2,3,4-tetrahydrodihydropyridine, 1,2-dihydropyridyl, 1,4-dihydropyridyl, 1,2,3,6-tetrahydropyridine, 1,4,5,6-tetrahydropyrimidine, 2-pyrrolinyl, 3-pyrrolinyl, 2-imidazolyl, 2-pyrazolyl, and the like. Exemplary oxaheterocyclenyl groups include, but are not limited to, 3,4-dihydro-2H-pyran, dihydrofuranyl, and fluorodihydrofuranyl. An exemplary multicyclic oxaheterocyclenyl group is 7-oxabicyclo[2.2.1]heptenyl.

[0116] "Heterocyclyl," or "heterocycloalkyl," denotes a non-aromatic saturated monocyclic or multicyclic ring system of about 3 to about 10 carbon atoms, desirably 4 to 8 carbon atoms, in which one or more of the carbon atoms in the ring system is/are hetero element(s) other than carbon, for example nitrogen, oxygen or sulfur. Ring sizes of rings of the ring system may include 5 to 6 ring atoms. The designation of the aza, oxa or thia as a prefix before heterocyclyl define that at least a nitrogen, oxygen or sulfur atom is present respectively as a ring atom. The heterocyclyl may be optionally substituted by one or more substituents which may be the same or different, and are as defined herein. The nitrogen or sulphur atom of the heterocyclyl may also be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide.

[0117] "Heterocyclyl" as used herein includes by way of example and not limitation those described in Paquette, Leo A.; "Principles of Modern Heterocyclic Chemistry" (W. A. Benjamin, New York, 1968), particularly Chapters 1, 3, 4, 6, 7, and 9; "The Chemistry of Heterocyclic Compounds, A series of Monographs" (John Wiley & Sons, New York, 1950 to present), in particular Volumes 13, 14, 16, 19, and 28; and "J. Am. Chem. Soc.", 82:5566 (1960). Exemplary monocyclic heterocyclyl rings include, but are not limited to, piperidyl, pyrrolidinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, 1,3-dioxolanyl, 1,4-dioxanyl, tetrahydrofuranyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, and the like.

[0118] "Heteroaryl" denotes an aromatic monocyclic or multicyclic ring system of about 5 to about 10 atoms, in which one or more of the atoms in the ring system is/are hetero element(s) other than carbon, for example nitrogen, oxygen or sulfur. Ring sizes of rings of the ring system include 5 to 6 ring atoms. The "heteroaryl" may also be substituted by one or more substituents which may be the same or different, and

are as defined herein. The designation of the aza, oxa or thia as a prefix before heteroaryl define that at least a nitrogen, oxygen or sulfur atom is present respectively as a ring atom. A nitrogen atom of a heteroaryl may be optionally oxidized to the corresponding N-oxide. Heteroaryl as used herein includes by way of example and not limitation those described in Paquette, Leo A.; "Principles of Modern Heterocyclic Chemistry" (W. A. Benjamin, New York, 1968), particularly Chapters 1, 3, 4, 6, 7, and 9; "The Chemistry of Heterocyclic Compounds, A series of Monographs" (John Wiley & Sons, New York, 1950 to present), in particular Volumes 13, 14, 16, 19, and 28; and "J. Am. Chem. Soc.", 82:5566 (1960). Exemplary heteroaryl and substituted heteroaryl groups include, but are not limited to, pyrazinyl, thienyl, isothiazolyl, oxazolyl, pyrazolyl, furazanyl, pyrrolyl, 1,2,4-thiadiazolyl, pyridazinyl, quinoxalyl, phthalazinyl, imidazo[1,2-a]pyridine, imidazo[2,1-b]thiazolyl, benzofurazanyl, azaindolyl, benzimidazolyl, benzothienyl, thienopyridyl, thienopyrimidyl, pyrrolopyridyl, imidazopyridyl, benzozaindole, 1,2,3-triazinyl, 1,2,4-triazinyl, 1,3,5-triazinyl, benzthiazolyl, dioxolyl, furanyl, imidazolyl, indolyl, indolizyl, isoxazolyl, isoquinolinyl, isothiazolyl, morpholino, oxadiazolyl, oxazinyl, oxiranyl, piperazinyl, piperidinyl, pyranyl, pyrazinyl, pyridazinyl, pyrazolyl, pyridyl, pyrimidinyl, pyrrolyl, pyrrolidinyl, quinazolinyl, quinolinyl, tetrazinyl, tetrazolyl, 1,3,4-thiadiazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, thiatiazolyl, thiazinyl, thiazolyl, thienyl, 5-thio-1,2,4-diazolyl, thiomorpholino, thiophenyl, thiopyranyl, triazolyl and triazolonyl.

[0119] The term "amino" denotes the radical —NH_2 wherein one or both of the hydrogen atoms may be replaced by an optionally substituted hydrocarbon group. Exemplary amino groups include, but are not limited to, n-butylamino, tert-butylamino, methylpropylamino and ethyldimethylamino.

[0120] The term "cycloalkylalkyl" denotes a cycloalkylalkyl group wherein a cycloalkyl as described above is bonded through an alkyl, as defined above. Cycloalkylalkyl groups may contain a lower alkyl moiety. Exemplary cycloalkylalkyl groups include, but are not limited to, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, cyclopropylethyl, cyclopentylethyl, cyclohexylpropyl, cyclopropylpropyl, cyclopentylpropyl, and cyclohexylpropyl.

[0121] The term "arylalkyl" denotes an aryl group as described above bonded through an alkyl, as defined above.

[0122] The term "heteroarylalkyl" denotes a heteroaryl group as described above bonded through an alkyl, as defined above.

[0123] The term "heterocyclalkyl," or "heterocycloalkyl," denotes a heterocyclyl group as described above bonded through an alkyl, as defined above.

[0124] The terms "halogen", "halo", or "hal", as used herein alone or as part of another group, denote chlorine, bromine, fluorine, and iodine.

[0125] The term "haloalkyl" denotes a halo group as described above bonded through an alkyl, as defined above. Fluoroalkyl is an exemplary group.

[0126] The term "aminoalkyl" denotes an amino group as defined above bonded through an alkyl, as defined above.

[0127] The phrase "bicyclic fused ring system wherein at least one ring is partially saturated" denotes an 8- to 13-membered fused bicyclic ring group in which at least one of the rings is non-aromatic. The ring group has carbon atoms and optionally 1-4 heteroatoms independently selected from N, O

and S. Illustrative examples include, but are not limited to, indanyl, tetrahydronaphthyl, tetrahydroquinolyl and benzo-cycloheptyl.

[0128] The pHrase “tricyclic fused ring system wherein at least one ring is partially saturated” denotes a 9- to 18-membered fused tricyclic ring group in which at least one of the rings is non-aromatic. The ring group has carbon atoms and optionally 1-7 heteroatoms independently selected from N, O and S. Illustrative examples include, but are not limited to, fluorene, 10,11-dihydro-5H-dibenzo[a,d]cycloheptene and 2,2a,7,7a-tetrahydro-1H-cyclobuta[a]indene.

[0129] The term “pharmaceutically acceptable salts” refers to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as, but not limited to, hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as, but not limited to, acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pantoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, and the like.

[0130] The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two. Organic solvents include, but are not limited to, nonaqueous media like ethers, ethyl acetate, ethanol, isopropanol, or acetonitrile. Lists of suitable salts are found in *Remington's Pharmaceutical Sciences*, 18th ed., Mack Publishing Company, Easton, Pa., 1990, p. 1445, the disclosure of which is hereby incorporated by reference.

[0131] The pHrase “pharmaceutically acceptable” denotes those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication commensurate with a reasonable benefit/risk ratio.

[0132] “Substituted” is intended to indicate that one or more hydrogens on the atom indicated in the expression using “substituted” is replaced with a selection from the indicated group(s), provided that the indicated atom's normal valency is not exceeded, and that the substitution results in a stable compound. When a substituent is keto (i.e., =O) group, then 2 hydrogens on the atom are replaced.

[0133] Unless moieties of a compound of the present invention are defined as being unsubstituted, the moieties of the compound may be substituted. In addition to any substituents provided above, the moieties of the compounds of the present invention may be optionally substituted with one or more groups independently selected from, but not limited to:

- [0134] C₁-C₄ alkyl;
- [0135] C₂-C₄ alkenyl;
- [0136] C₂-C₄ alkynyl;
- [0137] CF₃;
- [0138] halo;
- [0139] OH;
- [0140] O—(C₁-C₄ alkyl);
- [0141] OCH₂F;
- [0142] OCHF₂;
- [0143] OCF₃;
- [0144] COCF₃;
- [0145] OC(O)—(C₁-C₄ alkyl);
- [0146] OC(O)NH—(C₁-C₄ alkyl);
- [0147] OC(O)N(C₁-C₄ alkyl)₂;
- [0148] OC(S)NH—(C₁-C₄ alkyl);
- [0149] OC(S)N(C₁-C₄ alkyl)₂;
- [0150] ONO₂;
- [0151] SH;
- [0152] S—(C₁-C₄ alkyl);
- [0153] S(O)—(C₁-C₄ alkyl);
- [0154] S(O)₂—(C₁-C₄ alkyl);
- [0155] SC(O)—(C₁-C₄ alkyl);
- [0156] SC(O)O—(C₁-C₄ alkyl);
- [0157] NH₂;
- [0158] N(H)—(C₁-C₄ alkyl);
- [0159] N(C₁-C₄ alkyl)₂;
- [0160] N(H)C(O)—(C₁-C₄ alkyl);
- [0161] N(CH₃)C(O)—(C₁-C₄ alkyl);
- [0162] N(H)C(O)—CF₃;
- [0163] N(CH₃)C(O)—CF₃;
- [0164] N(H)C(S)—(C₁-C₄ alkyl);
- [0165] N(CH₃)C(S)—(C₁-C₄ alkyl);
- [0166] N(H)S(O)₂—(C₁-C₄ alkyl);
- [0167] N(H)C(O)NH₂;
- [0168] N(H)C(O)NH—(C₁-C₄ alkyl);
- [0169] N(CH₃)C(O)NH—(C₁-C₄ alkyl);
- [0170] N(H)C(O)N(C₁-C₄ alkyl)₂;
- [0171] N(CH₃)C(O)N(C₁-C₄ alkyl)₂;
- [0172] N(H)S(O)₂NH₂;
- [0173] N(H)S(O)₂NH—(C₁-C₄ alkyl);
- [0174] N(CH₃)S(O)₂NH—(C₁-C₄ alkyl);
- [0175] N(H)S(O)₂N(C₁-C₄ alkyl)₂;
- [0176] N(CH₃)S(O)₂N(C₁-C₄ alkyl)₂;
- [0177] N(H)C(O)O—(C₁-C₄ alkyl);
- [0178] N(CH₃)C(O)O—(C₁-C₄ alkyl);
- [0179] N(H)S(O)₂O—(C₁-C₄ alkyl);
- [0180] N(CH₃)S(O)₂O—(C₁-C₄ alkyl);
- [0181] N(CH₃)C(S)NH—(C₁-C₄ alkyl);
- [0182] N(CH₃)C(S)N(C₁-C₄ alkyl)₂;
- [0183] N(CH₃)C(S)O—(C₁-C₄ alkyl);
- [0184] N(H)C(S)NH₂;
- [0185] NO₂;
- [0186] CO₂H;
- [0187] CO₂—(C₁-C₄ alkyl);
- [0188] C(O)N(H)OH;
- [0189] C(O)N(CH₃)OH;
- [0190] C(O)N(CH₃)OH;
- [0191] C(O)N(CH₃)O—(C₁-C₄ alkyl);
- [0192] C(O)N(H)—(C₁-C₄ alkyl);
- [0193] C(O)N(C₁-C₄ alkyl)₂;
- [0194] C(S)N(H)—(C₁-C₄ alkyl);
- [0195] C(S)N(C₁-C₄ alkyl)₂;
- [0196] C(NH)N(H)—(C₁-C₄ alkyl);
- [0197] C(NH)N(C₁-C₄ alkyl)₂;

[0198] $C(NCH_3)N(H)-(C_1-C_4 \text{ alkyl})$;
 [0199] $C(NCH_3)N(C_1-C_4 \text{ alkyl})_2$;
 [0200] $C(O)-(C_1-C_4 \text{ alkyl})$;
 [0201] $C(NH)-(C_1-C_4 \text{ alkyl})$;
 [0202] $C(NCH_3)-(C_1-C_4 \text{ alkyl})$;
 [0203] $C(NO_2)-(C_1-C_4 \text{ alkyl})$;
 [0204] $C(NOCH_3)-(C_1-C_4 \text{ alkyl})$;
 [0205] CN ;
 [0206] CHO ;
 [0207] CH_2OH ;
 [0208] $CH_2O-(C_1-C_4 \text{ alkyl})$;
 [0209] CH_2NH_2 ;
 [0210] $CH_2N(H)-(C_1-C_4 \text{ alkyl})$;
 [0211] $CH_2N(C_1-C_4 \text{ alkyl})_2$;
 [0212] aryl;
 [0213] heteroaryl;
 [0214] cycloalkyl; and
 [0215] heterocyclyl.
 [0216] The term “cleave” or “cleaving” means splitting a complex molecule into at least two separate molecules. “Cleavage products” are the separate molecules which result from cleaving.
 [0217] The term “metabolite” refers to a composition which results from a metabolic process. Examples of the results of metabolism on the compounds of the present invention include addition of $-OH$, hydrolysis, and cleavage.
 [0218] The term “polymorphs” refers to the various crystalline structures of the compounds of the present invention. This may include, but is not limited to, crystal morphologies (and amorphous materials), all crystal lattice forms, and all salts. Salts of the present invention can be crystalline and may exist as more than one polymorph. Each polymorph forms another aspect of the invention. Hydrates as well as anhydrous forms of the salt are also encompassed by the invention.
 [0219] “Teoc” is 2-(trimethylsilyl)ethoxycarbonyl
 [0220] “Et” is ethyl ($-CH_2CH_3$) or ethylene ($-CH_2CH_2-$).
 [0221] “Me” is methyl ($-CH_3$) or methylene ($-CH_2-$).
 [0222] “Boc” is tert-butyloxycarbonyl.
 [0223] “PHCH₂” is benzyl.
 [0224] The term “pharmaceutically-acceptable tricyclic moiety” is meant to include, but is not limited to, benzocycloheptapyridyl, benzodiazepinyl, and benzozapinyl
 [0225] In another embodiment of the present invention, the DPP-IV inhibiting compounds are used in the manufacture of a medicament for the treatment of a disease mediated by an DPP-IV enzyme.
 [0226] In another aspect, the DPP-IV inhibiting compounds of the present invention are used in combination with another disease modifying drug. Examples of other disease modifying drugs include, but are not limited to: (a) other dipeptidyl peptidase IV (DPP-IV) inhibitors such as Vildagliptin (Novartis), Sitagliptin (Merck&Co.), Saxagliptin (BMS); (b) insulin sensitizers including (i) PPAR γ agonists such as the glitazones (e.g. troglitazone, pioglitazone, edagliptazone, rosiglitazone, and the like) and other PPAR ligands, including PPAR α/γ dual agonists such as muraglitazar (BMS) and tesaglitazar (AstraZeneca), and PPAR α agonists such as fenofibric acid derivatives (gemfibrozil, clofibrate, fenofibrate and bezafibrate), (ii) biguanides such as metformin and phenformin, and (iii) protein tyrosine phosphatase-1B (PTP-1B) inhibitors; (c) insulin or insulin mimetics; (d) incretin and incretin mimetics such as (i) Exenatide available from Amylin Pharmaceuticals, (i) amylin and amylin mimetics such as pramlintide acetate, available as Symlin®, (iii) GLP-1, GLP-1 mimetics, and GLP-1 receptor agonists, (iv) GIP, GIP mimetics and GIP receptor agonists; (e)

sulfonylureas and other insulin secretagogues, such as tolbutamide, glyburide, glipizide, glimepiride, meglitinides, and repaglinide; (f) α -glucosidase inhibitors (such as acarbose and miglitol); (g) glucagon receptor antagonists; (h) PACAP, PACAP mimetics, and PACAP receptor agonists; (i) cholesterol lowering agents such as (i) HMG-CoA reductase inhibitors (lovastatin, simvastatin, pravastatin, cerivastatin, fluvastatin, atorvastatin, itavastatin, and rosuvastatin, and other statins), (ii) sequestrants such as cholestyramine, colestipol and dialkylaminoalkyl derivatives of a cross-linked dextran, (iii) nicotinic alcohol, nicotinic acid or a salt thereof, (iv) PPAR α agonists such as fenofibric acid derivatives (gemfibrozil, clofibrate, fenofibrate and bezafibrate), (v) PPAR α/γ dual agonists such as muraglitazar (BMS) and tesaglitazar (AstraZeneca), (vi) inhibitors of cholesterol absorption, such as beta-sitosterol and ezetimibe, (vii) acyl CoA:cholesterol acyltransferase inhibitors such as avasimibe, and (viii) antioxidants such as probucol; (J) PPAR δ agonists such as GW-501516 from GSK; (k) anti-obesity compounds such as fenfluramine, dexfenfluramine, phentemine, sibutramine, orlistat, neuropeptide Y1 or Y5 antagonists, MTP inhibitors, squalene synthase inhibitor, lipoxigenase inhibitor, ACAT inhibitor, Neuropeptide Cannabinoid CB-1 receptor antagonists, CB-1 receptor inverse agonists and antagonists, fatty acid oxidation inhibitors, appetite suppressants (l) adrenergic receptor agonists, melanocortin receptor agonists, in particular—melanocortin-4 receptor agonists, ghrelin antagonists, and melanin-concentrating hormone (MCH) receptor antagonists; (m) ileal bile acid transporter inhibitors; (n) agents intended for use in inflammatory conditions such as aspirin, non steroidal anti-inflammatory drugs, glucocorticoids, azalfidine, and selective cyclooxygenase-2 inhibitors; (o) antihypertensive agents such as ACE inhibitors (enalapril, lisinopril, captopril, quinapril, fosinopril, ramipril, spirapril, tandolapril), angiotensin-II (AT-1) receptor blockers (losartan, candesartan, irbesartan, valsartan, telmisartan, eprosartan), beta blockers and calcium channel blockers; and (p) glucokinase activators (GKAs); (q) agents which can be used for the prevention, delay of progression or treatment of neurodegenerative disorders, cognitive disorders or a drug for improving memory such as anti-inflammatory drugs, antioxidants, neuroprotective agents, glutamate receptor antagonists, acetylcholine esterase inhibitors, butyrylcholinesterase inhibitors, MAO inhibitors, dopamine agonists or antagonists, inhibitors of gamma and beta secretases, inhibitors of amyloid aggregation, amyloid beta peptide, antibodies to amyloid beta peptide, inhibitors of acetylcholinesterase, glucokinase activators, agents directed at modulating GABA, NMDA, cannabinoid, AMPA, kainate, phosphodiesterase (PDE), PKA, PKC, CREB or nootropic systems; (r) leukocyte growth promoters intended for the treatment and prevention of reduced bone marrow production, infectious diseases, hormone dependent disorders, inflammatory diseases, HIV, allergies, leukocytopenia, and rheumatism; (s) SGLT2 inhibitor; (t) glycogen phosphorylase inhibitor; (u) αP_2 inhibitors; (v) aminopeptidase N inhibitor (w) vasopeptidase inhibitors like neprilysin inhibitors and/or ACE inhibitors or dual NEP/ACE inhibitor; (x) growth hormone secretagogue for enhancing growth hormone levels and for treating growth retardation/dwarfism or metabolic disorders or where the disorder is an injury, or a wound in need of healing, or a mammalian patient recovering from surgery; (y) 5-HT 3 or 5-HT 4 receptor modulators (tegaserod, cisapride, nor-cisapride, renzapride, zacopride, mosapride, prucalopride, buspirone, nor-cisapride, cilansetron, ramosetron, azasetron, ondansetron, etc.); (Za) aldose reductase inhibitors; (Zb) sorbitol dehydro-

genase inhibitors; (Zc) AGE inhibitors; (Zd) erythropoietin agonist such as EPO, EPO mimetics, and EPO receptor agonists.

[0227] In a further aspect, the DPP-IV inhibiting compounds of the present invention are used in the treatment diseases or symptoms mediated by an DPP-IV enzyme. Examples of diseases or symptoms mediated by a DPP-IV enzyme include, but are not limited to, Type II (Type-2) Diabetes and Related Disorders, such as hyperglycemia, low glucose tolerance, insulin resistance, obesity, lipid disorders, dyslipidemia, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, low HDL levels, high LDL levels, atherosclerosis and its 30 sequelae, vascular restenosis, irritable bowel syndrome, inflammatory bowel disease, including Crohn's disease and ulcerative colitis, other inflammatory conditions, pancreatitis, abdominal obesity, neurodegenerative disease, retinopathy, nephropathy, neuropathy, cataracts, glaucoma, glomerulosclerosis, foot ulcerations and ulcerative colitis, altered gastrointestinal motility, Syndrome X, ovarian hyperandrogenism, polycystic ovarian syndrome, premenstrual syndrome, other disorders where insulin resistance is a component. In Syndrome X, also known as Metabolic Syndrome, obesity is thought to promote insulin resistance, diabetes, dyslipidemia, hypertension, and increased cardiovascular risk, growth hormone deficiency, neutropenia, neuronal disorders, tumor invasion and metastasis, benign prostatic hypertrophy, gingivitis, osteoporosis, frailty of aging, intestinal injury, benign prostatic hypertrophy (BPH), and sperm motility/male contraception.

[0228] In a further aspect, the DPP-IV inhibiting compounds of the present invention are useful for the prevention, delay of progression or the treatment of an early cardiac or early cardiovascular diseases or damages, renal diseases or damages, heart Failure, or heart Failure associated diseases like (i) cardiovascular diseases or damages e.g. cardiac hypertrophy, cardiac remodelling after myocardial infarction, pulmonary congestion and cardiac fibrosis in dilated or in hypertrophic cardiomyopathy, cardiomyopathy such as dilated cardiomyopathy or hypertrophic cardiomyopathy, mesangial hypertrophy, or diabetic cardiomyopathy, left or right ventricular hypertrophy, arrhythmia, cardiac dysrhythmia, syncope, angina pectoris, cardiac bypass reocclusion, intermittent claudication, diastolic and/or systolic dysfunction, diabetic myopathy, stroke prevention in congestive heart failure, hypertrophic medial thickening in arteries and/or large vessels, mesenteric vasculature hypertrophy or arteriosclerosis, preferably arteriosclerosis in mammalian patients with hypertension of diabetes; (ii) renal diseases or damages like renal hyperfiltration such as after portal renal ablation, proteinuria in chronic renal disease, renal arteriopathy as a consequence of hypertension, nephrosclerosis, hypertensive nephrosclerosis or mesangial hypertrophy; (iii) Heart Failure to be treated is secondary to idiopathic dilated cardiomyopathy and/or coronary ischemic disease;

[0229] In another aspect, the DPP-IV inhibiting compounds of the present invention are used for the prevention, the delay of the onset, the delay of progression or the treatment of neurodegenerative disorders, cognitive disorders and for improving memory (both short term and long term) and learning ability wherein the (i) neurodegenerative disorder is dementia, senile dementia, schizophrenia, mild cognitive impairment, Alzheimer related dementia, Huntington's chorea, tardive dyskinesia, hyperkinesias, mania, Morbus Parkinson, Steel-Richard syndrome, Down's syndrome, myasthenia gravis, nerve and brain trauma, vascular amyloidosis, cerebral haemorrhage with amyloidosis, brain inflammation, Friedrich ataxia, acute confusion disorders, acute

confusion disorders with apoptotic necrocytosis, amyotrophic lateral sclerosis, glaucoma, and Alzheimer's disease; (ii) cognitive disorders like cognitive deficits associated with schizophrenia, age-induced memory impairment, cognitive deficits associated with psychosis, cognitive impairment associated with diabetes, cognitive deficits associated with post-stroke, memory defects associated hypoxia, cognitive and attention deficits associated with senile dementia, attention deficits disorders, memory problems associated with mild cognitive impairment, impaired cognitive function associated with vascular dementia, cognitive problems associated with brain tumors, Pick's disease, cognitive deficits due to autism, cognitive deficits post electroconvulsive therapy, cognitive deficits associated with traumatic brain injury, amnesic disorders, deliriums, vitamin deficiency, dementias, impaired cognitive function associated with Parkinson's disease, attention-deficit disorders; (iii) prevention of memory impairment as a result of Alzheimer disease, Creutzfeld-Jakob disease, Pick disease, Huntington disease, AIDS, brain injury, brain aneurysm, epilepsy, stroke, toxicant exposure, mental retardation in children, Huntington's disease; (iv) to improve learning speed and potential in educational and rehabilitation contexts.

[0230] In another aspect, the DPP-IV inhibiting compounds of the present invention are used for stimulating an immune response in a subject having or at risk of having cancer wherein the cancer is selected from the group consisting of basal cell carcinomas including cancers of the binary tract, bladder, urinary system, bone, brain, breast, cervical, endometrial, ovarian, uterine, choriocarcinoma, central nervous system, colon and rectal cancers, connective tissue cancer, cancer of the digestive system, esophageal, gastric, stomach, larynx, liver, pancreatic, colorectal, renal cancers; cancers of the urinary system; cancers of eye, head and neck, oral cavity, skin, prostate; cancers of biliary tract, testicular, thyroid; intra-epithelial neoplasm, leukemia, acute myeloid leukemia, acute lymphoid leukemia, chronic myeloid leukemia, chronic lymphoid leukemia; and other cancers of the respiratory system, lung, small cell lung, non-small cell lung; lymphoma, Hodgkin's lymphoma, Non-Hodgkin's lymphoma; melanoma, myeloma, neuroblastoma, retinoblastoma, fibrosarcoma (bone or connective tissue sarcoma), rhabdomyosarcoma; and other cancers including neoplastic conditions, adipose cell tumors, adipose cell carcinomas, such as liposarcoma;

[0231] In a further aspect, the DPP-IV inhibiting compounds of the present invention are useful for the treatment or prophylaxis of chronic inflammatory diseases such as autoimmune disorders like rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, psoriasis, allergies or asthma.

[0232] In another aspect, the DPP-IV inhibiting compounds of the present invention may be useful in the treatment of pain, neuropathic pain, rheumatoid pain, osteoarthritis pain, anesthesia adjunct in mammalian patients undergoing surgery, chronic pain in advanced cancer, treatment of refractory diarrhea, biliary pain caused by gallstones.

[0233] In a further aspect, the DPP-IV inhibiting compounds of the present invention are useful for the treatment of mammalian patients undergoing islet/pancreas transplantation, for the prevention or the delay of transplant rejection, or allograft rejection in transplantation, for improving pancreatic function by increasing the number and size of pancreatic beta-cells in the treatment of Type 1 diabetes patients, and for improving pancreatic function by increasing the number and size of pancreatic beta-cells in general.

[0234] Furthermore, the DPP-IV inhibiting compounds of the present invention are useful for the treatment of mammalian patients with acne, skin disorders (e.g. pigmentation disorders or psoriasis), scleroderma, mycoses; anxiety, anxiety neurosis, major depression disorder, drug abuse, alcohol addiction, insomnia, chronic fatigue, sleep apnea; anorexia nervosa; epilepsy; migraine; encephalomyelitis; osteoarthritis, osteoporosis, calcitonin-induced osteoporosis; male and female sexual dysfunction, infertility; Type 1 diabetes; immunosuppression, HIV infection; hematopoiesis, anemia; and for weight reduction.

[0235] In a further aspect, the DPP-IV inhibiting compounds of the present invention are useful for the prevention, delay of progression or treatment of (i) bacterial infections from *Escherichia coli*, *Staphylococcus*, *Streptococcus*, *Pseudomonas*, *Clostridium difficile* infection, *Legionella*, *Pneumococcus*, *Haemophilus*, *Klebsiella*, *Enterobacter*, *Citrobacter*, *Neisseria*, *Shigella*, *Salmonella*, *Listeria*, *Pasteurella*, *Streptobacillus*, *Spirillum*, *Treponema*, *Actinomyces*, *Borrelia*, *Corynebacterium*, *Nocardia*, *Gardnerella*, *Campylobacter*, *Spirochaeta*, *Proteus*, *Bacteriodes*, *Helicobacter pylori*, and anthrax infection; (ii) mycobacterial infection from tuberculosis and leprosy; (iii) viral infection from HIV, Herpes simplex virus 1, Herpes simplex virus 2, Cytomegalovirus, hepatitis A virus, hepatitis B virus, hepatitis C virus, human papilloma virus, Epstein Barr virus, rotavi-

rus, adenovirus, influenza A virus, respiratory syncytial virus, varicella-zoster virus, small pox, monkey pox and SARS; (iv) fungal infection from candidiasis, ringworm, histoplasmosis, blastomycosis, paracoccidioidomycosis, cryptococcosis, aspergillosis, chromomycosis, mycetoma infections, pseudallescheriasis, *Tinea versicolor* infection; (v) parasite infection from amebiasis, *Trypanosoma cruzi*, Fascioliasis, Leishmaniasis, *Plasmodium*, Onchocerciasis, Paragonimiasis, *Trypanosoma brucei*, *Pneumocystis*, *Trichomonas vaginalis*, *Taenia*, *Hymenolepis*, *Echinococcus*, Schistosomiasis, neurocysticercosis, *Necator americanus*, and *Trichuris trichuria*.

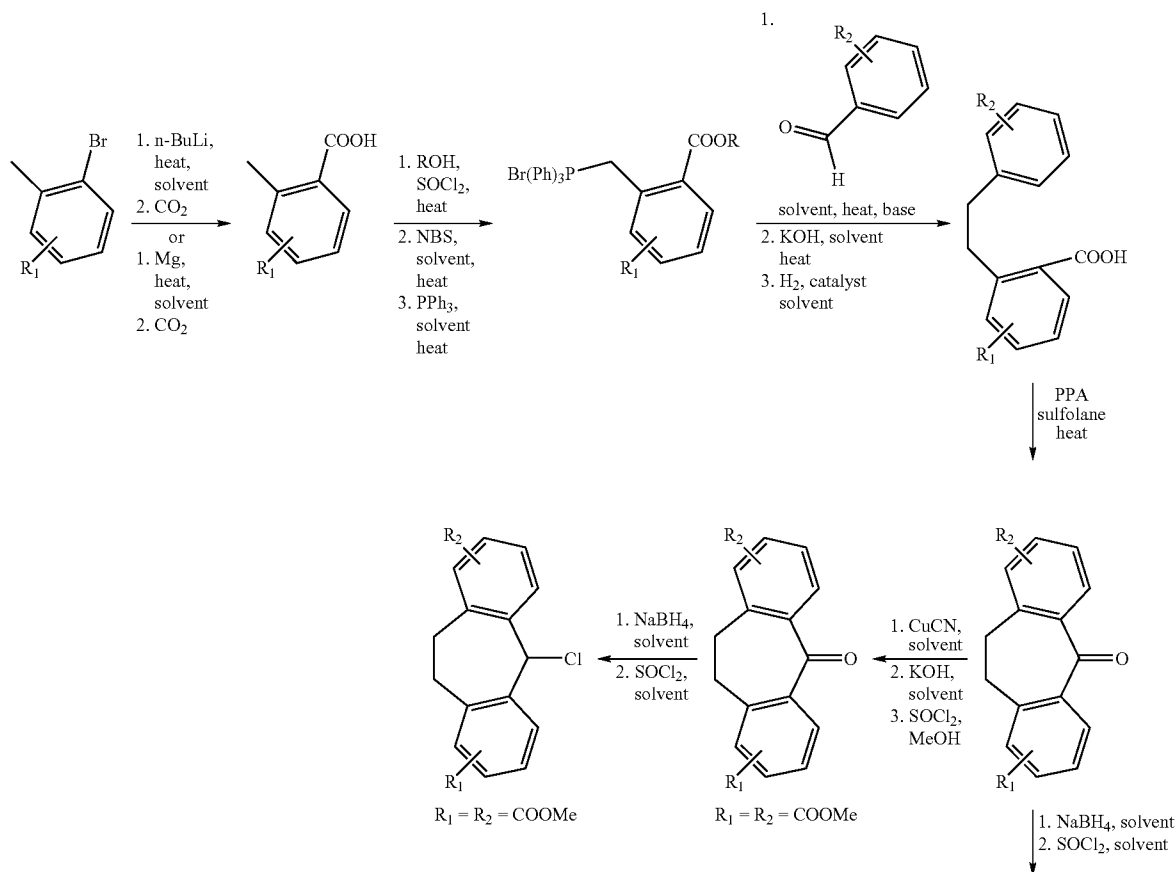
[0236] The compounds from this invention are suitable for oral, sublingual, rectal, topical, parenteral (including subcutaneous, intramuscular, and intravenous), ocular (ophthalmic), pulmonary (aerosol inhalation), or nasal administration, although the most suitable route in any given case will depend on the nature and severity of the conditions being treated and on the nature of the active ingredient. The compounds from this invention are conveniently presented in unit dosage form and prepared by any of the methods well-known in the art of pharmacy.

[0237] The DPP-IV inhibiting compounds of the present invention are synthesized by the general method shown in Schemes 1-14.

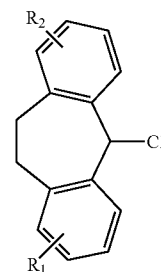
[0238] Generic Schemes

[0239] General synthetic schemes for the preparation of tricyclic building blocks of this invention:

SCHEME 1



-continued

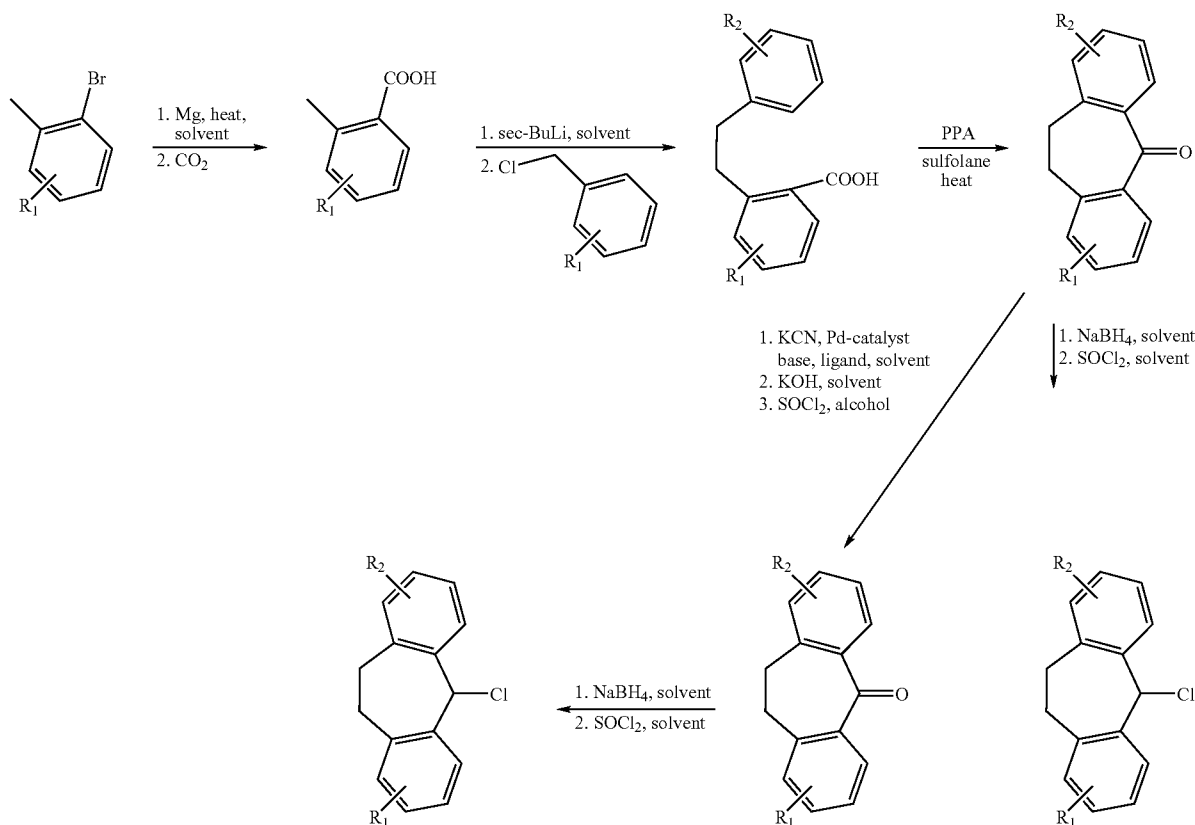


[0240] Commercially available bromotoluene derivatives were treated with *n*-butyllithium and heated, followed by treatment with dry-ice in an appropriate solvent to afford the desired compound. Alternatively, the acid can be prepared by Grignard reaction followed by treatment with dry-ice in an appropriate solvent. Esterification of the compound followed by NBS bromination and subsequent conversion to the phosphonium salt in a suitable solvent and heating affords the desired compound. Wittig reaction of the phosphonium salt with a suitable aldehyde in an appropriate solvent and heating, followed by saponification of the ester moiety and subsequent catalytic hydrogenation affords the desired compound. Cyclisation of the compound with polyphosphoric acid in sulfolane and heating affords the desired compound after purification. For $R_1=COOMe$ the tricyclic product

from the polyphosphoric acid step was treated with thionylchloride in an alcohol. Reduction of the ketone with a metal hydride in an appropriate solvent yields the compound after purification. Treatment of the alcohol with thionylchloride in a suitable solvent affords the final desired compound. In order to obtain the compounds with $R_1=R_2=COOMe$, the tricyclic product from the polyphosphoric acid step with $R_1=COOH$ and $R_2=Br$ was treated with $CuCN$ in a suitable solvent, followed by saponification of the nitrile to the acid. Ester formation using thionylchloride in an alcohol and reduction of the ketone with a metal hydride in an appropriate solvent yields the compound after purification. Treatment of the alcohol with thionylchloride in a suitable solvent affords the final desired compound.

[0241] Alternative synthetic scheme for the preparation of tricyclic building blocks of this invention:

SCHEME 2

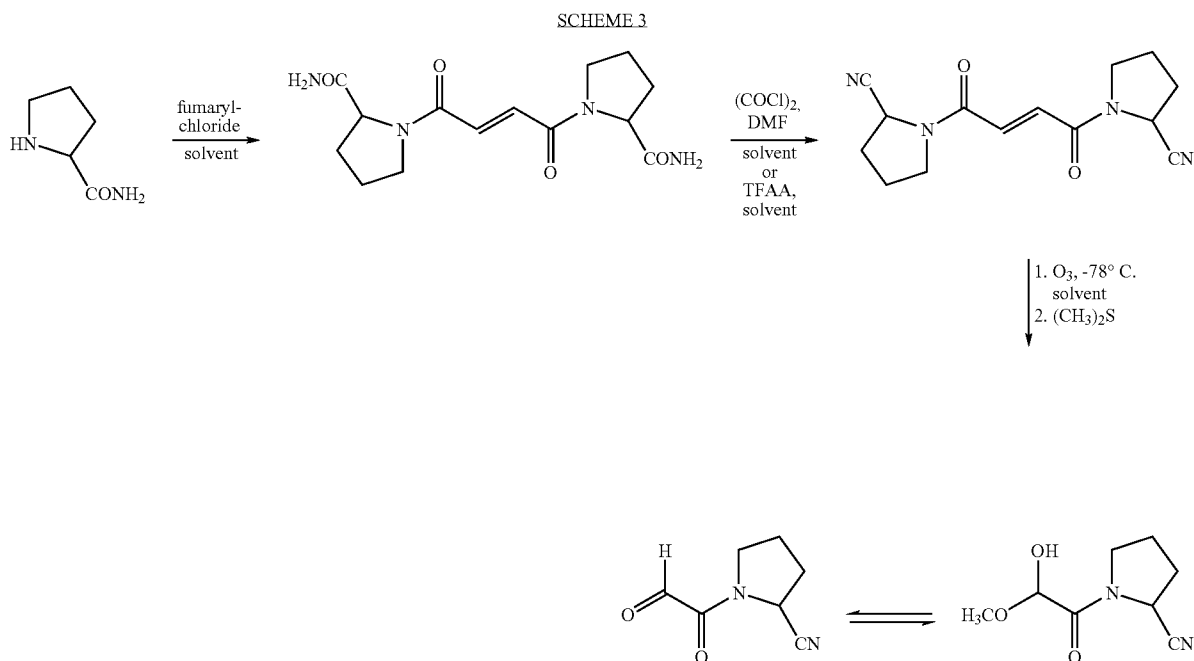


[0242] Commercially available bromotoluene derivatives are treated with Magnesium in a Grignard reaction followed by treatment with dry-ice in an appropriate solvent to yield the desired acid. This acid is then treated with sec-butyl-lithium in an appropriate solvent at lower temperature. The anion is added at lower temperature to a solution of a commercially available benzylchloride in an appropriate solvent to afford the desired compound. Cyclisation of the compound with polyphosphoric acid in sulfolane and heating affords the desired compound. To obtain the compounds with $R_1=R_2=COOMe$, the tricyclic product from the polyphosphoric acid step with $R_1=R_2=Cl$ was treated with KCN, a Pd-catalyst, a suitable ligand and a suitable base in an appropriate solvent to afford the dicyano compound, which was converted to the diacid by treatment with base in a suitable solvent. Ester formation using thionylchloride in an alcohol and reduction of the ketone with a metal hydride in an appropriate solvent yields the compound after purification. Treatment of the alcohol with thionylchloride in a suitable solvent affords the final desired compound.

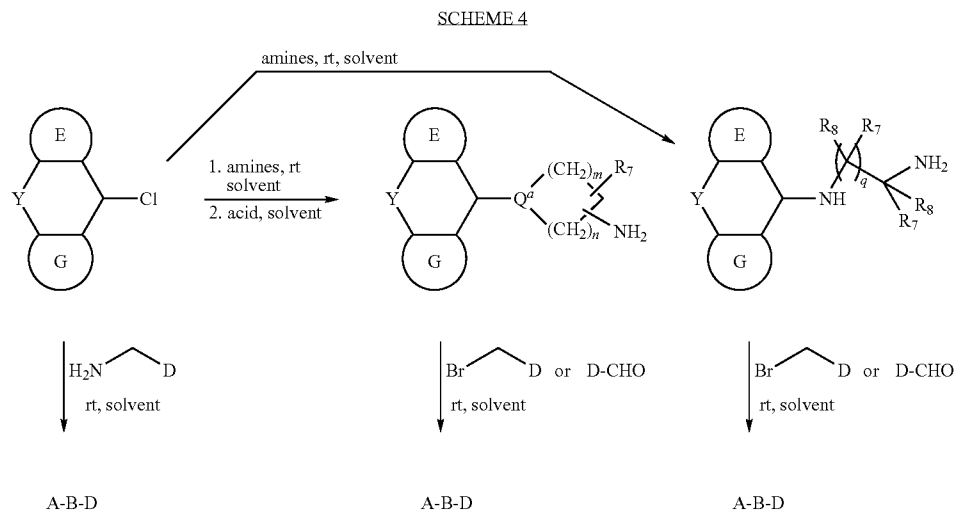
[0243] General synthetic scheme for the preparation of aldehyde building blocks of this invention:

[0244] Commercially available prolinamide is treated with fumarylchloride in an appropriate solvent to afford the desired compound. This compound is then treated with oxalylchloride in dimethylformamide to afford the desired compound after purification. Alternatively, the coupling product of prolinamide with fumarylchloride can be treated with trifluoroacetic acid anhydride in a suitable solvent to afford the desired compound. Ozonolysis of this compound at -78°C . in a suitable solvent, followed by reductive workup affords the desired final compound as a mixture of the aldehyde and its methyl hemiacetal.

[0245] Treatment of 2-Aza-bicyclo[3.1.0]hexane-3-carboxylic acid amide, prepared according to WO 01/68603, in the same manner as described above yields the desired final compound containing a cyclopropyl moiety at the 4,5-position of the pyrrolidine moiety.

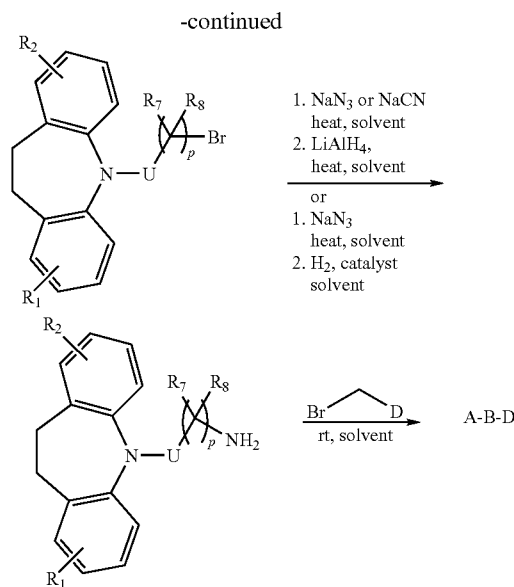
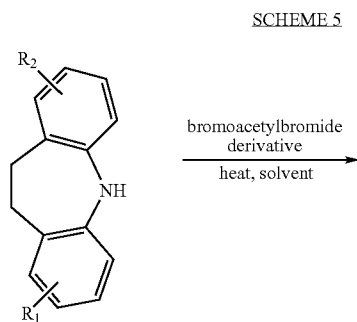


[0246] General synthetic scheme for the preparation of tricyclic compounds of this invention with $R^3=H$:



[0247] The reaction of substituted or unsubstituted tricyclic chlorides with an amino derivative in a suitable solvent as described above affords the desired final product after purification. Substituted or unsubstituted tricyclic chlorides are treated in an appropriate solvent with an excess of suitable amines to afford the desired product after purification. In case the reaction product contains additional amino protecting groups like Boc, they are cleaved by acid treatment to afford the desired compound. Using these amines for a nucleophilic displacement reaction in a suitable solvent with a suitable bromo derivative yields the final desired product after purification. Alternatively, the amines are treated with a suitable aldehyde (D-CHO) via reductive amination to afford the final compound after purification.

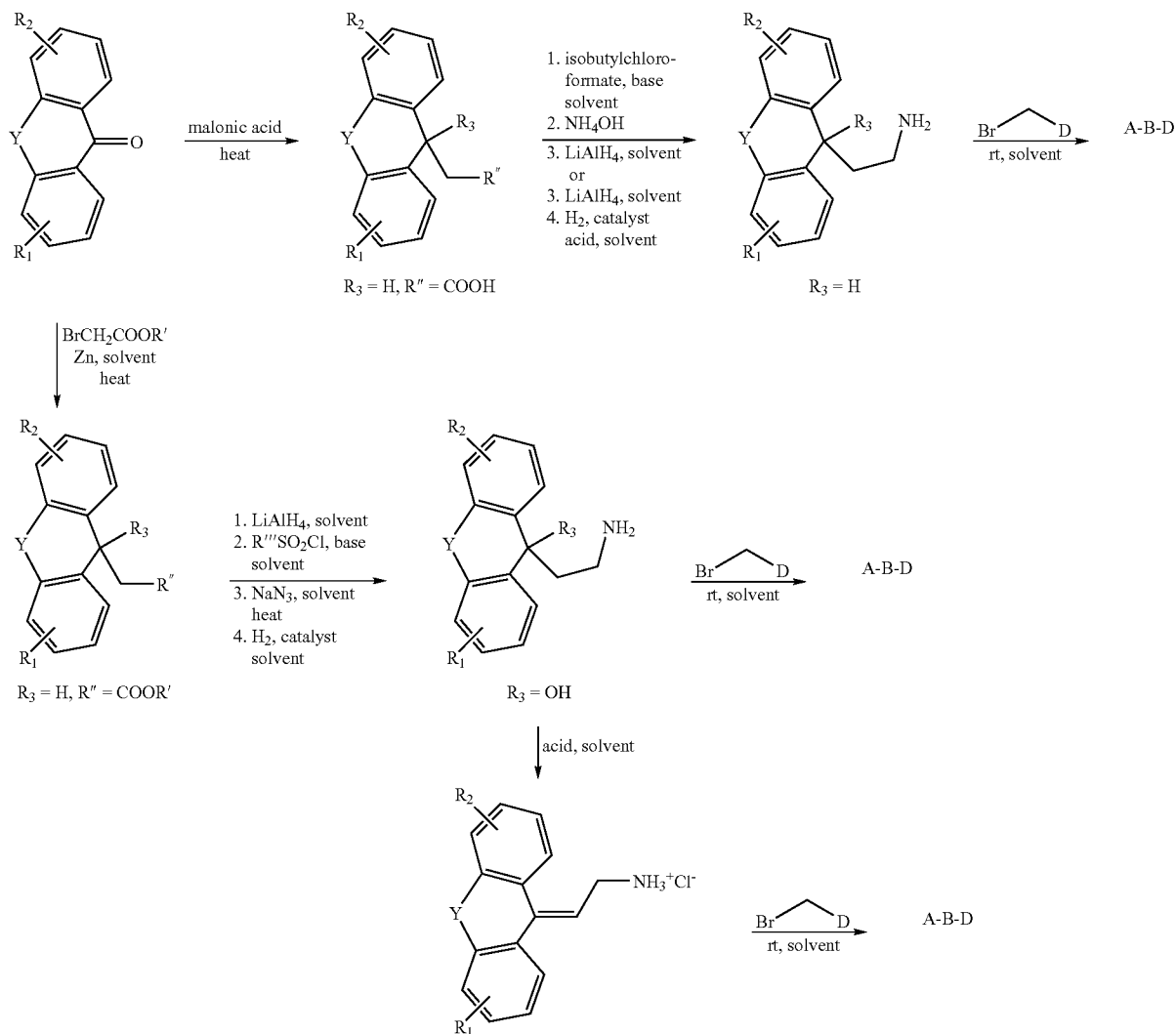
[0248] General synthetic scheme for the preparation of tricyclic compounds of this invention with $Z=N$:



[0249] Substituted or unsubstituted tricycles containing a nitrogen at the doubly benzylic position are treated with bromoacetyl bromide and heated to afford the desired compounds. Treating these compounds with sodium azide or sodium cyanide in a suitable solvent and heating affords the desired azido or cyano compounds after purification. Catalytic hydrogenation or reduction with Lithium aluminium hydride in a suitable solvent affords the desired amine compounds. Using these amines for a nucleophilic displacement reaction in a suitable solvent with a suitable bromo derivative yields the final desired product after purification.

[0250] General synthetic scheme for the preparation of tricyclic compounds of this invention having H, OH or no substituent at R^3

SCHEME 6



[0251] Substituted or unsubstituted tricyclic ketones with $Y=C(R_4)=C(R_5)$ are treated with malonic acid at elevated temperatures to afford the desired product after purification. These compounds are converted to the corresponding amides by treatment with isobutylchloroformate and ammonia. The amides are then converted to the desired amine products with $Y=C(R_4)=C(R_5)$ by reduction with lithium aluminium hydride or to the desired amine products with $Y=C(R_4R_5)C(R_4R_5)$ by reduction with lithium aluminium hydride followed by catalytic hydrogenation with a suitable catalyst. Using these amines for a nucleophilic displacement reaction in a suitable solvent with a suitable bromo derivative described above yields the final desired product after purification.

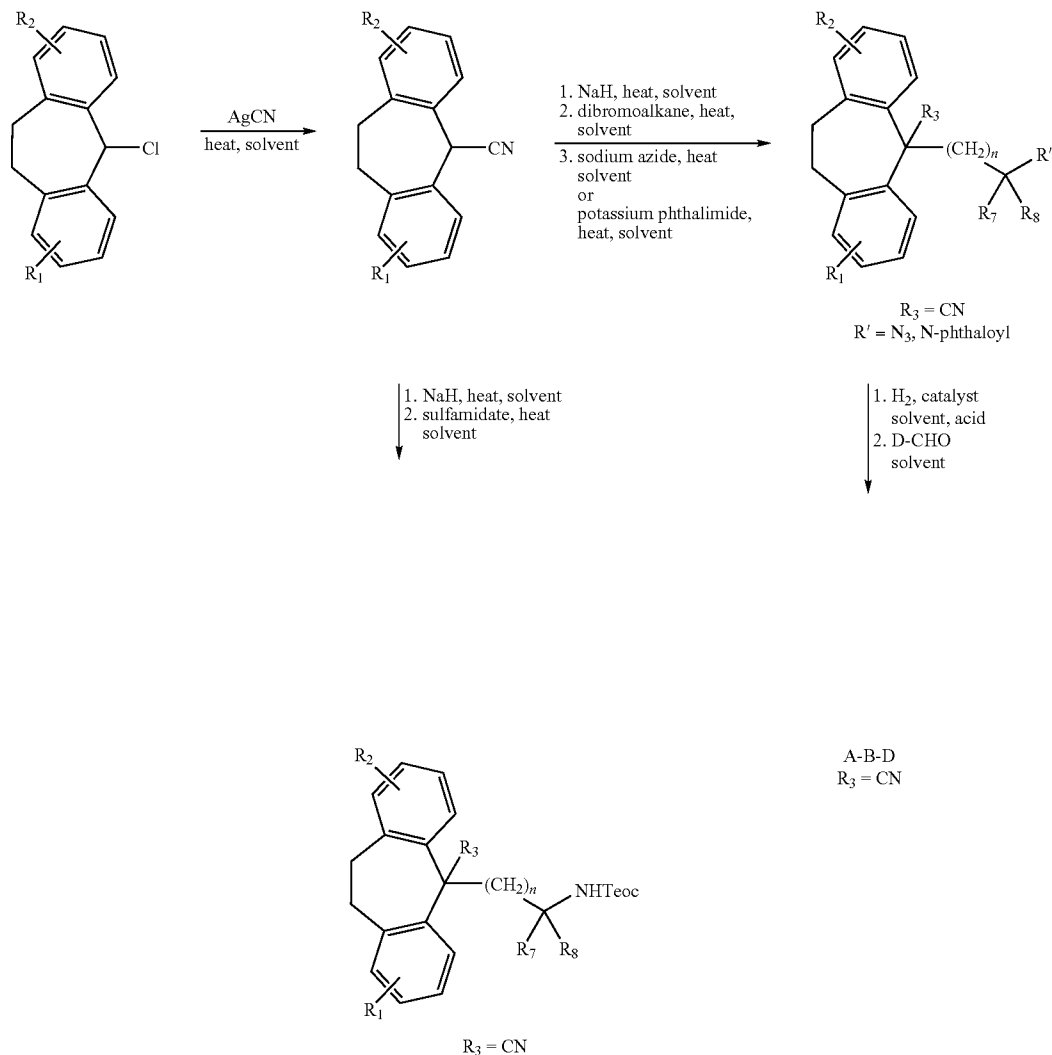
[0252] Treating tricyclic ketones in a Reformatskij reaction affords the desired product after purification. Reduction with LiAlH_4 in a suitable solvent affords the alcohol products with $\text{R}_2=\text{OH}$ after purification. Activation of one of the hydroxyl

groups with sulfonylchlorides in a suitable solvent followed by treatment with NaN_3 affords the desired compounds after purification. Reduction of the azide reaction products with a catalyst in a suitable solvent affords the desired amine compounds after purification. Using these amines for a nucleophilic displacement reaction in a suitable solvent with a suitable bromo derivative described above yields the final desired products after purification.

[0253] Treating the amines with $R_3\text{—OH}$ with acid in a suitable solvent yields the desired unsaturated amine products. Using these amines for a nucleophilic displacement reaction in a suitable solvent with a suitable bromo derivative described above yields the final desired products after purification.

[0254] General synthetic schemes (7-9) for the preparation of tricyclic compounds of this invention with R^3 =nitrile, amide, tetrazolyl or N-alkyl-tetrazolyl

SCHEME 7

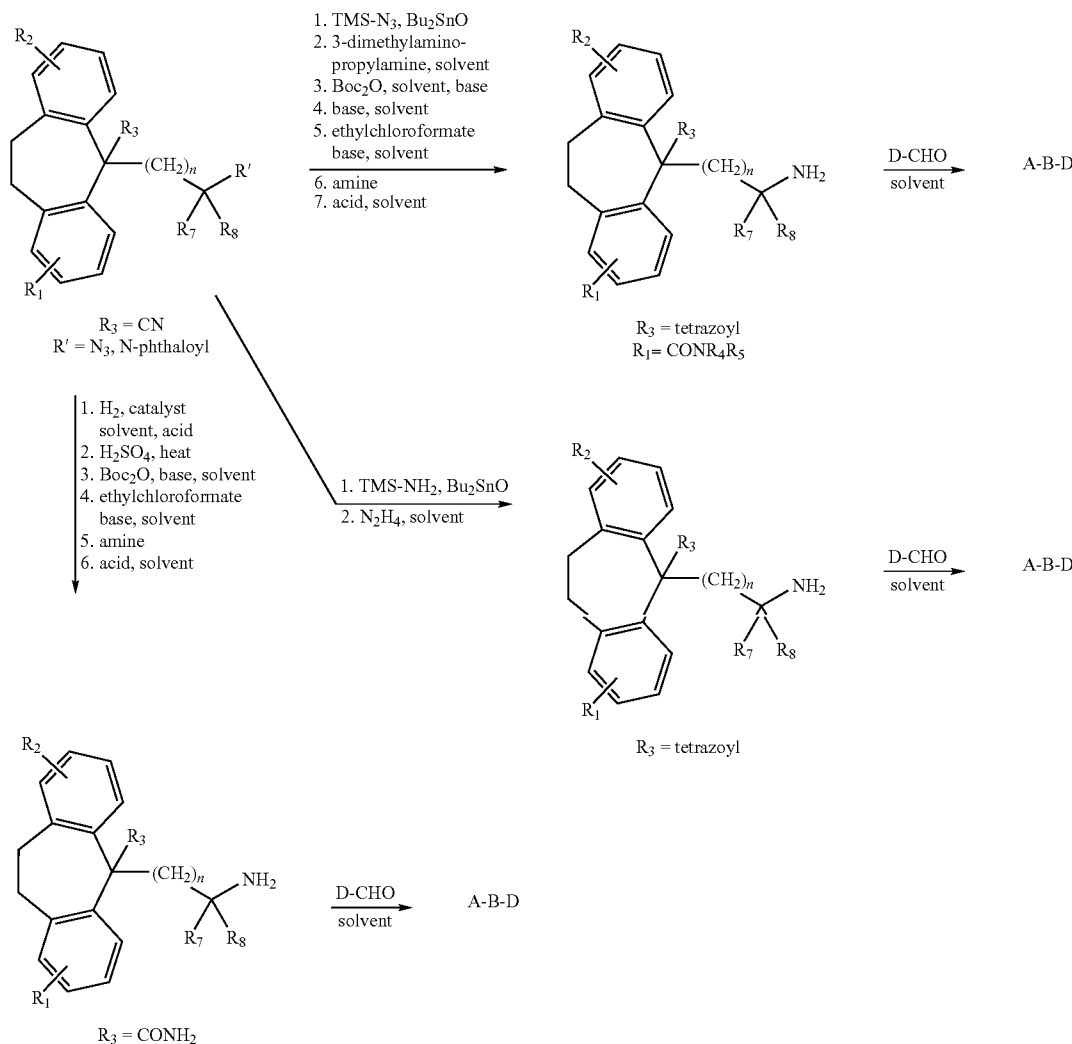


[0255] Substituted or unsubstituted suberylchlorides are treated in a suitable solvent with a slight excess of AgCN and heated to afford the desired product after purification. The nitrile containing compound is then treated with sodium hydride in a suitable solvent and heated. The mixture is then treated at rt with a suitable dibromoalkene and heated to give an intermediate which after treatment with sodium azide or potassium phthalimide in an appropriate solvent and heating affords the desired compound after purification. Treating the mixture after the addition of sodium hydride at rt with a

suitable sulfamidate in an appropriate solvent affords the desired Teoc-protected compound after heating for several hours and subsequent purification.

[0256] Catalytic hydrogenation of compounds with $R^1= N_3$ in a suitable solvent and in the presence of a slight excess of acid affords the free amine compounds. Coupling of these amines with a suitable aldehyde (CHO-D) via reductive amination and subsequent purification affords the final desired compounds with $R^3= CN$.

SCHEME 8

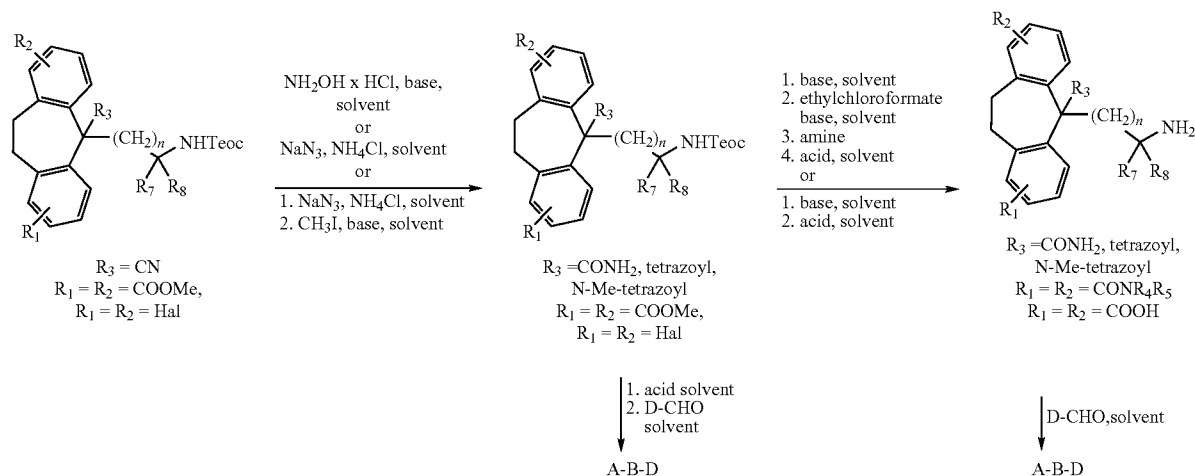


[0257] Catalytic hydrogenation of compounds with $R_3=CN$ and $R'=N_3$ in a suitable solvent and in the presence of a slight excess of acid affords the free amine compounds. Treatment of the hydrogenation products with sulphuric acid affords the desired compounds after purification. In case $R_1=R_2\neq COOH$, the amines are reacted with a suitable aldehyde (D-CHO) in an appropriate solvent to yield the desired final compounds with $R_3=CONH_2$ and $R_1=R_2\neq COOH$, $CONR_4R_5$, $COOMe$. In case $R_1=COOH$, the amines are treated with Boc_2O in a suitable solvent to afford the Boc-protected amines. These compounds are then treated with ethylchloroformate, followed by treatment with an amine to yield the desired compounds after purification. The compounds are then treated with acid, followed by reaction with a suitable aldehyde (D-CHO) in an appropriate solvent to yield the desired final compounds with $R_3=CONH_2$ and $R_1=CONR_4R_5$ after purification.

[0258] The compounds with $R_3=CN$ and $R'=N$ -phthaloyl are treated with an excess of trimethylsilyl azide and Bu_2SnO

in an appropriate solvent and heating to afford the desired compounds with $R_3=tetrazoyl$ and $R'=N$ -phthaloyl. In case $R_1=R_2\neq COOH$, the compounds are treated with hydrazine hydrate at elevated temperature in an appropriate solvent to yield the desired amines with $R_3=tetrazoyl$. The reaction of these amines with a suitable aldehyde (D-CHO) in an appropriate solvent affords the desired final compound with $R_3=tetrazoyl$ and $R_1=R_2\neq COOH$, $CONR_4R_5$, $COOMe$ after purification. In case $R_1=COOMe$, the compounds are treated with an appropriate amine in a suitable solvent to afford the free amine compounds. Protection of the amines with Boc_2O affords the Boc-protected products after purification. Saponification of the ester moieties affords the desired fNH-Boc-protected carboxylic acid derivatives. The acid derivatives are then treated with ethylchloroformate, followed by an amine to afford the desired products after acid treatment. The reaction of these amines with a suitable aldehyde (D-CHO) in an appropriate solvent affords the desired final compound with $R_3=tetrazoyl$ and $R_1=CONR_4R_5$ after purification.

SCHEME 9

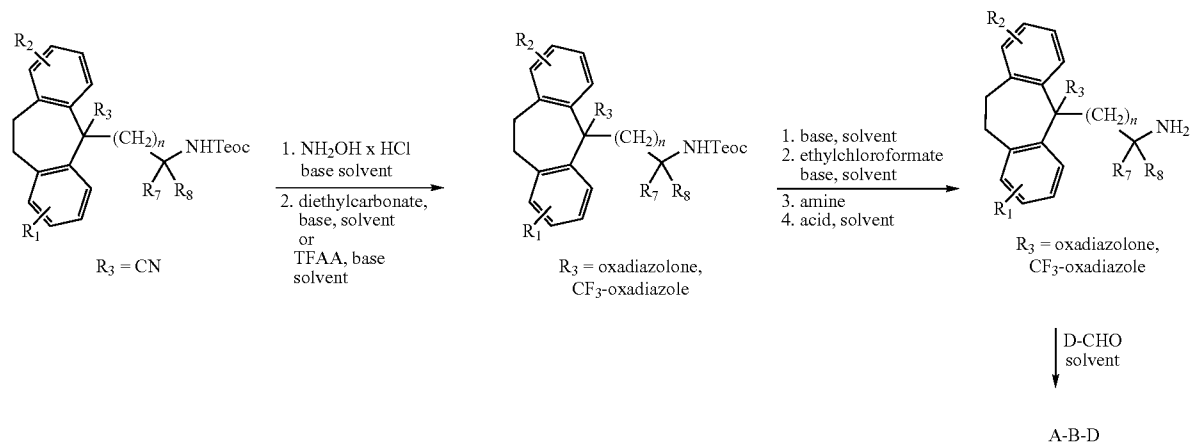


[0259] The NH Teoc-protected compounds with $R_3 = \text{CN}$ and $R_1 = R_2 = \text{COOMe}$ or $R_1 = R_2 = \text{Hal}$ were treated with hydroxylamine hydrochloride and an excess of base at elevated temperatures in an appropriate solvent to afford the desired compounds with $R_3 = \text{CONH}_2$ after purification. The same NH Teoc protected compounds are also reacted with sodium azide and ammonium chloride in a suitable solvent to yield the desired compounds with $R_3 = \text{tetrazoyl}$ after purification. Further reaction of the compound with $R_3 = \text{tetrazoyl}$ with methyl iodide and base in a suitable solvent leads to the formation of the desired compound with $R_3 = \text{N-Me-tetrazoyl}$ after purification. For the compounds with $R_3 = \text{tetrazoyl}$, N-Me-tetrazoyl and $R_1 = R_2 = \text{COOMe}$, Hal, the Teoc protecting group is removed by treatment with acid to afford the desired amine compounds. The reaction of these amines with a suitable aldehyde (D-CHO) in an appropriate solvent affords the desired final compound with $R_3 = \text{tetrazoyl}$, N-Me-tetrazoyl and $R_1 = R_2 = \text{COOMe}$, Hal after purification. For

the compounds with $R_3 = \text{tetrazoyl}$, N-Me-tetrazoyl and $R_1 = R_2 = \text{COOMe}$, the ester moieties are removed by treatment with base in an appropriate solvent to afford the desired dicarboxylic acid derivatives after purification. Treatment of these compounds with ethylchloroformate, followed by an amine yields the desired amine compounds with $R_3 = \text{tetrazoyl}$, N-Me-tetrazoyl and $R_1 = R_2 = \text{CONR}_4\text{R}_5$ after purification. Cleavage of the Teoc protecting group with acid affords the corresponding amine compounds. The reaction of these amines with a suitable aldehyde (D-CHO) in an appropriate solvent affords the desired final compounds with $R_3 = \text{tetrazoyl}$, N-Me-tetrazoyl and $R_1 = R_2 = \text{CONR}_4\text{R}_5$ after purification. To obtain the desired final compounds with $R_3 = \text{tetrazoyl}$, N-Me-tetrazoyl and $R_1 = R_2 = \text{COOH}$ after purification, the amide formation steps 2 and 3 are omitted.

[0260] General synthetic scheme for the preparation of tricyclic compounds of this invention with $R^3 = \text{heteroaryl}$ (e.g., oxadiazolone or trifluoroxadiazole)

SCHEME 10



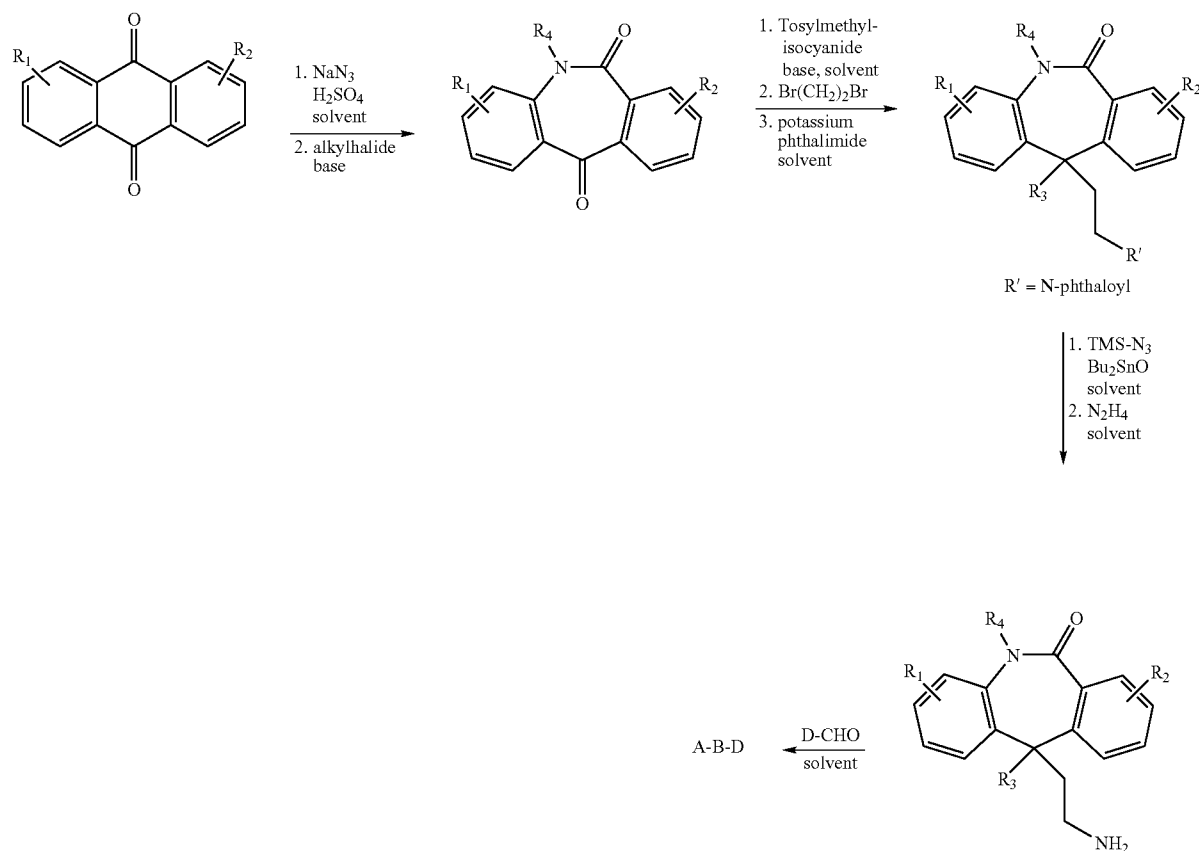
[0261] The NH Teoc-protected compounds with $R_3=\text{CN}$ and $R_1=R_2=\text{COOMe}$ were treated with hydroxylamine hydrochloride and a base at elevated temperatures, followed by diethylcarbonate in an appropriate solvent to afford the desired compounds with $R_3=\text{oxadiazolone}$ after purification. In case trifluoroacetic acid anhydride and base are used in a suitable solvent for step 2 of the above scheme, the desired compounds with $R_3=\text{CF}_3\text{-oxadiazole}$ are obtained after purification. The compounds with $R_3=\text{oxadiazolone}$ and $R_3=\text{CF}_3\text{-oxadiazole}$ are then treated with base to afford the dicarboxylic acid derivatives. These acids are treated with ethylchloroformate, followed by an amine to afford the desired NH-Teoc protected compounds with $R_3=\text{oxadiazolone}$, $\text{CF}_3\text{-oxadiazole}$ and $R_1=R_2=\text{CONR}_4\text{R}_5$ after purification. Cleavage of the Teoc protecting group with acid affords the corresponding amine compounds. The reaction of these amines with a suitable aldehyde (D-CHO) in an appropriate solvent affords the desired final compounds with $R_3=\text{oxadiazolone}$, $\text{CF}_3\text{-oxadiazole}$ and $R_1=R_2=\text{CONR}_4\text{R}_5$ after purification.

[0262] General synthetic scheme for the preparation of tricyclic compounds of this invention with $R^3=\text{tetrazole}$ and $Y=\text{CONR}^4$

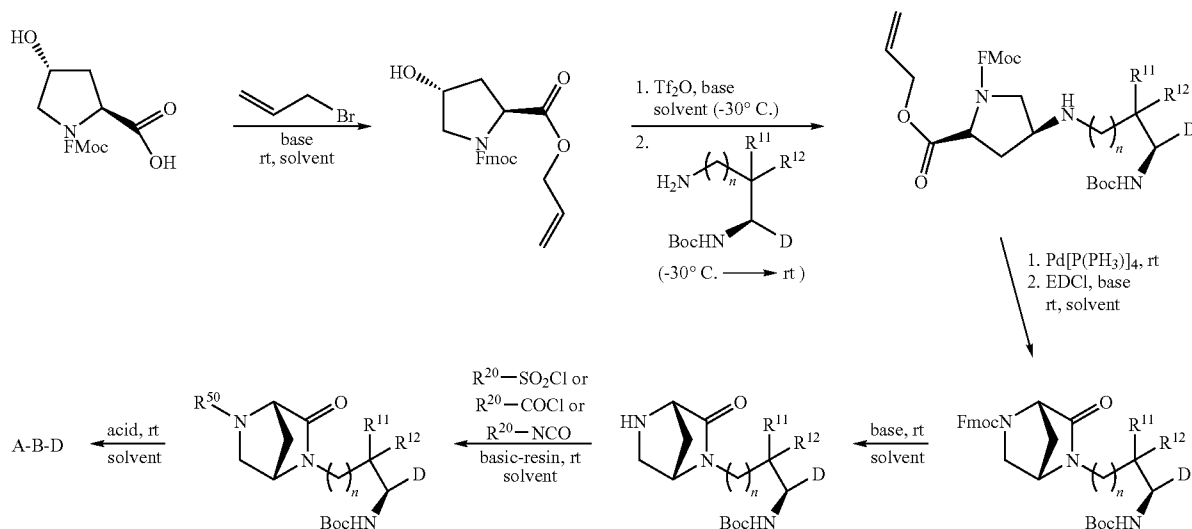
[0263] Anthraquinone derivatives are treated with sodium azide and sulphuric acid in a suitable solvent to yield the desired compounds. These compounds are then treated with alkyl halides and base in a suitable solvent to obtain the desired compounds after purification. Reaction of these compounds with tosylmethyl isocyanide and base in a suitable solvent, followed by treatment with dibromoethane and potassium phthalimide affords the desired compounds with $R_3=\text{CN}$ and $R'=\text{N-phthaloyl}$ after purification. The reaction of these compounds with trimethylsilyl-azide and dibutyltin oxide in a suitable solvent affords the compounds with $R_3=\text{tetrazoyl}$ and $R'=\text{N-phthaloyl}$. Cleavage of the protecting group with hydrazine hydrate affords the desired amines, which are reacted with a suitable aldehyde (D-CHO) in an appropriate solvent to afford the desired final compound with $R_3=\text{tetrazoyl}$. The desired final compound with $R_3=\text{tetrazoyl}$ and $R_4=\text{H}$ can be obtained by omitting the alkylation step with alkyl halides in the above scheme.

[0264] General synthetic scheme for the preparation of compounds with bridged piperazinones of this invention with $R^{1,4,a,b}=(=\text{O})$

SCHEME 11



SCHEME 12



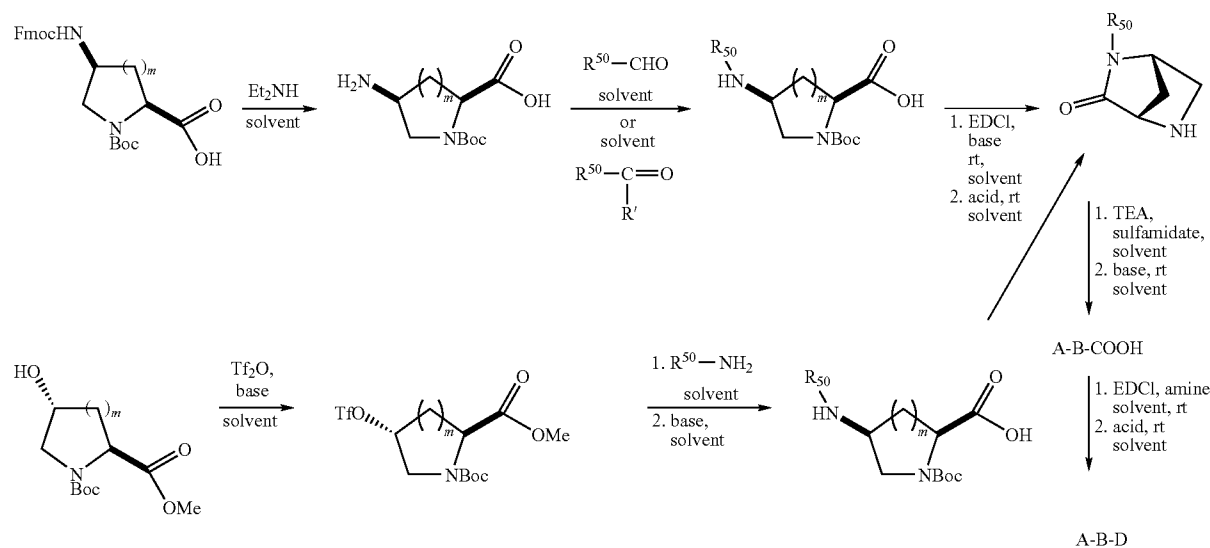
[0265] A commercially available hydroxyl-proline derivative is treated with base and alkylated with allylbromide in an appropriate solvent to afford the allyl-protected amino acid after purification. This compound is then treated at -30°C . with an appropriate base, triflic anhydride and then an appropriately protected diamino acid in an appropriate solvent to afford the desired compound after purification. After cleavage of the ester moiety with palladium(0) in an appropriate solvent, the compound is treated with EDCI and base in an appropriate solvent to afford the desired compound after purification. Cleavage of Fmoc protecting group by treatment with a suitable base affords the desired product. The free

amine is then treated in the presence of a suitable polymer supported base with sulfonyl chlorides, acid chlorides or isocyanates to afford the desired compounds after purification. Removal of the Boc-protecting group with acid in a suitable solvent affords the final desired compounds after purification.

[0266] Starting with the enantiomers of the amino acid derivatives above, and proceeding through the general procedures as described above, the enantiomeric piperazinone derivatives can be made.

[0267] General synthetic scheme for the preparation of compounds with bridged piperazinones of this invention with $\text{R}^{13a,b}(\text{=O})$

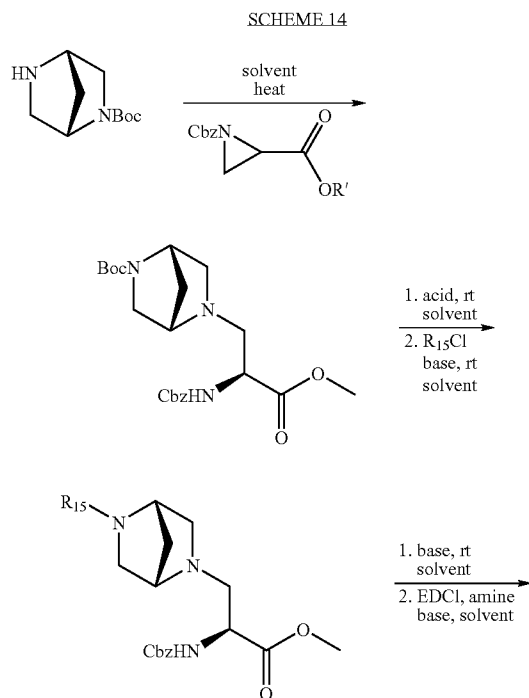
SCHEME 13



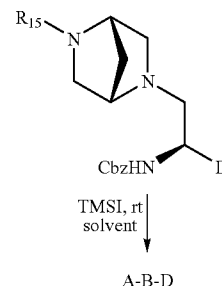
[0268] After removing the Fmoc group of the commercially available amino acid with Et_2NH , the primary amine is treated in an appropriate solvent with aldehydes or ketones in a reductive amination reaction to afford the desired products. Alternatively, the commercially available N-Boc-protected hydroxy amino acid ester can be treated with trifluoroacetic acid anhydride. The nucleophilic displacement reaction of the triflate with commercially available amines affords the desired products, after saponification of the ester moiety with base and purification. These compounds are then treated with EDCI and a base in a suitable solvent to afford the cyclic amides after purification. These compounds are converted to the desired products by removing the Boc-protection group. These compounds are then reacted in a suitable solvent with a cyclic sulfamidate, derived from a serine derivative, in the presence of base. Saponification of the ester of the reaction product with a suitable base yields the desired acid compounds after purification. Further treatment of the free acids with EDCI in the presence of an appropriate base and a suitable amine derivative, followed by acidic removal of the Boc-protecting group yields the desired compounds after purification.

[0269] Starting with the enantiomers of the amino acid and amine derivatives above, and proceeding through the general procedures as described above, the enantiomeric piperazine derivatives can be made.

[0270] General synthetic scheme for the preparation of compounds with bridged piperazines of this invention with $\text{R}^{13a,b}$ and $\text{R}^{14a,b}=\text{H}$



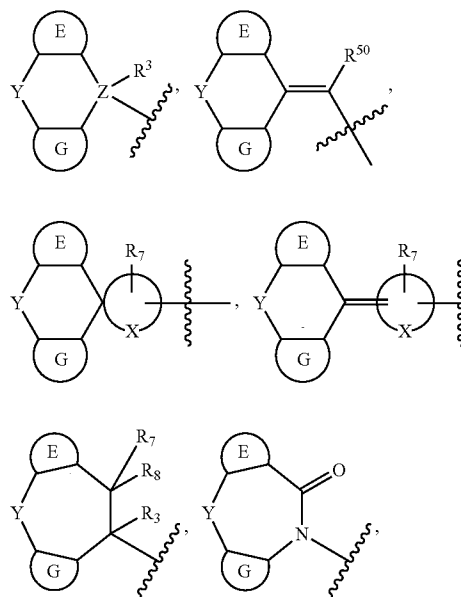
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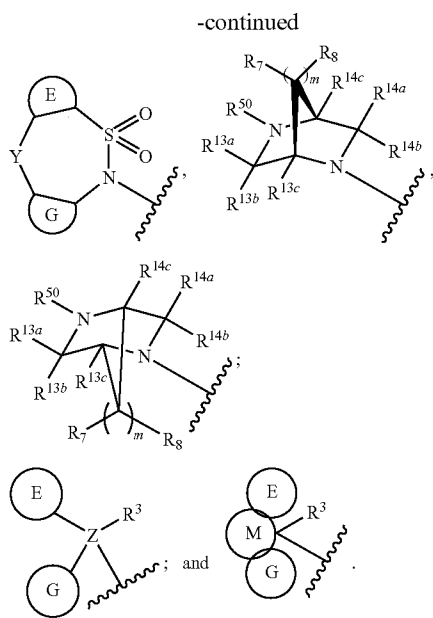


[0271] The commercially available bridged piperazine derivative is treated with a commercially available aziridine ester in an appropriate solvent to afford the desired compound after purification. After acidic removal of the Boc-protection group, the desired product reacts in presence of a base with an acid chloride or sulfonic acid chloride to yield the desired products after purification. After basic saponification, the free acids are treated with EDCI in the presence of an appropriate base and a suitable amine derivative to afford the desired compounds after purification. The Cbz-protecting group is then removed by treatment with TMSI and subsequent purification to afford the desired final compounds.

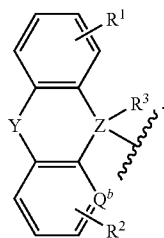
[0272] Starting with the enantiomers of the amine and aziridine derivatives above, and proceeding through the general procedures as described above, the enantiomeric piperazine derivatives can be made.

[0273] As can be seen by the generic schemes, each of the structures of "B" bonds to the "A" structures on its left side and to the "D" structures on its right side as each is depicted below. The compound A-B-D chooses an "A" which includes the following:

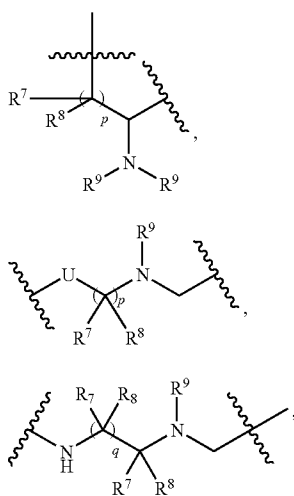




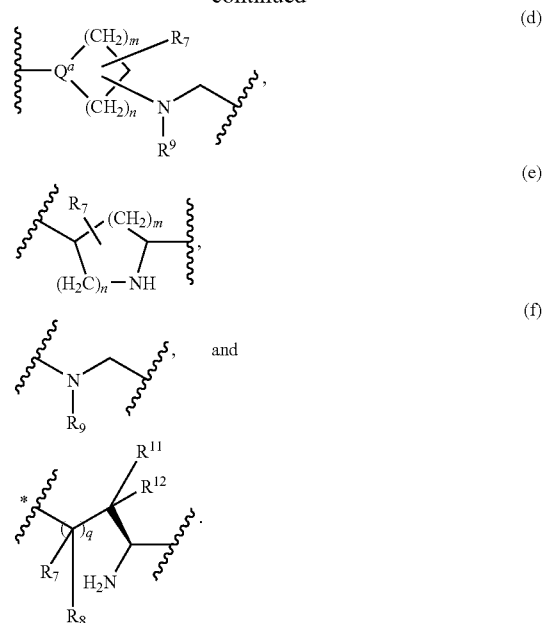
[0274] A is desirably



[0275] The "B" structures are chosen from:

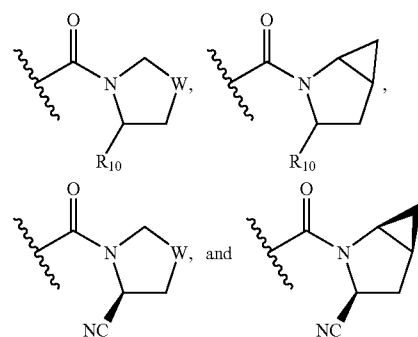


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Desirably, B is one of structure (a), (b), (c), and (d). More desirably, B is structure (b)

[0276] The "D" structures are chosen from:



(a)

[0277] The substituents are selected as follows:

[0278] E, G, and M represent a three ring system wherein M shares two carbon atoms with each of E and G;

[0279] E and G are each independently selected from 6-membered aryl, 5-membered heteroaryl; 6-membered heteroaryl; a 5-7-membered saturated or partially saturated carbocyclic ring; and a 5-7 membered saturated or partially saturated heterocyclic ring; desirably E and G are substituted phenyl; M is a 5-7-membered saturated or partially saturated carboxylic or heterocyclic ring, or a 5-6-membered aromatic or heteroaromatic ring.

[0280] E may be substituted with one or more R¹ groups;

[0281] G may be substituted with one or more R² groups;

[0282] X and Y are divalent and are each independently: a bond, CR⁴R⁵, O, NR⁴, S, S=O, S(=O)₂, C(=O), (C=O)N(R⁴), S(=O)₂N(R⁴), C=N-OR⁴, -C(R⁴R⁵)C(R⁴R⁵)-, -C(R⁴R⁵)C(R⁵)-, -C(R⁴R⁵)NR⁴-, -C(R⁴R⁵)O-, -C(R⁴R⁵)S(=O)_t-, -(C=O)O-, -(C=NR⁴)N(R⁴)-,

—(C=NR^a)—, N(C=O)NR⁴NR⁵, N(C=O)R⁴, N(C=O)OR⁴, NS(=O)₂NR⁴NR⁵, NS(=O)₂R⁴; or aryl, heteroaryl, cycloalkyl or heterocyclic ring, all may be optionally substituted;

[0283] R¹ and R² are each independently: halogen, CF₃, COR⁴, OR⁴, NR⁴R⁵, NO₂, CN, SO₂OR⁴, CO₂R⁴, CONR⁴R⁵, CO₂H, SO₂NR⁴R⁵, S(O)₂R⁴, SO₃H, OC(O)R⁴, OC(O)NR⁴R⁵, NR⁴C(O)R⁵, NR⁴CO₂R⁵, (C₀-C₆)-alkyl-C(=NR^a)NHR⁴, (C₀-C₆)-alkyl-C(=NR^a)NHR^a, (C₀-C₆)-alkyl-NR⁴C(=NR⁴)NR⁵, (C₀-C₆)-alkyl-C(O)OR⁴, (C₀-C₆)-alkyl-C(O)NR⁴R⁵, (C₀-C₆)-alkyl-C(O)—NH—CN, O—(C₀-C₆)-alkyl-C(O)NR⁴R⁵, S(O)₂—(C₀-C₆)-alkyl-C(O)OR⁴, S(O)₂—(C₀-C₆)-alkyl-C(O)NR⁴R⁵, (C₀-C₆)-alkyl-C(O)NR⁴—(C₀-C₆)-alkyl-NR⁴R⁵, (C₀-C₆)-alkyl-NR⁴—C(O)R⁵, (C₀-C₆)-alkyl-NR⁴—C(O)OR⁴, (C₀-C₆)-alkyl-NR⁴—C(O)R⁵, (C₀-C₆)-alkyl-NR⁴—C(O)OR⁴, (C₀-C₆)-alkyl-NR⁴—C(O)—NR⁴R⁵, (C₀-C₆)-alkyl-NR⁴—SO₂R⁴, hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, haloalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, alkoxyalkyl or aminoalkyl, wherein alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, alkoxyalkyl and aminoalkyl all of which may be optionally substituted. Desirably, R¹ and R² may be defined independently as —H, —F, —Cl, —CONR⁴R⁵, —CO₂H, —CN or —SO₂NR⁴R⁵.

[0284] R³ is absent or is halogen, CF₃, COR⁴, OR⁴, NR⁴R⁵, NO₂, CN, SO₂OR⁴, CO₂R⁴, CONR⁴R⁵, CO₂H, SO₂NR⁴R⁵, S(O)₂R⁴, SO₃H, OC(O)R⁴, OC(O)NR⁴R⁵, NR⁴C(O)R⁵, NR⁴CO₂R⁵, (C₀-C₆)-alkyl-C(=NR^a)NHR⁴, (C₀-C₆)-alkyl-C(=NR^a)NHR^a, (C₀-C₆)-alkyl-NR⁴C(=NR⁴)NR⁵, (C₀-C₆)-alkyl-C(O)OR⁴, (C₀-C₆)-alkyl-C(O)NR⁴R⁵, (C₀-C₆)-alkyl-C(O)—NH—CN, O—(C₀-C₆)-alkyl-C(O)NR⁴R⁵, S(O)₂—(C₀-C₆)-alkyl-C(O)OR⁴, S(O)₂—(C₀-C₆)-alkyl-C(O)NR⁴R⁵, (C₀-C₆)-alkyl-C(O)NR⁴—(C₀-C₆)-alkyl-NR⁴R⁵, (C₀-C₆)-alkyl-NR⁴—C(O)R⁵, (C₀-C₆)-alkyl-NR⁴—C(O)OR⁴, (C₀-C₆)-alkyl-NR⁴—C(O)—NR⁴R⁵, (C₀-C₆)-alkyl-NR⁴—SO₂R⁴, hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, haloalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, alkoxyalkyl or aminoalkyl, wherein alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, alkoxyalkyl and aminoalkyl all of which may be optionally substituted. Desirably, R³ is absent or is —H, —OH, —CO₂H, —CN, —CONR⁴R⁵, R⁵, aryl, NH(C=O)R⁴, NH(SO₂)R⁴, heteroaryl —SO₃H, —PO₃H₂, —CONR⁴R⁵, R⁵, aryl, NH(C=O)R⁴, or NH(SO₂)R⁴, and more desirably, R³ is —CONR⁴R⁵ or tetrazolyl.

[0285] R^a is hydrogen, CN, NO₂, alkyl, haloalkyl, S(O)₂NR⁴R⁵, S(O)₂R⁴, C(O)OR⁴, C(O)R⁴, or C(O)NR⁴R⁵;

[0286] each occurrence of R⁴, R⁵, R²⁰ and R²¹ are each independently: hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl or aminoalkyl, wherein alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl are all optionally substituted, or R⁴ and R⁵ when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and may optionally contain a heteroatom selected from O, S, or NR⁵⁰ and the

3- to 8-membered ring may be optionally substituted. Desirably, R⁴ and R⁵ are each independently —H or alkyl.

[0287] R⁵⁰ is, in each occurrence, R²⁰, CN, NO₂, S(O)₂NR²⁰R²¹, S(O)₂R²⁰, C(O)OR²⁰, C(O)R²⁰C(=NR^a)NR²⁰R²¹, C(=NR²⁰)NR²¹R^a, C(=NOR²⁰)R²¹ or C(O)NR²⁰R²¹;

[0288] each occurrence of R⁷ and R⁸ are each independently: halogen, CF₃, COR⁴, OR⁴, NR⁴R⁵, NO₂, CN, SO₂OR⁴, CO₂R⁴, CONR⁴R⁵, CO₂H, SO₂NR⁴R⁵, S(O)₂R⁴, SO₃H, OC(O)R⁴, OC(O)NR⁴R⁵, NR⁴C(O)R⁵, NR⁴CO₂R⁵, (C₀-C₆)-alkyl-C(=NR^a)NHR⁴, (C₀-C₆)-alkyl-C(=NR^a)NHR^a, (C₀-C₆)-alkyl-NR⁴C(=NR⁴)NR⁵, (C₀-C₆)-alkyl-C(O)OR⁴, (C₀-C₆)-alkyl-C(O)NR⁴R⁵, (C₀-C₆)-alkyl-C(O)—NH—CN, O—(C₀-C₆)-alkyl-C(O)NR⁴R⁵, S(O)₂—(C₀-C₆)-alkyl-C(O)OR⁴, S(O)₂—(C₀-C₆)-alkyl-C(O)NR⁴R⁵, (C₀-C₆)-alkyl-C(O)NR⁴—(C₀-C₆)-alkyl-NR⁴R⁵, (C₀-C₆)-alkyl-NR⁴—C(O)R⁵, (C₀-C₆)-alkyl-NR⁴—C(O)OR⁴, (C₀-C₆)-alkyl-NR⁴—C(O)—NR⁴R⁵, (C₀-C₆)-alkyl-NR⁴—SO₂R⁴, hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, haloalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, alkoxyalkyl or aminoalkyl, wherein alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, alkoxyalkyl and aminoalkyl all may be optionally substituted. Desirably, R⁷ and R⁸ are independently H or alkyl.

[0289] R⁹ is H or C₁₋₆ alkyl, desirably H.

[0290] R¹⁰ is halogen, CF₃, COR⁴, OR⁴, NR⁴R⁵, NO₂, CN, SO₂OR⁴, CO₂R⁴, CONR⁴R⁵, CO₂H, SO₂NR⁴R⁵, S(O)₂R⁴, SO₃H, OC(O)R⁴, OC(O)NR⁴R⁵, NR⁴C(O)R⁵, NR⁴CO₂R⁵, (CO—C₆)-alkyl-C(=NR^a)NHR⁴, (C₀-C₆)-alkyl-C(=NR^a)NHR^a, (C₀-C₆)-alkyl-NR⁴C(=NR⁴)NR⁵, (CO—C₆)-alkyl-C(O)OR⁴, (C₀-C₆)-alkyl-C(O)NR⁴R⁵, (C₀-C₆)-alkyl-C(O)—NH—CN, O—(C₀-C₆)-alkyl-C(O)NR⁴R⁵, S(O)₂—(C₀-C₆)-alkyl-C(O)OR⁴, S(O)₂—(C₀-C₆)-alkyl-C(O)NR⁴R⁵, (C₀-C₆)-alkyl-C(O)NR⁴—(C₀-C₆)-alkyl-NR⁴R⁵, (C₀-C₆)-alkyl-NR⁴—C(O)R⁵, (C₀-C₆)-alkyl-NR⁴—C(O)OR⁴, (C₀-C₆)-alkyl-NR⁴—C(O)—NR⁴R⁵, (C₀-C₆)-alkyl-NR⁴—SO₂R⁴, hydrogen, B(OH)₂, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, haloalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, alkoxyalkyl or aminoalkyl, wherein alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, alkoxyalkyl and aminoalkyl are all optionally substituted. Desirably R¹⁰ is CN.

[0291] R¹¹ and R¹² are each independently: halogen, CF₃, COR⁴, OR⁴, NR⁴R⁵, NO₂, CN, SO₂OR⁴, CO₂R⁴, CONR⁴R⁵, CO₂H, SO₂NR⁴R⁵, S(O)₂R⁴, SO₃H, OC(O)R⁴, OC(O)NR⁴R⁵, NR⁴C(O)R⁵, NR⁴CO₂R⁵, (C₀-C₆)-alkyl-C(=NR^a)NHR⁴, (C₀-C₆)-alkyl-C(=NR^a)NHR^a, (C₀-C₆)-alkyl-NR⁴C(=NR⁴)NR⁵, (CO—C₆)-alkyl-NR⁴C(=NR⁴)NR⁵, (C₀-C₆)-alkyl-C(O)OR⁴, (C₀-C₆)-alkyl-C(O)NR⁴R⁵, (C₀-C₆)-alkyl-C(O)—NH—CN, O—(C₀-C₆)-alkyl-C(O)NR⁴R⁵, S(O)₂—(C₀-C₆)-alkyl-C(O)OR⁴, S(O)₂—(C₀-C₆)-alkyl-C(O)NR⁴R⁵, (C₀-C₆)-alkyl-C(O)NR⁴—(C₀-C₆)-alkyl-NR⁴R⁵, (C₀-C₆)-alkyl-NR⁴—C(O)R⁵, (C₀-C₆)-alkyl-NR⁴—C(O)OR⁴, (C₀-C₆)-alkyl-NR⁴—C(O)—NR⁴R⁵, (C₀-C₆)-alkyl-NR⁴—SO₂R⁴, hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, haloalkyl, alkenyl, alkynyl, aryl, het-

eroaryl, arylalkyl, heteroarylalkyl, alkoxyalkyl or aminoalkyl, wherein alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, alkoxyalkyl and aminoalkyl all may be optionally substituted;

[0292] R^{13a} and R^{13b} are each independently R^5 or together are =O;

[0293] R^{14a} and R^{14b} are each independently R^5 or together are =O;

[0294] R^{13c} and R^{14c} are each independently R^5 ;

[0295] Q^a is CH or N;

[0296] Q^b is CH or N;

[0297] U is $-C(O)-$, $-C(=NR^4)-$, $-(CR^4R^5)_p$, NR^{50} , $S(=O)_2$, $C(=O)$, $(C=O)N(R^4)$, $N(R^4)(C=O)$, $S(=O)_2N(R^4)$, $N(R^4)S(=O)_2$, $C=N-OR^4$, $-C(R^4)=C(R^5)-$, $-C(R^4R^5)_pNR^{50}-$, $N(R^{50})C(R^4R^5)_p-$, $-O-C(R^4R^5)-$, $-C(R^4R^5)S(=O)-$, $-(C=O)O-$, $-(C=NR^a)N(R^4)-$, $-(C=NR^a)-$, $N(C=O)NR^4NR^5$, $N(C=O)R^4$, $N(C=O)OR^4$, $NS(=O)_2NR^4NR^5$, $NS(=O)_2R^4$, or an optionally substituted aryl, heteroaryl, cycloalkyl or heterocyclic ring, all of which may be optionally substituted. Desirably, U is CH_2 .

[0298] W is $-CH_2-$, $-S-$, $-CHF-$ or $-CF_2-$;

[0299] Z is C or N;

[0300] m is 1, or 2;

[0301] n is 0, 1, or 2;

[0302] p is 0 to 6;

[0303] q is 0 to 6; and

[0304] t is 0, 1, or 2.

EXAMPLES

[0305] Compounds of the present invention having one or more optically active carbons can exist as racemates and racemic mixtures, diastereomeric mixtures and individual diastereomers, enantiomeric mixtures and single enantiomers, tautomers, atropisomers, and rotamers, with all isomeric forms being included in the present invention. Compounds described in this invention containing olefinic double bonds include both E and Z geometric isomers. Also included in this invention are all salt forms, polymorphs, hydrates and solvates. All of the above mentioned compounds are included within the scope of the invention.

[0306] The DPP-IV inhibition activity of the DPP-IV inhibitor compounds of the present invention may be measured using any suitable assay known in the art. A standard in vitro assay for measuring DPP-IV inhibitor activity is described.

[0307] The synthesis of DPP-IV inhibiting compounds of the invention and their biological activity assay are described in the following examples which are not intended to be limiting in any way.

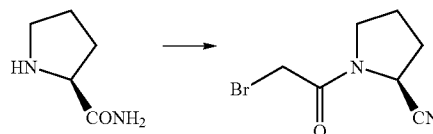
Examples and Methods

[0308] All reagents and solvents were obtained from commercial sources and used without further purification. Proton (1H) spectra were recorded on a 250 MHz NMR spectrometer in deuterated solvents. Chromatography was performed using Roth silica gel (Si 60, 0.06-0.2 mm) and suitable organic solvents as indicated in specific examples. For flash chromatography Roth silica gel (Si 60, 0.04-0.063 mm) was used. Thin layer chromatography (TLC) was carried out on silica gel plates with UV detection. Preparative thin layer chroma-

tography (Prep-TLC) was conducted with 0.5 mm or 1 mm silica gel plates (Merck Si 60, F₂₅₄) and the solvents indicated in the specific examples.

Preparative Example 1

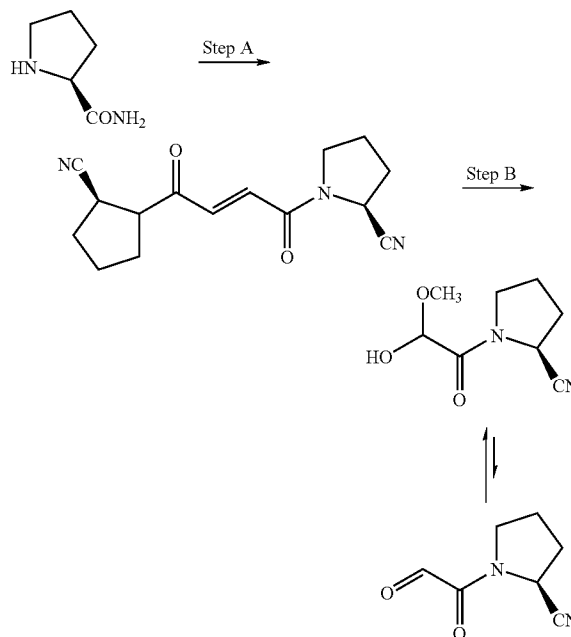
[0309]



[0310] Commercially available prolinamide (5 g) was first treated with bromoacetyl bromide (4.2 ml) in CH_2Cl_2 and then with trifluoroacetic acid anhydride in CH_2Cl_2 as described in WO 98/19998 to afford the title compound (7.85 g; 83%). 1H NMR δ ($CDCl_3$) 2.05-2.40 (m, 4H), 3.51-3.70 (m, 2H), 3.80-3.85 (m, 2H), 4.70-4.86 (m, 1H).

Preparative Example 2

[0311]



Step A

[0312] Commercially available L-prolinamide (25 g) was dissolved in CH_2Cl_2 (1200 ml) and triethylamine (30 ml) and 4-dimethylaminopyridine (1.9 g) added. The mixture was cooled to 0° C. and treated with fumaryl chloride (11.7 ml). The dark mixture was stirred at rt for 16 h and cooled to 0° C. TFAA (77 ml) was added dropwise under stirring and the solution allowed to warm to rt over 6 hours. The reaction mixture was stirred at rt for 1 to 2 days. Ice (500 g) was added followed by cautious addition of sat. $NaHCO_3$ (600 ml). After the evolution of gas had ceased, the organic phase was separated and washed with sat. $NaHCO_3$ (350 ml), H_2O (350 ml), and brine (200 ml). The organic phase was dried over $MgSO_4$ and concentrated to afford the title compound (28.6 g; 98%). [0313] 1H NMR δ ($CDCl_3$) 2.12-2.30 (m, 8H), 3.58-3.69 (m, 2H), 3.73-3.89 (m, 2H), 4.72-4.83 (m, 2H), 7.26 (s, 2H).

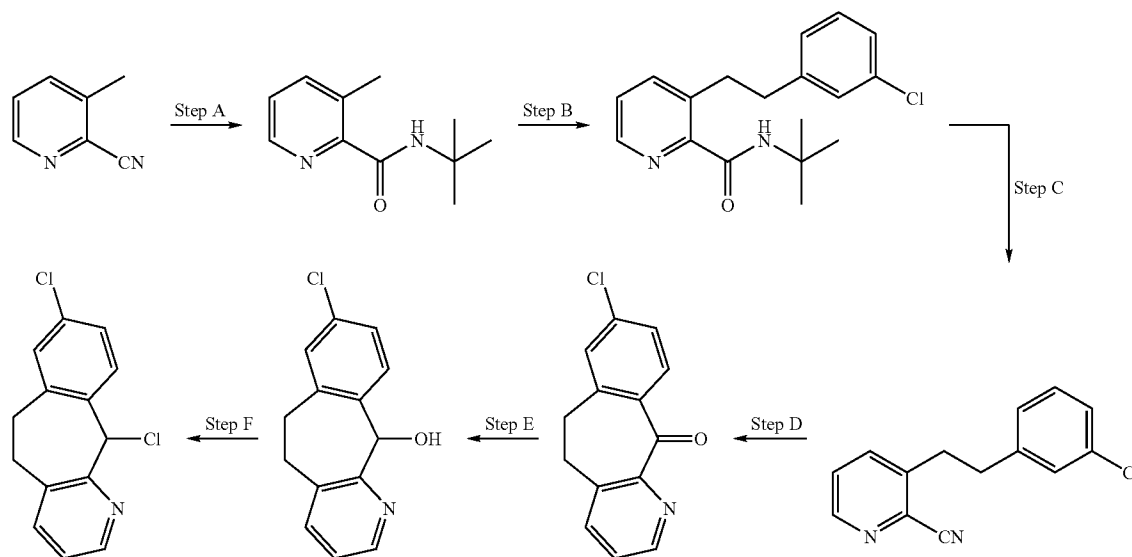
Step B

[0314] The title compound from Step A above (9.6 g) was dissolved in CHCl_3 (90 ml) and MeOH (90 ml) and cooled to -78°C . At -78°C , a slow flow of ozone (originating from an O_2 cylinder) was passed through the mixture for 3 h. The mixture was purged with N_2 and dimethylsulfide (6 ml) added. The mixture was stirred for 1 h, allowed to reach rt and concentrated. The residue was purified by chromatography on silica ($\text{CH}_2\text{Cl}_2/\text{MeOH}$, 100:0 \rightarrow 92:8) to afford the title compound as a mixture of the aldehyde and methoxy hemiacetal in a ratio of $\sim 1:9$ (8.9 g; 69%).

[0315] $^1\text{H NMR}$ δ (D_2O) 2.10-2.38 (m, 4H), 3.32 (s, 3H), 3.60-3.84 (m, 2H), 4.72-4.81 (m, 1H), 5.5 (s, $\frac{1}{10}\text{H}$), 7.9 (s, $\frac{1}{10}\text{H}$).

Preparative Example 3

[0316]



Step A

[0317] Commercially available 2-cyano-3-methylpyridine (25 g) was dissolved in t-butanol (50 ml) and stirred at 80°C . Concentrated sulphuric acid (25 ml) was slowly added over a period of 45 minutes. After complete addition of the acid stirring was continued at 80°C for 1 h. The reaction was diluted with water (50 ml) and toluene (125 ml). The pH was adjusted to 10 with 25% aqueous ammonia (110 ml). The separated organic phase was concentrated in vacuum affording the desired product (27 g, 90%).

[0318] $^1\text{H NMR}$ δ (CDCl_3) 1.4 (s, 9H), 2.7 (s, 3H), 7.2-7.3 (m, 1H), 7.6 (m, 1H), 8.1 (s br, 1H), 8.4 (m, 1H)

Step B

[0319] The title compound of Step A (12 g) above was dissolved in THF (150 ml) and cooled to -64°C . n-Butyllithium (1.6 M in hexane, 77 ml) was added over a period of 30 min. After addition of sodium bromide (0.6 g) stirring was continued for 30 min at -64°C . m-Chlorobenzylchloride (11 g) was added while the temperature was kept below -55°C .

The mixture was stirred for 2 hours at -60°C and for further 2 h at -110°C . Subsequently, the reaction was quenched with water (100 ml) and concentrated. The aqueous phase was extracted with chloroform (3×100 ml). The combined organic phase was dried over MgSO_4 and concentrated in vacuum affording the title compound (22 g; 82%).

[0320] $^1\text{H NMR}$ δ (CDCl_3) 1.4 (s, 9H), 2.9-3.0 (m, 2H), 3.4-3.5 (m, 2H), 7.0-7.4 (m, 6H), 8.0 (s br, 1H), 8.4 (m, 1H)

Step C

[0321] The title compound of Step B (21.5 g) above was dissolved in phosphorus oxychloride (80 ml) and refluxed for 5 h. The reaction was concentrated and neutralized with 50% aqueous NaOH. The solid was separated and washed with hot isopropanol to afford the title compound (10.4 g; 63%)

[0322] $^1\text{H NMR}$ δ (CDCl_3) 2.9-3.0 (m, 2H), 3.0-3.2 (m, 2H), 7.0-7.3 (m, 4H), 7.3-7.4 (m, 1H), 7.4-7.5 (m, 1H), 8.5-8.6 (m, 1H)

Step D

[0323] The title compound of Step C (10 g) above was dissolved in trifluorosulfonic acid (80 ml) and stirred at 60°C for 1 h. At rt 6 N aqueous HCl (80 ml) was dropwise added. The reaction was refluxed for 1 h and subsequently, poured on ice. After neutralization with 50% aqueous NaOH the precipitate was separated, washed with water and recrystallized from isopropanol/water (3.1) affording the title compound. The mother liquor was concentrated and the residue washed with water and chloroform to afford additional title compound (9.4 g; 94%).

[0324] $^1\text{H NMR}$ δ ($\text{MeOD}-d_4$) 3.3-3.4 (m, 2H), 3.4-3.5 (m, 2H), 7.5 (m, 2H), 8.1-8.2 (m, 2H), 8.7 (d, 1H), 8.9 (d, 1H)

Step E

[0325] The title compound of Step D (700 mg) above was dissolved in MeOH (10 ml) and cooled to 0°C . NaBH_4 (95 mg) was added in one portion. The mixture was allowed to warm to RT and stirred for 1 h. The reaction was acidified with 1 N HCl and subsequently, brought to pH 12 with 1 N NaOH.

The mixture was poured in water (100 ml) and extracted with CHCl_3 (100 ml). The organic phase was dried over MgSO_4 and concentrated affording the title compound (705 mg; 100%).

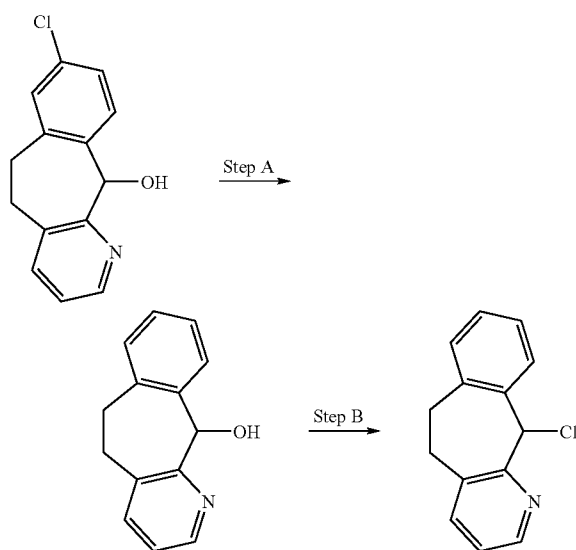
[0326] $^1\text{H-NMR}$ δ (MeOD-d_4) 3.0-3.4 (m, 4H), 6.1 (s, 1H), 7.1-7.3 (m, 3H), 7.5-7.6 (m, 2H), 8.3-8.4 (m, 1H)

Step F

[0327] The title compound of step E (370 mg) above was dissolved in toluene (5 ml) and cooled to -15°C . Thionyl chloride (286 mg) was slowly added and the reaction was allowed to come to RT and run overnight. The solution was neutralized with triethylamine and directly used in the next step.

Preparative Example 4

[0328]



Step A

[0329] The title compound from Preparative Example 3 Step E (285 mg) was dissolved in ethanol (10 ml) and 10% Pd/C (100 mg) and ammonium formate (916 mg) were added. The mixture was refluxed for 2 h. Subsequently, the reaction was treated with water (20 ml) and extracted twice

with chloroform (50 ml). The combined organic phase was dried over MgSO_4 and concentrated. The residue was purified by chromatography on silica (EtOAc/cyclohexane 1:4) to afford the title compound (200 mg; 82%).

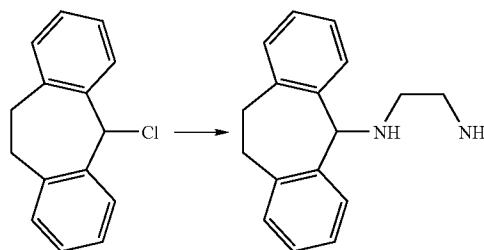
[0330] $^1\text{H-NMR}$ δ (MeOD-d_4) 2.9-3.1 (m, 2H), 3.3-3.6 (m, 2H), 6.3 (s, 1H), 7.0-7.3 (m, 4H), 7.4 (m, 1H), 7.8 (m, 1H), 8.3 (m, 1H)

Step B

[0331] The title compound of Step A (200 mg) above was dissolved in toluene (5 ml) and cooled to -15°C . Thionyl chloride (235 mg) was slowly added and the reaction was allowed to come to RT and run overnight. The solution was neutralized with triethylamine directly used.

Preparative Example 5

[0332]



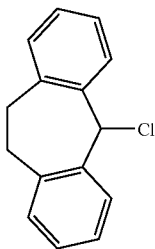
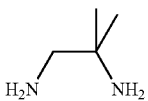
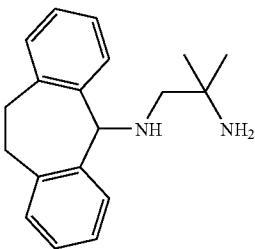
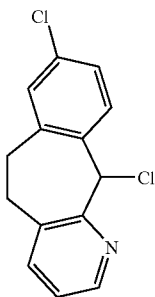

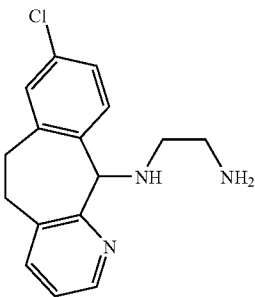
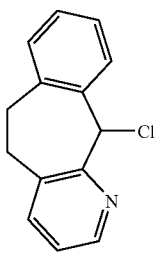
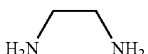
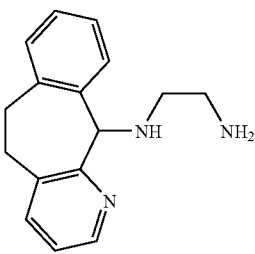
[0333] To a cooled solution (12°C) of commercially available ethylenediamine (30 ml) was added within 5 min commercially available dibenzosuberylbromide (3.3 g). The mixture was stirred at rt for 1 h and then K_2CO_3 (5.8 g) was added. After an additional 30 min at rt, the mixture was filtered, the salts washed with 5 ml ethylenediamine and the filtrates concentrated. The residue was dissolved in 80 ml EtOAc , 20 ml H_2O and 5 ml NH_4OH -solution (25%). The organic phase was separated, dried over MgSO_4 and concentrated to afford the title compound (3.4 g; 93%; $\text{MH}^+=253$).

Preparative Example 6-9

[0334] The title compounds from Preparative Example 6 to 9 were prepared according to the procedure described in Preparative Example 5 using the chlorides and amines as indicated in the Table below. In case the chlorides did not dissolve in the amines after 10 Min, CH_3CN or THF was added until a clear solution was obtained.

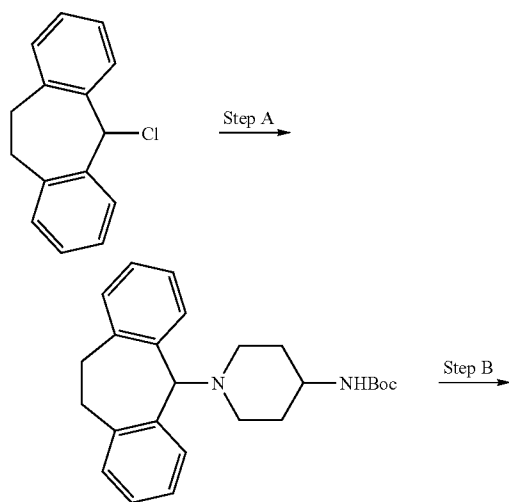
Preparative Example	Chloride	Amine	Product	1. Yield 2. MH^+
6		NH_4OH		1. 61% 2. $^1\text{H-NMR}$ δ (CDCl_3) 2.0 (s, 2H), 3.10-3.24 (m, 2H), 3.31-3.45 (m, 2H), 5.43 (s, 1H), 7.10-7.19 (m, 6H), 7.36-7.41 (m, 2H)

-continued

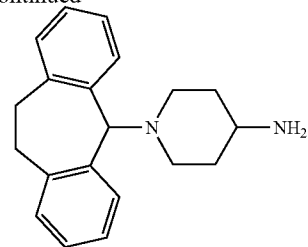
Preparative Example	Chloride	Amine	Product	1. Yield 2. MH ⁺
7				1. 97% 2. 281
8				1. 60% 2. 288
9				1. 78% 2. ¹ H-NMR δ (CD ₃ OD) 2.6-2.8 (m, 4H), 3.0-3.2 (m, 2H), 3.3-3.6 (m, 2H), 5.2 (s, 1H), 7.1-7.2 (m, 4H), 7.3-7.4 (m, 1H), 7.5 (m, 1H), 8.2-8.3 (m, 1H)

Preparative Example 10

[0335]



-continued



Step A

[0336] Commercially available dibenzosuberonechloride (300 mg) and 4-N-Boc-amino-piperidine (290 mg) were suspended in CH₃CN (10 ml). After 10 min K₂CO₃ (545 mg) was added and the mixture was stirred at rt for 3 h. The mixture was diluted with EtOAc (30 ml) and H₂O (15 ml), the organic phase separated, dried over MgSO₄ and concentrated to afford the title compound (460 mg; 89%; MH⁺=393).

Step B

[0337] The title compound from Step A above (460 mg) was dissolved in a solution of 4 M HCl in dioxane (20 ml). The mixture was stirred at rt for 2 h and concentrated to afford the title compound (335 mg; 97%; $MH^+=293$).

Preparative Example 11-12

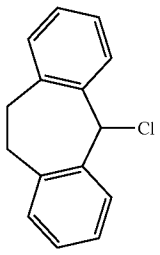
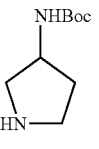
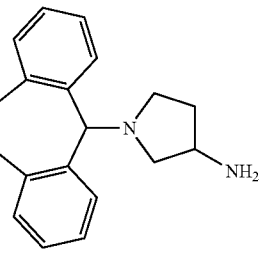
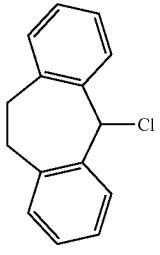
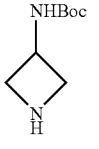
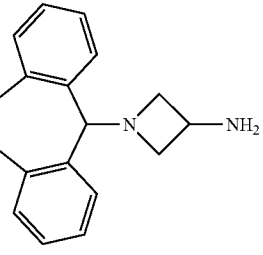
[0338] The title compounds from Preparative Example 11 and 12 were prepared according to the procedure described in Preparative Example 10 using the chlorides and amines as indicated in the Table below.

Step A

[0340] To a suspension of AgCN (4.7 g) in CH_3CN (60 ml) under nitrogen was added at rt a solution of commercially available dibenzosuberylbromide (6 g) in CH_3CN (60 ml) and benzene (10 ml). The mixture was heated at reflux for 2 h, cooled to rt and filtered. The salts were washed with 20 ml CH_3CN and the filtrates concentrated. The residue was purified by chromatography on silica (EtOAc/cyclohexane, 1:9) to afford the title compound (5 g; 87%; $MNa^+=242$).

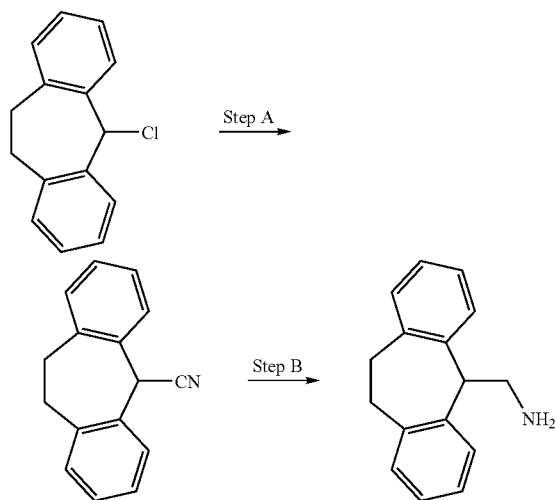
Step B

[0341] A suspension of $LiAlH_4$ (360 mg) in Et_2O (20 ml) was slowly treated with a solution of $AlCl_3$ (950 mg) in Et_2O

Preparative Example	Chloride	Amine	Product	1. Yield 2. MH^+
11				1. 64% 2. 279
12				1. 56% 2. 265

Preparative Example 13

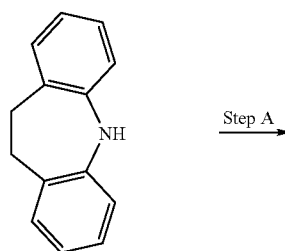
[0339]

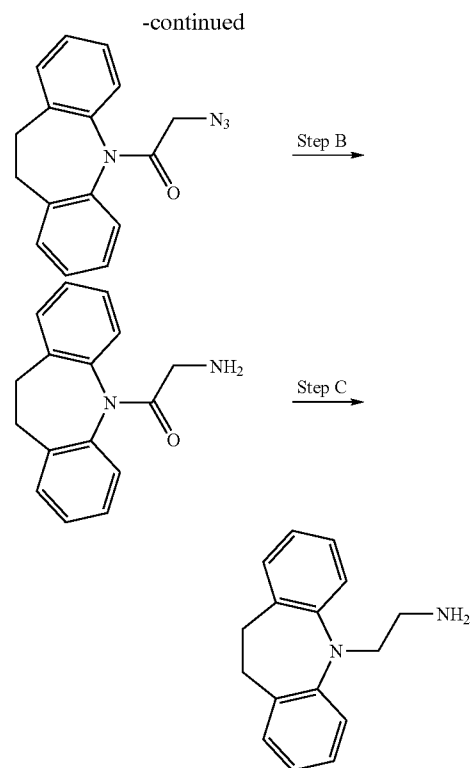


(20 ml). The mixture was stirred at rt for 10 min and then the title compound from Step A above (1.03 g) was added within 5 min. The mixture was stirred at rt for 10 min and then refluxed for 8 h. After the addition of H_2O (20 ml) and 25% NH_4OH (6 ml), the mixture was filtered and the salts washed with H_2O (20 ml) and Et_2O (10 ml). The organic phase was separated, dried over $MgSO_4$ and concentrated to afford the title compound (157 mg; 15%; $MH^+=224$).

Preparative Example 14

[0342]





Step A

[0343] To a solution of commercially available iminodibenzyl (5 g) in toluene (25 ml) was added commercially available bromoacetyl bromide (4.35 ml). The mixture was heated under reflux for 2 h 30 Min, cooled and concentrated. A portion of the crude product (800 mg) was dissolved in DMA (6 ml) and treated with NaN_3 (815 mg). The mixture was heated at 60-70° C. overnight and diluted with EtOAc (30 ml) and H_2O (10 ml). The organic phase was separated, dried over MgSO_4 and concentrated. The residue was treated with EtOAc/cyclohexane (1:9) (2 ml), sonicated for 2 min and the solvents removed by syringe. The residue was dried to afford the title compound (483 mg; 69%; $\text{MH}^+=279$).

Step B

[0344] The title compound from Step A above (483 mg) was dissolved in MeOH (25 ml) and 10% Pd/C (100 mg) added. The mixture was hydrogenated for 1 h, filtered and the catalyst washed with MeOH (10 ml). The filtrates were concentrated and the residue purified by chromatography on silica ($\text{CH}_2\text{Cl}_2/\text{MeOH}$, 9:1) to afford the title compound (415 mg; 95%; $\text{MH}^+=253$).

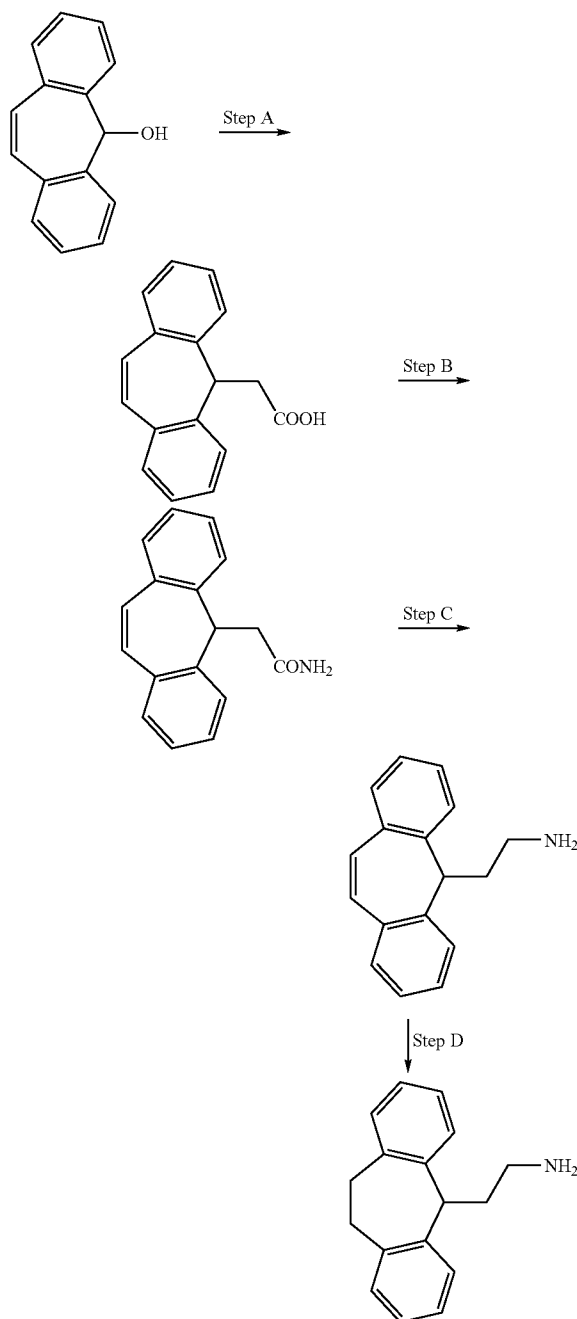
Step C

[0345] To a suspension of LiAlH_4 (242 mg) in THF (6 ml) was added a solution of the title compound from Step B above (322 mg) in THF (6 ml). The mixture was heated under reflux for 2 h 30 min. The mixture was cooled to 0° C., quenched with H_2O (0.3 ml) and diluted with 15% NH_4OH -solution (0.3 ml) and H_2O (0.8 ml). The mixture was stirred at rt for 45 Min, filtered and the salts washed with THF (8 ml). The

filtrates were concentrated and the residue purified by chromatography on silica ($\text{CH}_2\text{Cl}_2/\text{MeOH}$, 9:1) to afford the title compound (79 mg; 26%; $\text{MH}^+=239$).

Preparative Example 15

[0346]



Step A

[0347] A mixture of commercially available dibenzosuberone (1.5 g) and malonic acid (830 mg) was heated at 160-

170° C. for 2 h. A mixture of H₂O (5 ml) and 0.1 M HCl (5 ml) was added and the mixture cooled to rt. The mixture was diluted with EtOAc (100 ml) and H₂O (10 ml), the organic phase separated, dried over MgSO₄ and concentrated. The residue was purified by chromatography on silica (CH₂Cl₂/acetone, 98:2→CH₂Cl₂/acetone, 9:1) to afford the title compound (775 mg; 43%; MNa⁺=273).

Step B

[0348] A mixture of title compound from Step A above (775 mg) and triethylamine (0.59 ml) in THF (20 ml) was cooled to -40° C. and treated with isobutylchloroformate. After stirring at -40° C. for 1 h, the mixture was filtered and the salts washed with THF (5 ml). The filtrates were then treated at 0° C. with 25% NH₄OH (15 ml) for 1 h 30 min. The mixture was diluted with EtOAc (60 ml), the organic phase separated, dried over MgSO₄ and concentrated. The residue was treated with CHCl₃ (1.5 ml), the solvent removed by syringe and the residue dried to afford the title compound (677 mg; 88%; MH⁺=250).

Step C

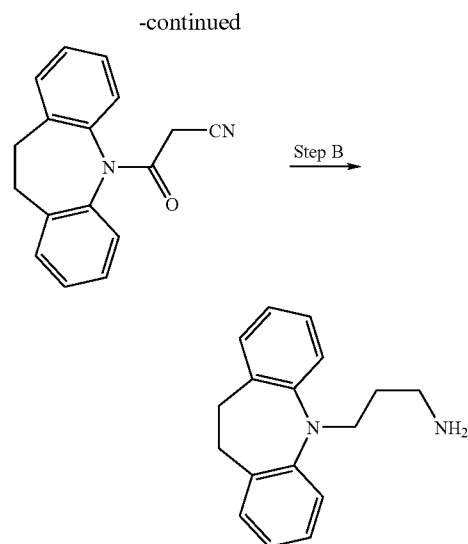
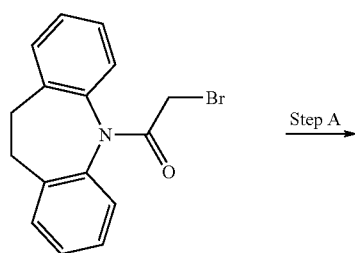
[0349] To a suspension of LiAlH₄ (513 mg) in THF (15 ml) was added a solution of the title compound from Step B above (677 mg) in THF (25 ml). The mixture was heated under reflux for 2 h. The mixture was cooled to 0° C., quenched with H₂O (0.65 ml) and diluted with 4 M NaOH-solution (2.5 ml). The mixture was stirred at rt for 45 Min, filtered and the salts washed with THF (15 ml). The filtrates were concentrated and the residue purified by chromatography on silica (CH₂Cl₂/MeOH, 9:1) to afford the title compound (560 mg; 88%; MH⁺=236).

Step D

[0350] The title compound from Step C above (350 mg) was dissolved in MeOH (15 ml) and 10% Pd/C (300 mg) and 1 M HCl (1.5 ml) were added. The mixture was hydrogenated overnight, filtered and the catalyst washed with MeOH (10 ml). The filtrates were concentrated and the residue dissolved in EtOAc (30 ml) and sat. NaHCO₃ (10 ml). The organic phase was separated and the aqueous phase extracted with EtOAc (20 ml). The combined organic phase was dried over MgSO₄ and concentrated to afford the title compound (232 mg; 66%; MH⁺=238).

Preparative Example 16

[0351]



Step A

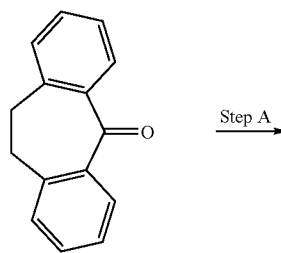
[0352] The intermediate from Preparative Example 14 Step A (1 g) was dissolved in DMA (6 ml) and treated with NaCN (368 mg). The mixture was heated at 60-70° C. overnight and diluted with EtOAc (50 ml) and H₂O (15 ml). The organic phase was separated, dried over MgSO₄ and concentrated. The residue was purified by chromatography on silica (CH₂Cl₂/acetone, 98:2) to afford the title compound (282 mg; 34%; MH⁺=263).

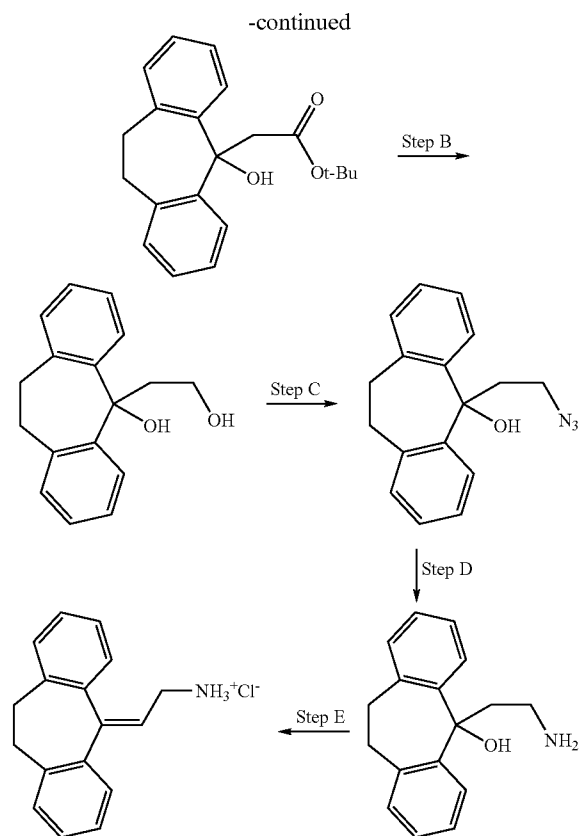
Step B

[0353] To a suspension of LiAlH₄ (123 mg) in THF (6 ml) was added a solution of the title compound from Step A above (282 mg) in THF (6 ml). The mixture was heated at 50° C. for 2 h, cooled to 0° C. and treated with H₂O (0.2 ml) and 4 M NaOH (0.8 ml). The mixture was stirred at rt for 45 Min, treated with MgSO₄ and filtered. The filtrate was concentrated and the residue purified by chromatography on silica (CH₂Cl₂/MeOH, 95:5→CH₂Cl₂/MeOH, 9:1) to afford the title compound (32 mg; 12%; MH⁺=253).

Preparative Example 17

[0354]





Step A

[0355] To a suspension of magnesium (701 mg) in Et₂O (7 ml) was slowly added ethylbromide (2.15 ml). After the formation of the Grignard reagent, the mixture was cooled to 5° C. and a solution of diethylamine (3 ml) in Et₂O (5 ml) was slowly added. The mixture was refluxed for 30 Min, cooled to 5° C. and treated with a mixture of commercially available dibenzosuberone (3 g) and tert-butylacetate (1.95 ml) in Et₂O (15 ml). The mixture was heated under reflux for 2 h, cooled to rt and poured onto ice-water containing an excess of NH₄Cl. The mixture was extracted with CH₂Cl₂ (3×100 ml), the organic phase dried over MgSO₄ and concentrated. The residue was purified by chromatography on silica (EtOAc/cyclohexane, 1:9) to afford the title compound (3.5 g; 75%; MNa⁺=347).

Step B

[0356] To a suspension of LiAlH₄ (346 mg) in THF (12 ml) was added a solution of the title compound from Step A above (2 g) in THF (12 ml). The mixture was heated under reflux for 2 h, cooled to 0° C. and treated 4 M NaOH (4.5 ml). The mixture was stirred at rt for 45 min and filtered. The filtrate was concentrated and the residue dissolved in EtOAc (100 ml), H₂O (10 ml) and sat. NH₄Cl (10 ml). The organic phase was separated, dried over MgSO₄ and concentrated. The residue was purified by chromatography on silica (EtOAc/cyclohexane, 3:7) to afford the title compound (937 mg; 60%; MNa⁺=277).

Step C

[0357] The title compound from Step B above (937 mg) was dissolved in benzene (1.5 ml) and pyridine (1.5 ml). The

mixture was cooled to 5° C. and treated with a solution of p-tosylchloride in benzene (1.5 ml). The mixture was stirred at rt for 7 h, diluted with EtOAc (40 ml) and washed with 0.1 M HCl (10 ml), sat. NaHCO₃ (10 ml) and brine (10 ml). The organic phase was separated, dried over MgSO₄ and concentrated. The crude intermediate was dissolved in DMA (9 ml) and treated with NaN₃ (1.2 g). The mixture was heated at 70° C. overnight and the DMA removed. The residue was dissolved in EtOAc (50 ml), sat. NaHCO₃ (10 ml) and brine (10 ml). The organic phase was separated, dried over MgSO₄ and concentrated. The residue was purified by chromatography on silica (EtOAc/cyclohexane, 1:4) to afford the title compound (704 mg; 68%; MNa⁺=302).

Step D

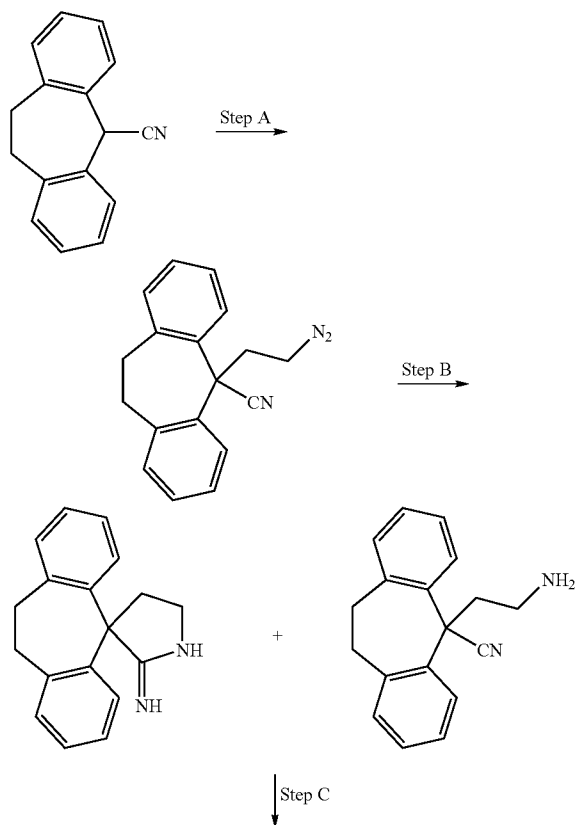
[0358] The title compound from Step C above (200 mg) was dissolved in MeOH (8 ml) and 10% Pd/C (40 mg) added. The mixture was hydrogenated for 1 h 30 Min, filtered and the catalyst washed with MeOH (10 ml). The filtrates were concentrated to afford the title compound (175 mg; 96%; MH⁺=254).

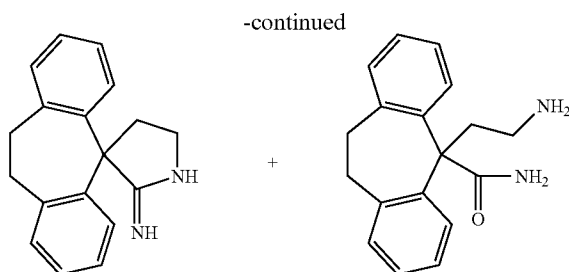
Step E

[0359] The title compound from Step D above (75 mg) was dissolved in EtOH (1 ml) and a 4 M solution of HCl in dioxane (1 ml) added. The mixture was stirred at rt for 12 h and concentrated. The residue was dissolved in EtOAc (20 ml) and sat. NaHCO₃ (5 ml). The organic phase was separated, dried over MgSO₄ and concentrated to afford the title compound (67 mg; 96%; M⁺—NH₃=219).

Preparative Example 18

[0360]





Step A

[0361] The title compound from Preparative Example 13 Step A (1.1 g) was dissolved in THF (5 ml) and added to a suspension of NaH (132 mg) in THF (5 ml). The mixture was heated under reflux for 1 h, cooled to rt and treated with 1,2-dibromoethane (0.9 ml) in THF (1 ml). The mixture was heated under reflux for 4 h, cooled to rt and filtered. The salts were washed with THF (5 ml) and the filtrates concentrated. The residue was dissolved in DMA (12 ml) and treated with NaN₃ (1.6 g). The mixture was heated at 60-70° C. overnight and the DMA removed. The residue was dissolved in EtOAc (40 ml) and H₂O (10 ml), the organic phase separated, dried over MgSO₄ and concentrated. The residue was purified by chromatography on silica (EtOAc/cyclohexane, 1:9) to afford the title compound (1.14 g; 78%; MH⁺=289).

Step B

[0362] The title compound from Step A above (510 mg) was dissolved in MeOH (20 ml) and 10% Pd/C (150 mg) and 2 M HCl (0.9 ml) added. The mixture was hydrogenated for 1 h 30 Min, filtered and the catalyst washed with MeOH (10 ml). The filtrates were concentrated and the residue purified by chromatography on silica (CH₂Cl₂/MeOH, 95:5 to CH₂Cl₂/MeOH, 4:1) to afford a mixture of the title compound and the cyclic amidine (450 mg; 96%; MH⁺=263).

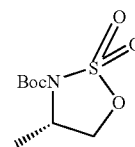
Step C

[0363] The title compounds from Step B above (350 mg) were treated with 2 ml 57% H₂SO₄. The mixture was heated at 100° C. for 3 h, cooled to rt and diluted with H₂O (10 ml). The mixture was made alkaline (pH~11) by adding 10% NaOH and extracted with EtOAc (3×30 ml). The organic phase was dried over MgSO₄ and concentrated. The residue was purified by chromatography on silica (CH₂Cl₂/MeOH, 9:1 to CH₂Cl₂/MeOH (7 M NH₃), 9:1) to afford a mixture of the title compound and the cyclic amidine (223 mg; 60%; MH⁺=281).

Preparative Example 19

[0364]

-continued



Step A

[0365] Commercially available (S)-2-aminopropan-1-ol (2.0 g) was dissolved in CH₂Cl₂ (20 ml) and Boc₂O (6.4 g) was added. After stirring for 4 h at room temperature the solvent was removed to afford the title compound (4.7 g, 99%).

[0366] ¹H-NMR δ (CDCl₃): 1.10 (s, 3H), 1.50 (s, 9H), 2.40 (s, 1H), 3.45-3.70 (m, 2H), 3.75-3.80 (m, 1H), 4.80 (s, 1H).

Step B

[0367] Imidazole (4.1 g) was dissolved in CH₂Cl₂ (50 ml) and cooled to 0° C. Thionyl chloride (1.3 ml) dissolved in CH₂Cl₂ (10 ml) was added dropwise and the resulting suspension was allowed to warm to rt. Stirring was continued for 1 h at rt and then the mixture was cooled to -78° C. A solution of the title compound from Step A above (1.8 g) in CH₂Cl₂ (50 ml) was added over a period of 1 h and the resulting mixture was allowed to warm to rt and stirred overnight. The mixture was filtered through celite and the filter aid was washed well with CH₂Cl₂. The organic phase was diluted with CH₂Cl₂, washed with water and brine, dried over MgSO₄, filtered and concentrated to a volume of approx. 100 ml.

[0368] A solution of NaIO₄ (4.3 g) in water (100 ml) was added and the mixture was cooled to 0° C. Ru(IV)O₂ hydrate (150 mg) was added and the black suspension was stirred for 2 h at 0° C. It was then warmed to rt and stirred overnight. The mixture was filtered through celite and the filtrate was extracted with CH₂Cl₂. The combined organic phase was washed with brine, dried and filtered. Treatment of the filtrate with activated charcoal (2 g) for 30 min removed traces of ruthenium. The mixture was filtered again and evaporated to yield the title compound (1.5 g, 63%).

[0369] ¹H-NMR δ (CDCl₃): 1.45 (s, 3H), 1.49 (s, 9H), 4.14 (dd, 1H), 4.29-4.42 (m, 1H), 4.61 (dd, 1H).

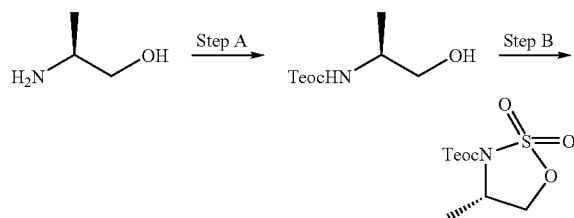
Preparative Example 20

[0370] The title compound from Preparative Example 20 was prepared according to the procedure described in Preparative Example 19 using the aminoalcohol as indicated in the Table below.

Preparative Example	Aminoalcohol	Product	1. Yield 2. ¹ H-NMR
20			1. 69% 2. ¹ H-NMR δ (CDCl ₃): 1.45 (s, 3 H), 1.49 (s, 9 H), 4.14 (dd, 1 H), 4.29-4.42 (m, 1 H), 4.61 (dd, 1 H).

Preparative Example 21

[0371]



Step A

[0372] To a stirred solution of the commercially available 2-(S)-amino propanol (17.4 g) in water (200 ml) was added a solution of triethylamine (32 ml) in dioxane (200 ml). To the solution was added commercially available 1-[2-(Trimethylsilyl)ethoxy-carbonyloxy]pyrrolidin-2,5-dione (60 g). The mixture was stirred at rt overnight, then diluted with water (200 ml), acidified with 1 N HCl, and extracted with Et₂O (2×500 ml). The combined organic phase was washed with brine, dried over MgSO₄ and evaporated to afford the title compound (44.2 g; 87%).

[0373] ¹H-NMR δ (CDCl₃): 0.02 (s, 9H), 0.90-1.05 (m, 2H), 1.20 (d, 3H), 2.80 (br s, 1H), 3.40-3.80 (m, 3H), 4.10-4.20 (m, 2H), 4.85 (s, 1H).

Step B

[0374] Imidazole (96 g) was dissolved in CH₂Cl₂ (1200 ml) and cooled to 0° C. Thionyl chloride (30.8 ml) was diluted with CH₂Cl₂ (600 ml) and added dropwise. The resulting suspension was allowed to warm to rt. Stirring was continued for 1 h at rt and then the mixture was cooled to -78° C. A solution of the title compound from Step A above (44.2 g) in CH₂Cl₂ (1200 ml) was added over a period of 1 h and the resulting mixture was allowed to warm to rt and stirred overnight. The mixture was filtered through celite, the filter aid was washed well with CH₂Cl₂. The organic phase was washed with water (2×700 ml), dried over MgSO₄, filtered and concentrated to a volume of approx. 1000 ml.

[0375] A solution of NaIO₄ (100 g) in water (1000 ml) was added and the mixture was cooled to 0° C. RuO₂×H₂O (1 g) was added and the black suspension was stirred for 2 h at 0° C. It was then warmed to rt and stirred overnight. The phases were separated and the organic phase was treated with granulated charcoal (~20 g). The mixture was stirred for approx. 1 h, filtered through celite and the filtrate was dried with MgSO₄, filtered and evaporated to yield the title compound (50.7 g, 89%).

[0376] ¹H-NMR δ (CDCl₃): 0.02 (s, 9H), 1.00-1.15 (m, 2H), 1.50 (d, 3H), 4.15 (dd, 1H), 4.35-4.45 (m, 3H), 4.65 (dd, 1H).

Preparative Example 22-23

[0377] Following a similar procedure as that described in Preparative Example 21 but using the aminoalcohols as indicated in the Table below, the title compounds were obtained.

Preparative Example	Aminoalcohol	Product	1. Yield 2. ¹ H-NMR
22			1. 58% 2. ¹ H-NMR δ (CDCl ₃): 0.02 (s, 9 H), 1.00-1.15 (m, 2 H), 4.00-4.10 (m, 2 H), 4.25-4.40 (m, 2 H), 4.55-4.65 (m, 2 H).
23			1. 32% (M + Na) ⁺ = 318

Preparative Example 24-46

[0378] If one were to follow a similar procedure as that described in Preparative Example 21 but using the aminoalcohols as indicated in the Table below, one would obtain the desired products.

Preparative Example	Aminoalcohol	Product
24		
25		
26		
27		

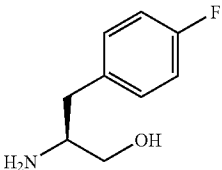
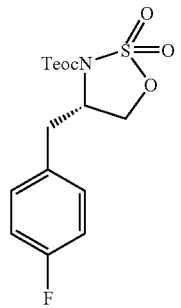
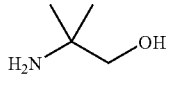
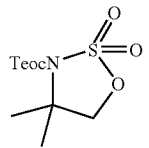
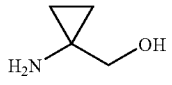
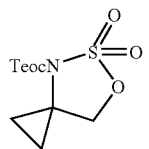
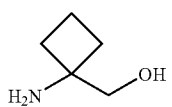
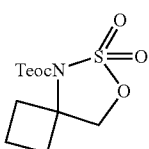
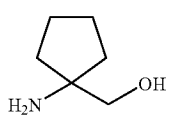
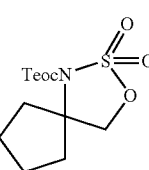
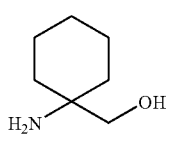
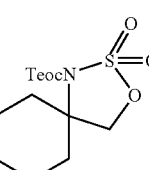
-continued

Preparative Example	Aminoalcohol	Product
28		
29		
30		
31		
32		
33		
34		
35		

-continued

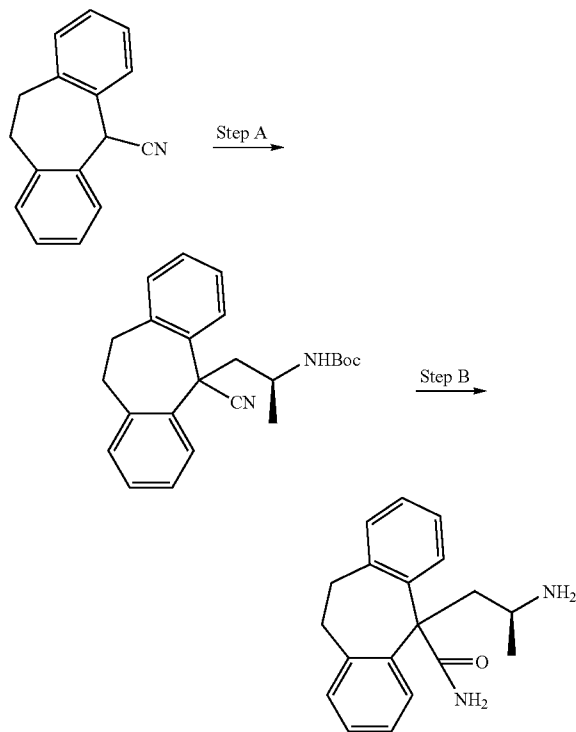
Preparative Example	Aminoalcohol	Product
36		
37		
38		
39		
40		

-continued

Preparative Example	Aminoalcohol	Product
41		
42		
43		
44		
45		
46		

Preparative Example 47

[0379]



Step A

[0380] A suspension of NaH (132 mg) in THF (10 ml) was added to a solution of Preparative Example 13 Step A (1.1 g) in THF (20 ml) and heated at 60° C. for 1 h. Then the mixture was cooled to 0° C. and a solution of Preparative Example 19 (1.2 g) in THF (10 ml) was added. The suspension was heated at 60° C. for 4 h and then diluted with ethyl acetate. The organic phase was washed with water, brine and dried over MgSO₄. Removal of the solvents and column chromatography (EtOAc/hexane, 1:4) afford the title compound (1.7 g, 90%, MH⁺=377).

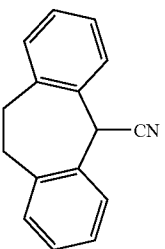
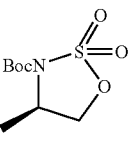
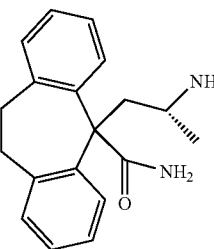
Step B

[0381] The title compound from Step A above (1.5 g) was dissolved in 57% H₂SO₄ and the solution was heated at 100° C. for 2 h. The mixture was diluted with water and extracted with ethyl acetate. The organic phase was discarded and 50%-aqueous KOH solution added to the aqueous phase until pH>8. The aqueous phase was extracted with ethyl acetate (2×75 ml). The organic phase was washed with water, brine, dried over MgSO₄ and evaporated to afford the title compound. (600 mg, 53%).

[0382] ¹H-NMR δ (CDCl₃): 0.95 (d, 3H), 1.82 (s, 2H), 2.37-2.58 (m, 2H), 2.82-2.92 (m, 1H), 3.18 (s, 4H), 5.60 (s, 2H), 7.08-7.24 (m, 6H), 7.40-7.48 (m, 2H).

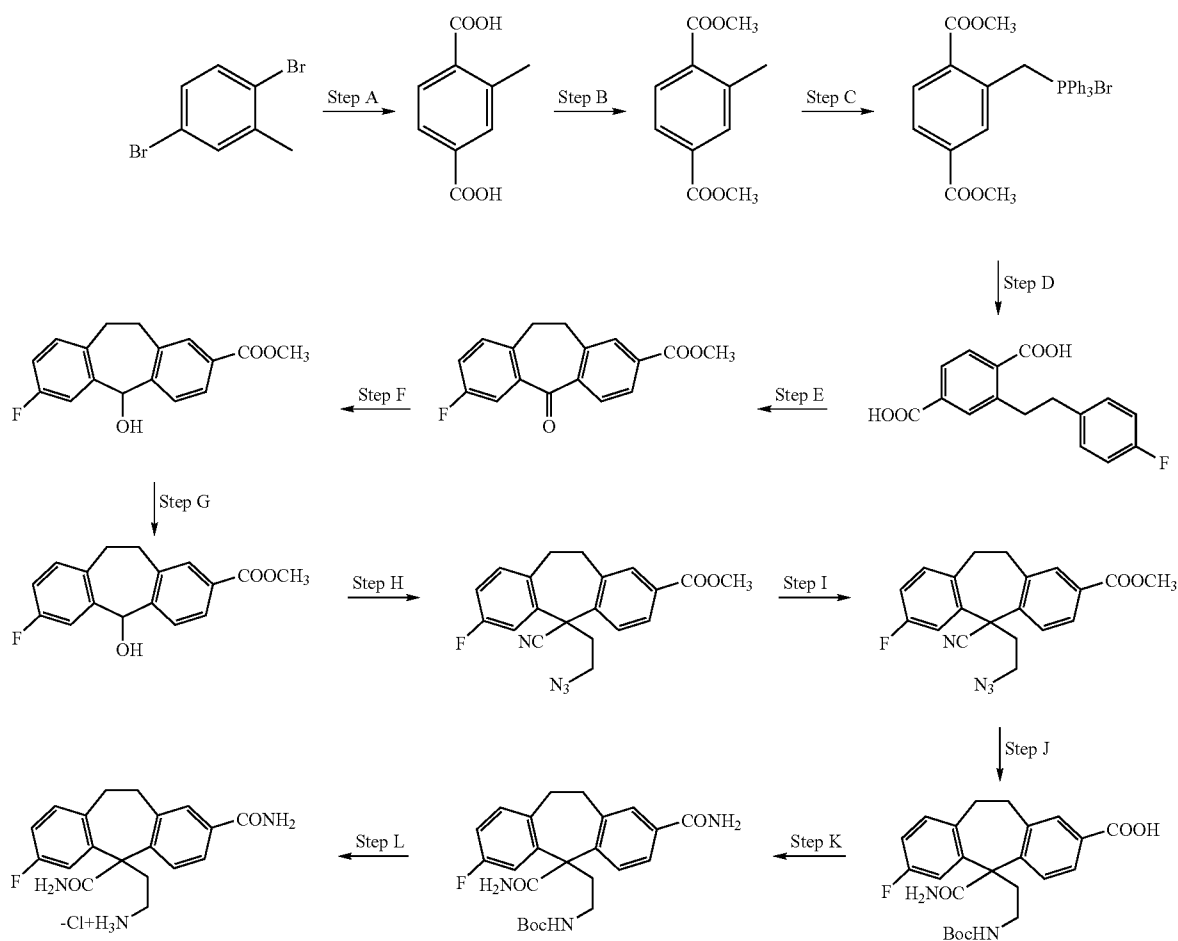
Preparative Example 48

[0383] The title compound was prepared according to the procedure described in Preparative Example 47 using the sulfamidate from Preparative Example 20 as indicated in the Table below.

Preparative Example	Nitrile	Sulfamate	Product	1. Yield 2. ¹ H-NMR
48				1. 80% 2. ¹ H-NMR δ (CDCl ₃): 0.95 (d, 3 H), 1.82 (s, 2 H), 2.37-2.58 (m, 2 H), 2.82-2.92 (m, 1 H), 3.18 (s, 4 H), 5.60 (s, 2 H), 7.08-7.24 (m, 6 H), 7.40-7.48 (m, 2 H).

Preparative Example 49

[0384]



Step A

[0385] Commercially available 2,5-dibromotoluene (8.28 ml) was dissolved in hexane (90 ml) and treated with a 1.6 M solution of butyllithium in hexane (160 ml). The mixture was heated at 60° C. for 20 h, cooled to rt and poured onto a

mixture of dry ice in Et₂O (750 ml). The mixture was allowed to warm to rt, filtered and the precipitate washed with 90 ml Et₂O. The precipitate was titrated with 140 ml glacial acetic acid to afford the title compound (10 g; 92%).

[0386] ¹H-NMR δ (DMSO-d₆) 2.58 (s, 3H), 7.80-7.90 (m, 3H)

Step B

[0387] The title compound from Step A above (13 g) was suspended in MeOH (300 ml) and slowly treated with thionyl chloride (15.7 ml). The mixture was heated under reflux for 2 h to become a clear solution. The solvents were concentrated to afford the title compound (13.3 g; 88%; MH⁺=209).

Step C

[0388] The title compound from Step B above (13.3 g) was dissolved in CCl₄ (500 ml) and commercially available N-bromosuccinimide (10.7 g) added. The mixture was heated to 80° C. and commercially available AIBN (327 mg) added. The mixture was then irradiated with a 100 W light bulb and heated at 100-105° C. for 2 h 30 min. The cooled mixture was filtered and the precipitate washed with 50 ml CCl₄. The filtrates were concentrated and the residue dissolved in CH₃CN (180 ml). The mixture was treated with triphenylphosphine (16 g) and heated under reflux for 3 h. The mixture was concentrated to ~100 ml and Et₂O (500 ml) added. The mixture was allowed to stand at rt for 30 Min, filtered and the precipitate washed with Et₂O (30 ml) to afford the title compound (20 g; 57%).

Step D

[0389] The title compound from Step C above (20 g) was suspended in CH₃CN (160 ml) and commercially available 4-Fluorobenzaldehyde (5.4 ml) added. The mixture was then treated with commercially available DBN (10 ml) and heated at 100° C. for 1 h. The mixture was concentrated to half its volume and poured into H₂O (150 ml). The mixture was extracted with EtOAc (2×150 ml), the organic phase washed with 5% HCl (2×75 ml), dried over MgSO₄ and concentrated. The residue was suspended in H₂O (240 ml) and MeOH (20 ml) and KOH (20 g) added. The mixture was heated at 100° C. for 16 h, cooled to rt and washed with CH₂Cl₂ (3×75 ml). The aqueous phase was acidified (pH~1) by adding conc. HCl, filtered, the precipitate washed with H₂O (20 ml) and air-dried. The residue was dissolved in MeOH (900 ml) and 10% Pd/C (1.5 g) added. The mixture was hydrogenated for 1 h, filtered, the catalyst washed with MeOH (50 ml) and concentrated to afford the title compound (8.6 g; 82%; MH⁺=289).

Step E

[0390] The title compound from Step D above (1.44 g) was suspended in sulfolane (9 ml) and treated with polyphosphoric acid (30 g). The mixture was heated under N₂ at 170-175° C. for 3 h and poured onto ice-water (150 ml). The mixture was stirred at rt for 1 h, extracted with EtOAc (2×150 ml), dried over MgSO₄ and concentrated. The residue was dissolved in MeOH (20 ml) and treated with thionyl chloride (1 ml). The mixture was heated under reflux for 1 h and concentrated. The residue was dissolved in Et₂O (100 ml) and washed with sat. NaHCO₃ (30 ml) and brine (30 ml). The organic phase was separated, dried over MgSO₄ and concentrated. The residue was purified by chromatography on silica (CH₂Cl₂) to afford the title compound (960 mg; 67%; MH⁺=285).

Step F

[0391] The title compound from Step E (1420 mg) was dissolved in CHCl₃ (20 ml) and MeOH (20 ml) and treated with NaBH₄ (230 mg). The mixture was stirred at rt for 1 h

and poured onto ice-water (150 ml). The mixture was extracted with EtOAc (2×150 ml), the organic phase dried over MgSO₄ and concentrated to afford the title compound (1420 mg; 99%, M⁺+Na=309).

Step G

[0392] The title compound from Step F above (1420 mg) was dissolved in THF (20 ml) and treated with thionyl chloride (0.91 ml). The mixture was stirred at rt for 16 h and concentrated without heating. The residue was dissolved in CH₃CN (17 ml) and treated with AgCN (785 mg). The mixture was heated at 90° C. for 2 h 30 Min, filtered and the salts washed with CH₃CN (40 ml). The filtrates were concentrated and the residue purified by chromatography on silica (CH₂Cl₂) to afford the title compound (1160 mg; 79%; MH⁺=296).

Step H

[0393] The title compound from Step G above (1327 mg) was dissolved in degassed THF (15 ml) and added to a suspension of NaH (119 mg) in degassed THF (5 ml). The mixture was heated at 90° C. for 1 h 15 min and cooled to rt. The mixture was then treated with 1,2-dibromoethane (0.81 ml) in THF (1 ml) and the mixture was heated at 90° C. for 4 h 30 min. The mixture was cooled to rt, diluted with 100 ml EtOAc, 10 ml brine and 10 ml sat. NH₄Cl. The organic phase was separated, dried over MgSO₄ and concentrated. The residue was dissolved in DMA (10 ml) and treated with NaN₃ (720 mg). The mixture was heated at 60° C. for 16 h and diluted with EtOAc (100 ml) and brine (15 ml). The organic phase was separated, washed with 0.1 M HCl (15 ml) and brine (15 ml). The organic phase was dried over MgSO₄, concentrated and the residue purified by chromatography on silica (EtOAc/cyclohexane, 1:4) to afford the title compound (931 mg; 57%; MH⁺=365).

Step I

[0394] The title compound from Step H above (1050 mg) was dissolved in MeOH (40 ml). The mixture was treated with concentrated HCl (0.25 ml) and 10% Pd/C (250 mg). The mixture was hydrogenated for 1 h, filtered and the catalyst washed with MeOH (20 ml). The filtrates were concentrated to afford a mixture of the title compound and the cyclic amidine in a 9:1 ratio (950 mg; 97%; MH⁺=339).

Step J

[0395] The title compounds from Step I above (950 mg) were treated with 57% H₂SO₄ (5 ml) and heated under N₂ at 90° C. for 3 h. The mixture was cooled, diluted with H₂O (80 ml) and made alkaline (pH~10) by adding 50% NaOH. The mixture was washed with EtOAc (20 ml) and the aqueous phase diluted with dioxane (40 ml). The mixture was treated with an excess of Boc₂O and stirred at rt for 16 h while the pH was kept at pH~10.0. The mixture was acidified to pH~4.0 by adding 1 M HCl and extracted with EtOAc (2×150 ml). The organic phase was dried over MgSO₄ and concentrated. The residue was purified by chromatography on silica (CH₂Cl₂/MeOH, 9:1) to elute the cyclic amidine side product, followed by CH₂Cl₂/MeOH (4:1) to afford the title compound (282 mg, 23%; MNa⁺=465).

Step K

[0396] The title compound from Step J above (135 mg) was dissolved in THF (6 ml) and triethylamine (0.056 ml). The

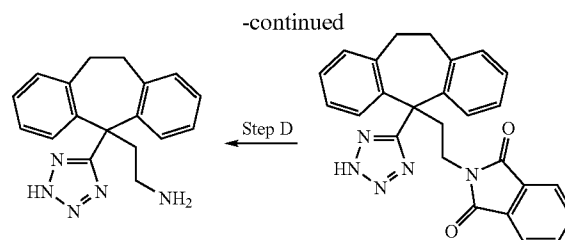
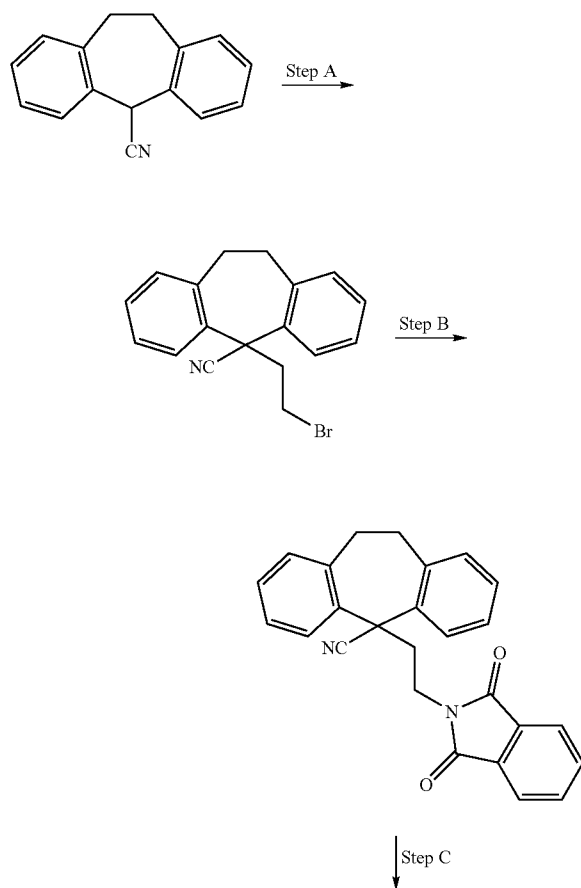
mixture was cooled to -40°C . and treated with ethyl chloroformate (0.031 ml). The mixture was stirred at -40°C . for 1 h, diluted with 4 ml THF and treated at 0°C . with 33% aqueous ammonia solution (10 ml). The mixture was stirred at 0°C . for 1 h and then 1 h at rt. The mixture was diluted with EtOAc (80 ml) and washed with brine (25 ml), sat. NH_4Cl (25 ml) and brine (25 ml). The organic phase was dried over MgSO_4 and concentrated. The residue was purified by chromatography on silica ($\text{CH}_2\text{Cl}_2/\text{MeOH}$, 9:1) to afford the title compound (97 mg, 72%, $\text{MNa}^+=464$).

Step L

[0397] The title compound from Step K above (94 mg) was treated with 4 M solution of HCl in dioxane (2.5 ml) and the flask was agitated for 30 min. The mixture was concentrated and the residue dissolved in 5 ml H_2O . The mixture was filtered through a Millex VV (0.1 μM) filter unit and the filtrate concentrated to afford the title compound (65.8 mg, 82%, $\text{MH}^+=342$).

Preparative Example 50

[0398]



Step A

[0399] The title compound from Preparative Example 13 Step A (3.3 g) was dissolved in THF (5 ml) and slowly added to a suspension of NaH (540 mg) in THF (10 ml). The mixture was heated at reflux for 30 min, cooled to rt and treated with 1,2-dibromoethane (4 ml). The reaction was stirred at 60°C . overnight, cooled to rt and filtered. The solvent was removed affording the title compound (4.8 g; 98%).

[0400] $^1\text{HNMR}$ δ CDCl_3 2.9-3.2 (m, 6H), 3.2-3.4 (m, 2H), 7.1-7.3 (m, 6H), 7.9-8.0 (m, 2H)

Step B

[0401] The title compound from Step A above (1.5 g) and potassium phthalimide (13.8 g) were suspended in DMF (20 ml) and stirred at 100°C . overnight. The precipitate was removed and the reaction was concentrated in vacuum. Chromatography of the residue on silica (EtOAc/cyclohexane) afforded the title compound (1.4 g; 78%).

[0402] $^1\text{HNMR}$ δ CDCl_3 2.8-2.9 (m, 2H), 3.0-3.2 (m, 2H), 3.4-3.6 (m, 2H), 3.6-3.8 (m, 2H), 7.1-7.3 (m, 6H), 7.6-7.7 (m, 2H), 7.7-7.8 (m, 2H), 7.9-8.0 (m, 2H)

Step C

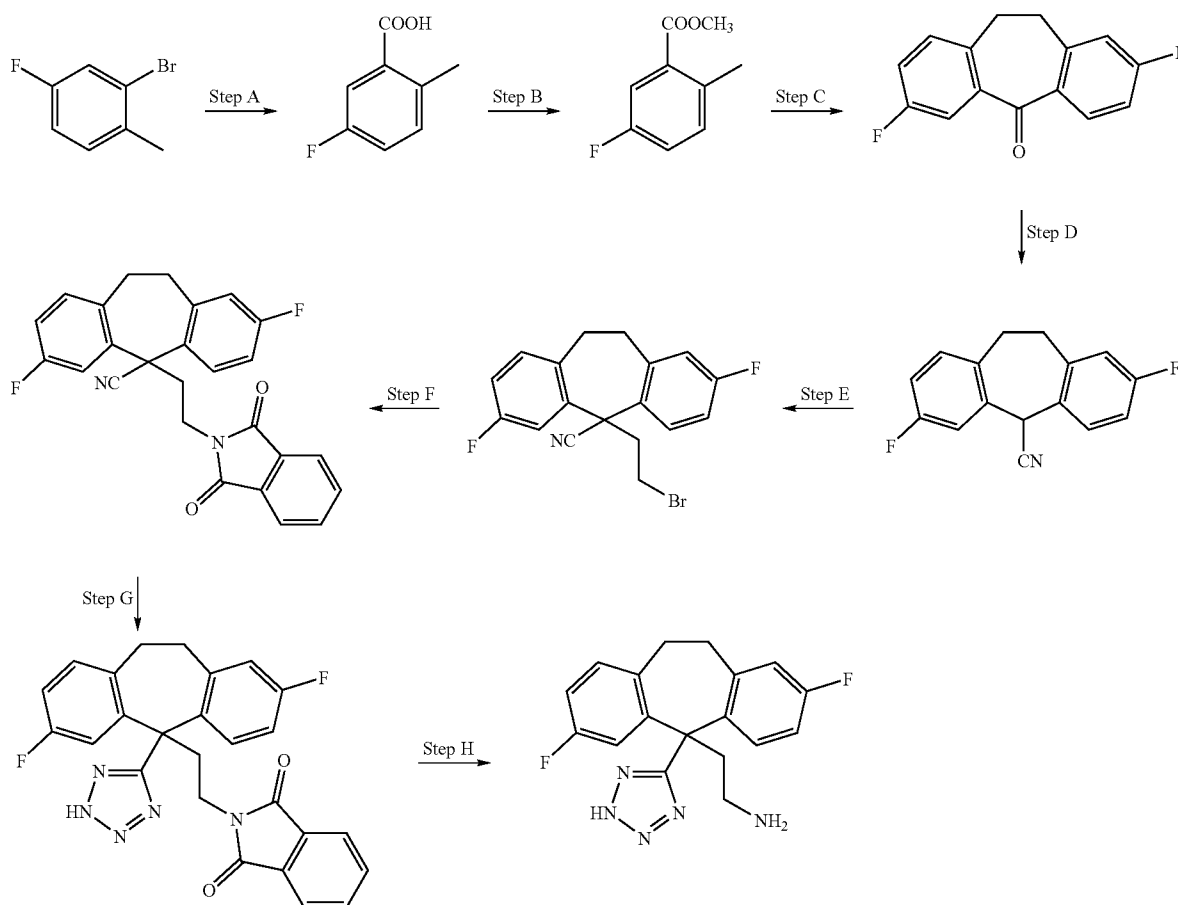
[0403] The title compound from Step B above (1.40 g) was dissolved in toluene (30 ml) and treated with dibutyltin oxide (446 mg) and trimethylsilylazide (2.3 ml). The mixture was heated under a N_2 atmosphere at 90°C . overnight. Additional dibutyltin oxide (200 mg) and trimethylsilylazide (2.3 ml) were added and the reaction was continued for 24 h at 90°C . The solvent was removed and the residue was treated with EtOAc (30 ml) and 1 N HCl (30 ml) at 50°C . for 1 h. The phases were separated and the organic phase was concentrated. The residue was purified by chromatography on silica (EtOAc/cyclohexane) to afford the title compound (600 mg, 39%, $\text{MH}^+=436$).

Step D

[0404] The title compound from Step C above (200 mg) was dissolved in ethanol (5 ml) and treated with hydrazine hydrate (100 mg) at rt. The solution was heated at 80°C . for 2 h and then stirred for 1 h at rt. The reaction was filtered and the filtrate was concentrated. The residue was treated with CHCl_3 and filtered again. The filtrate was concentrated to afford the title compound (60 mg, 43%, $\text{MH}^+=306$).

Preparative Example 51

[0405]



Step A

[0406] Commercially available 2-bromo-4-fluorotoluene (5 g) was diluted with diethyl ether (10 ml). About $\frac{1}{3}$ of the resulting solution was added to magnesium turnings (761 mg) which were overlaid with Et₂O (25 ml). The remaining 2-bromo-4-fluorotoluene solution was added dropwise after the reaction started. The reaction was kept at reflux for 2 h. The Grignard reagent was poured onto a mixture of crushed dry ice in Et₂O (750 ml). The resulting mixture was allowed to warm to rt. The solvent was removed, the resulting residue was treated with EtOAc (100 ml) and extracted with aqueous 1 N HCl (100 ml). The organic phase was dried over MgSO₄, filtered and concentrated to afford the title compound (2.3 g; 56%).

[0407] ¹H-NMR δ CDCl₃ 2.5 (s, 3H), 7.0-7.2 (m, 2H), 7.7 (m, 1H)

Step B

[0408] The title compound from Step A above (2.3 g) was dissolved in THF (50 ml). Methyl iodide (0.95 ml) and N,N-diisopropylethylamine (3.2 ml) were added. The reaction was

stirred at rt for 2 h. The reaction mixture was filtered and concentrated to afford the title compound (2.3 g; 90%).

[0409] ¹H-NMR δ CDCl₃ 2.6 (s, 3H), 3.9 (s, 3H), 7.0-7.2 (m, 2H), 7.6-7.7 (m, 1H)

Step C

[0410] The title compound from Step B above (8.9 g) and commercially available N-bromosuccinimide (14 g) were suspended in CCl₄ (500 ml). The mixture was heated to 80° C. and AIBN (270 mg) added. The mixture was irradiated with a 100 W light bulb and heated at 100-105° C. for 3.5 h. The cooled mixture was filtered. The filtrate was concentrated and the residue dissolved in CH₃CN (150 ml). The mixture was treated with triphenylphosphine (14 g), heated under reflux for 3 h and then concentrated. The residue was suspended in CH₃CN (160 ml) and treated with commercially available 3-fluorobenzaldehyde (6.5 g) and DBN (13 ml). The mixture was heated under reflux for 3 h. The reaction was concentrated to half its volume and poured into H₂O (150 ml). The mixture was extracted with EtOAc (3×150 ml), the organic phase separated and concentrated. The residue was suspended in 1:1 H₂O/MeOH-mixture (100 ml) and treated with KOH (30 g). The mixture was stirred at 60° C. overnight,

cooled to rt and washed with CHCl_3 (3×100 ml). The aqueous phase was acidified (pH~1) by adding conc. HCl and extracted with EtOAc. The organic phase was separated and concentrated. The crude residue was suspended in sulfolane (20 ml) and treated with polyphosphoric acid (25 g). The mixture was heated under N_2 at 200° C. for 2 h, poured onto ice-water (150 ml) and stirred at rt overnight. The mixture was extracted with EtOAc and concentrated. The residue was dissolved in Et_2O and extracted with H_2O . The organic phase was separated, dried over MgSO_4 and concentrated. The residue was purified by chromatography on silica (EtOAc/Cyclohexane) to afford the title compound (4.0 g; 31%; $\text{MH}^+=245$).

Step D

[0411] The title compound from Step C above (5.4 g) was dissolved in CHCl_3 (5 ml) and MeOH (30 ml) and treated with NaBH_4 (1.4 g). The mixture was stirred at rt for 1 h and concentrated. The residue was suspended in CHCl_3 (50 ml) and extracted with aqueous HCl (50 ml; pH=1). The organic phase was separated, concentrated, then resuspended in toluene and concentrated again. The residue was dissolved in toluene (50 ml). SOCl_2 (3.94 ml) was added at 0° C. The reaction was stirred overnight at RT. The solvent was removed and the remaining material was suspended in toluene and concentrated. The residue was dissolved in CH_3CN (50 ml) and treated with AgCN (2.96 g). The mixture was heated at reflux for 2 h and then stirred at 60° C. overnight. The mixture was filtered and the filtrate concentrated. The residue was purified by chromatography on silica (EtOAc/Cyclohexane) to afford the title compound (4.4 g; 78%).

[0412] $^1\text{H-NMR}$ δ CDCl_3 3.1-3.2 (m, 4H), 5.3 (s, 1H), 6.7-6.9 (m, 3H), 7.0-7.2 (m, 2H), 7.4 (m, 1H)

Step E

[0413] The title compound from Step D above (1.5 g) was dissolved in THF (5 ml) and slowly added at rt to a suspension of NaH (212 mg) in THF (10 ml). The mixture was heated at 60° C. for 30 min, then cooled to 0° C. and treated with 1,2-dibromoethane (2.3 ml). The reaction was stirred at 60° C. for 3 h, cooled to rt and filtered. The filtrate was concentrated to afford the title compound (2.1 g; 99%).

[0414] $^1\text{H-NMR}$ δ CDCl_3 2.8-3.0 (m, 4H), 3.0-3.2 (m, 2H), 3.2-3.4 (m, 2H), 6.8-7.2 (m, 4H), 7.6 (m, 1H), 7.8-7.9 (m, 1H)

Step F

[0415] The title compound from Step E above (2.1 g) and potassium phthalimide (5.4 g) were suspended in DMF (30 ml) and stirred at 60° C. overnight. The solvent was removed and the residue dissolved in CHCl_3 , filtrated and concentrated. The residue was purified by chromatography on silica (EtOAc/cyclohexane) to afford the title compound (1.91 g; 76%)

[0416] $^1\text{HNMR}$ δ CDCl_3 2.8-3.2 (m, 4H), 3.4-3.6 (m, 2H), 3.7-3.9 (m, 2H), 6.8-7.0 (m, 3H), 7.1-7.2 (m, 1H), 7.7-8.0 (m, 6H)

Step G

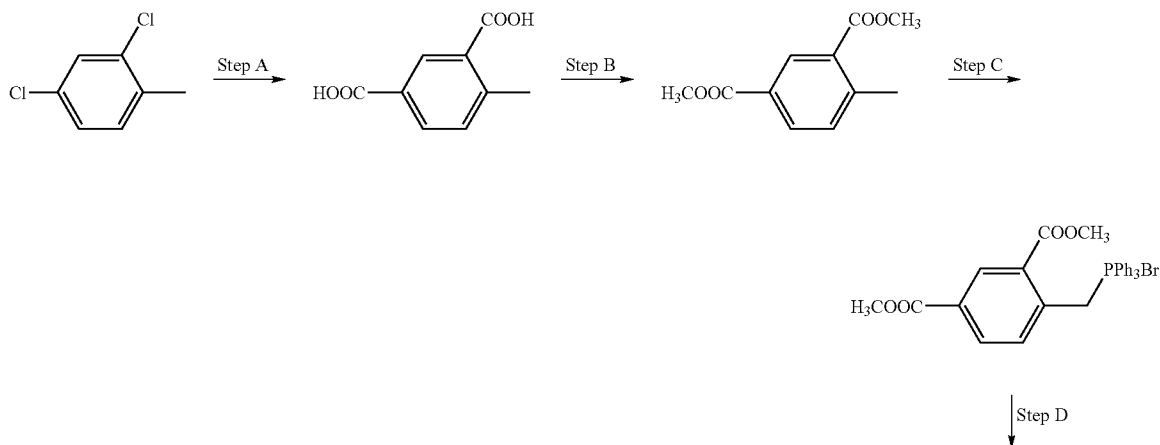
[0417] The title compound from Step F (1.90 g) was dissolved in toluene (20 ml) and treated with dibutyltin oxide (553 mg) and trimethylsilylazide (3.7 ml). The mixture was heated under a N_2 atmosphere at 90° C. for 4 d. The reaction was quenched with aqueous 1 N HCl (20 ml) and stirred for 1 h at 50° C. The phases were separated, the aqueous phase was extracted with toluene and the combined organic phase concentrated. The residue was purified by chromatography on silica (EtOAc/cyclohexane) to afford the title compound (600 mg, 33%, $\text{MH}^+=472$).

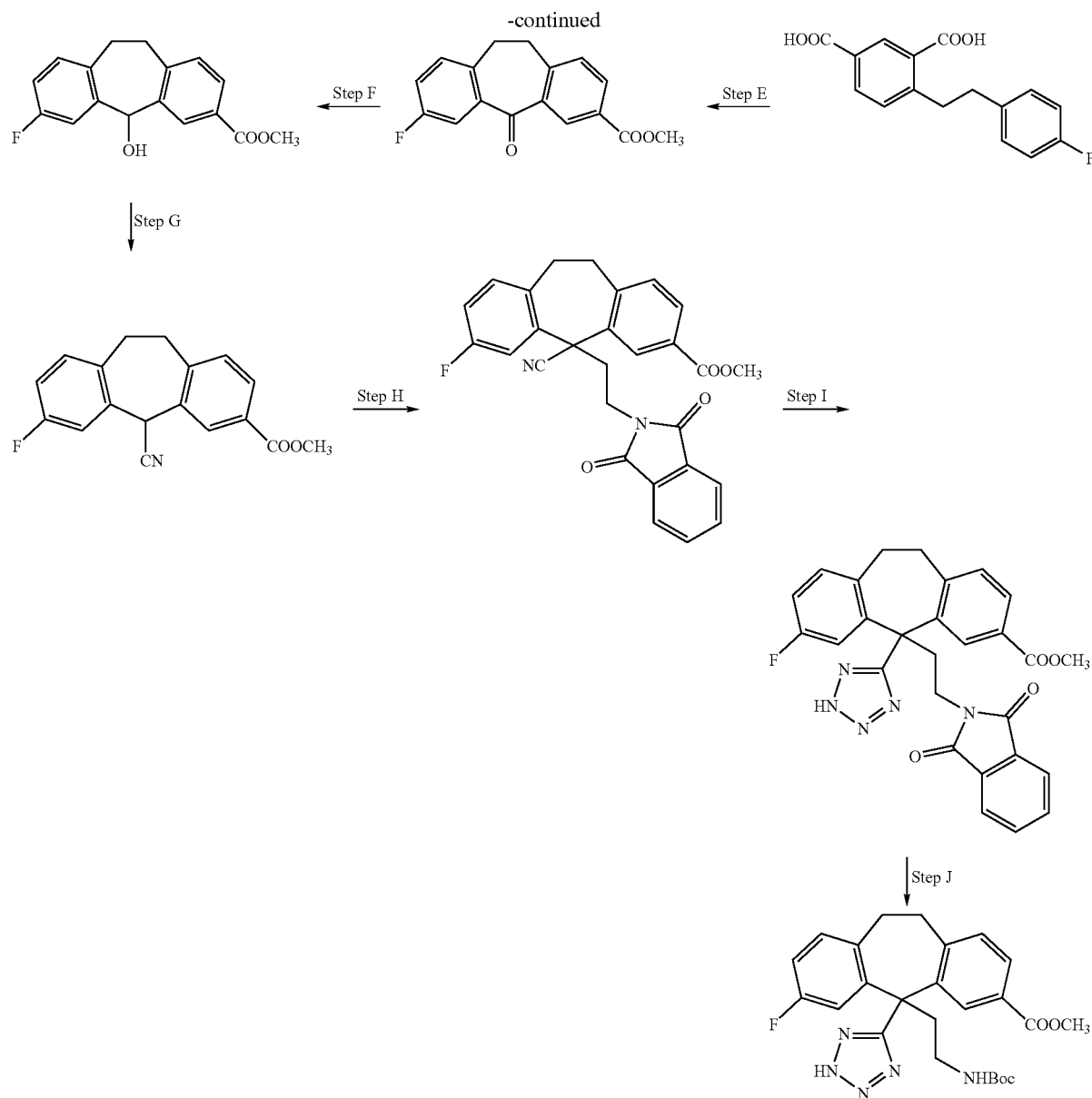
Step H

[0418] The title compound from Step G above (300 mg) was dissolved in ethanol (5 ml) and treated with hydrazine hydrate (127 mg). The solution was stirred at 80° C. for 2 h and subsequently stirred for 1 h at rt. The solvent was removed and the residue treated with 1 N HCl (20 ml) and CHCl_3 (10 ml). The aqueous phase was separated, filtered and concentrated affording the title compound (240 mg, 100% $\text{MH}^+=342$).

Preparative Example 52

[0419]





Step A

[0420] Commercially available 2,4-dichlorotoluene (24.6 g) and dry copper(I) cyanide (50 g) in N-methylpyrrolidone (130 ml) were heated under reflux (200-216° C.) for 4 d. While hot (110° C.), the mixture was poured into a flask containing 33% aq. NH_4OH solution (390 ml) and toluene (100 ml) and stirred to break up the lumps. After the mixture was cooled to rt, Et_2O (100 ml) was added and filtered through cloth. The precipitate was washed (2×100 ml $\text{Et}_2\text{O}/\text{CHCl}_3$ 1:1). The dark filtrate was poured into a separatory funnel and the phases were separated with the aid of additional Et_2O (100 ml). The aqueous phase was extracted with $\text{Et}_2\text{O}/\text{CHCl}_3$ 1:1 (2×100 ml). The combined organic phases were washed with 10% NH_4OH solution (4×110 ml, until the basic phase was no longer blue), with H_2O (100 ml), and brine

(100 ml). The organic phase was separated, dried over MgSO_4 and concentrated. The residue was mixed with NaOH (24.8 g) and diethylene glycol (275 ml) was added together with a few drops of H_2O . The mixture was heated at 215-220° C. overnight. The cooled mixture was diluted with H_2O (220 ml) and acidified to pH 1 with 10% aq. HCl . The suspension was filtered and the precipitate washed with 0.1 N HCl (50 ml). The solid was crystallised from glacial acetic acid to afford the title compound (18.4 g, 78%; $\text{MH}^+=181$).

Step B

[0421] Following a similar procedure as that described in Preparative Example 49 Step B, the title compound from Step A above (22.1 g) was reacted to afford the title compound (30.0 g, 100%).

[0422] $^1\text{H-NMR}$ (CDCl_3) δ : 2.65 (s, 3H), 3.91 (s, 3H), 3.92 (s, 3H), 7.32 (d, 1H), 8.04 (dd, 1H), 8.56 (d, 1H).

Step C

[0423] Following a similar procedure as that described in Preparative Example 49 Step C, the title compound from Step B above (30.0 g) was reacted. Differing from the cited example, the final mixture was allowed to stand over the weekend to form the precipitate. After filtration, the crude title compound was obtained (38.0 g, 100%; $[\text{M-Br}]^+=469$).

Step D

[0424] Following a similar procedure as that described in Preparative Example 49 Step D, the title compound from Step C above (38.0 g) was reacted. Differing from the cited example, the hydrogenation was run for 2 days. (29.2 g, 77%; $\text{MH}^+=289$).

Step E

[0425] Following a similar procedure as that described in Preparative Example 49 Step E, the title compound from Step D above (4.32 g) was reacted and the title compound obtained (1.77 g, 41%; $\text{MH}^+=285$).

Step F

[0426] Following a similar procedure as that described in Preparative Example 49 Step F, the title compound from Step E above (2.39 g) was reacted and the title compound obtained (2.45 g, 100%; $\text{MNa}^+=309$).

Step G

[0427] Following a similar procedure as that described in Preparative Example 49 Step G, the title compound from Step F above (3.07 g) was reacted and the title compound was obtained (2.17 g, 69%; $\text{MH}^+=296$).

Step H

[0428] The title compound from Step G above (2.17 g) was dissolved in THF (30 ml) and added to a suspension of NaH (250 mg) in THF (9 ml). The mixture was heated at 90°C . for 1 h 15 min and cooled to rt. The mixture was then treated with 1,2-dibromoethane (1.6 ml) in THF (3.7 ml) and the mixture was heated at 90°C . for 4 h 30 min. The mixture was cooled to rt, diluted with 200 ml EtOAc, 20 ml brine and 20 ml sat. NH_4Cl . The organic phase was separated, dried over MgSO_4 and the residue purified by chromatography on silica (CH_2Cl_2) to afford the bromoethyl intermediate (1.42 g, 50%; $[\text{MNH}_4]^+=419$) and starting material (636 mg, 24%). The bromoethyl compound (1.42 g) was dissolved in anhydrous DMF (18 ml) and treated with potassium phthalimide (1.96 g). The suspension was stirred at 80°C . overnight. The solvent was removed and the residue partitioned between EtOAc (50 ml), H_2O (50 ml) and brine (50 ml). The aqueous phase was extracted with EtOAc (2 \times 50 ml) and the combined organic phase dried over MgSO_4 and concentrated. The residue was purified by chromatography on silica ($\text{CH}_2\text{Cl}_2/\text{MeOH}$) to afford the title compound (1525 mg; 92%; $\text{MH}^+=469$).

Step I

[0429] The title compound from Step H above (1475 mg) was dissolved in anhydrous toluene (25 ml) and treated with

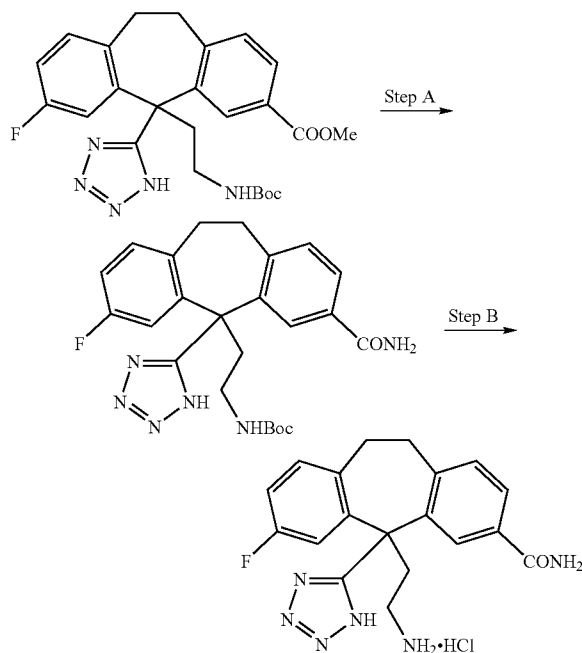
dibutyltin oxide (784 mg) and trimethylsilylazide (8.3 ml). The mixture was heated under a N_2 atmosphere at 90°C . for 3 days. The solvent was removed, the residue dissolved in MeOH (10 ml) and concentrated. The residue was partitioned between EtOAc (100 ml) and 10% NaHCO_3 (100 ml). The aqueous phase was extracted with EtOAc (2 \times 70 ml) and the combined organic phase dried over MgSO_4 and concentrated. The residue was purified by chromatography on silica ($\text{CH}_2\text{Cl}_2/\text{MeOH}$) to afford the title compound (1216 mg, 75%, $\text{MH}^+=512$).

Step J

[0430] The title compound from Step I above (1216 mg) was dissolved in anhydrous MeOH (14 ml) and Et_3N (0.66 ml). The mixture was cooled to 5°C . and $\text{N,N'$ -dimethylamino-propylamine (0.71 ml) added. The mixture was stirred at rt for 25 h and subsequently evaporated, toluene (10 ml) added, evaporated again and dried in HV. The residue was dissolved in dioxane (8 ml) and H_2O (8 ml). To the slightly turbid solution was added Boc_2O (2.6 g) and Et_3N (1.2 ml) and the mixture was stirred at rt overnight. After evaporation of the solvent, H_2O (20 ml) was added and the solution acidified to pH \sim 4.0 by adding 1 M HCl and the aqueous solution extracted with EtOAc (3 \times 50 ml). The combined organic phase was washed with brine (15 ml), separated, dried over MgSO_4 and concentrated. The residue was purified by chromatography on silica ($\text{CH}_2\text{Cl}_2/\text{MeOH}$) to afford the title compound (567 mg, 50%, $\text{MNa}^+=504$).

Preparative Example 53

[0431]



Step A

[0432] The title compound from Preparative Example 52 (215 mg) was dissolved in THF (4 ml) and 33% NH_4OH

solution (40 ml) was added. The solution was stirred in a closed vessel at 80° C. overnight. The reaction mixture was allowed to cool to rt and subsequently evaporated to dryness. The crude product, which consisted of a mixture of the amide ($MNa^+=489$) and the free acid ($MNa^+=490$), was dissolved in anhydrous THF (8.5 ml) and triethylamine (0.28 ml) added. The ensuing precipitate was dissolved by adding anhydrous CH_3CN (6 ml). The mixture was cooled to -40° C. and ethylchloroformate (0.17 ml) was slowly added. The mixture was stirred at -25° C. for 1 h and allowed to warm to 0° C. At 0° C. 7 M $NH_3/MeOH$ -solution (10 ml) was added and the mixture was stirred at 0° C. for 30 min and for 1 h at rt. The mixture was concentrated and the residue dissolved in H_2O (14 ml) and THF (3 ml). The pH was adjusted to pH~4.0 by adding 0.1 N HCl and the aqueous phase—after addition of brine (10 ml)—extracted with EtOAc containing 10% THF (4×33 ml) and CH_2Cl_2 containing 10% THF (1×25 ml)). The

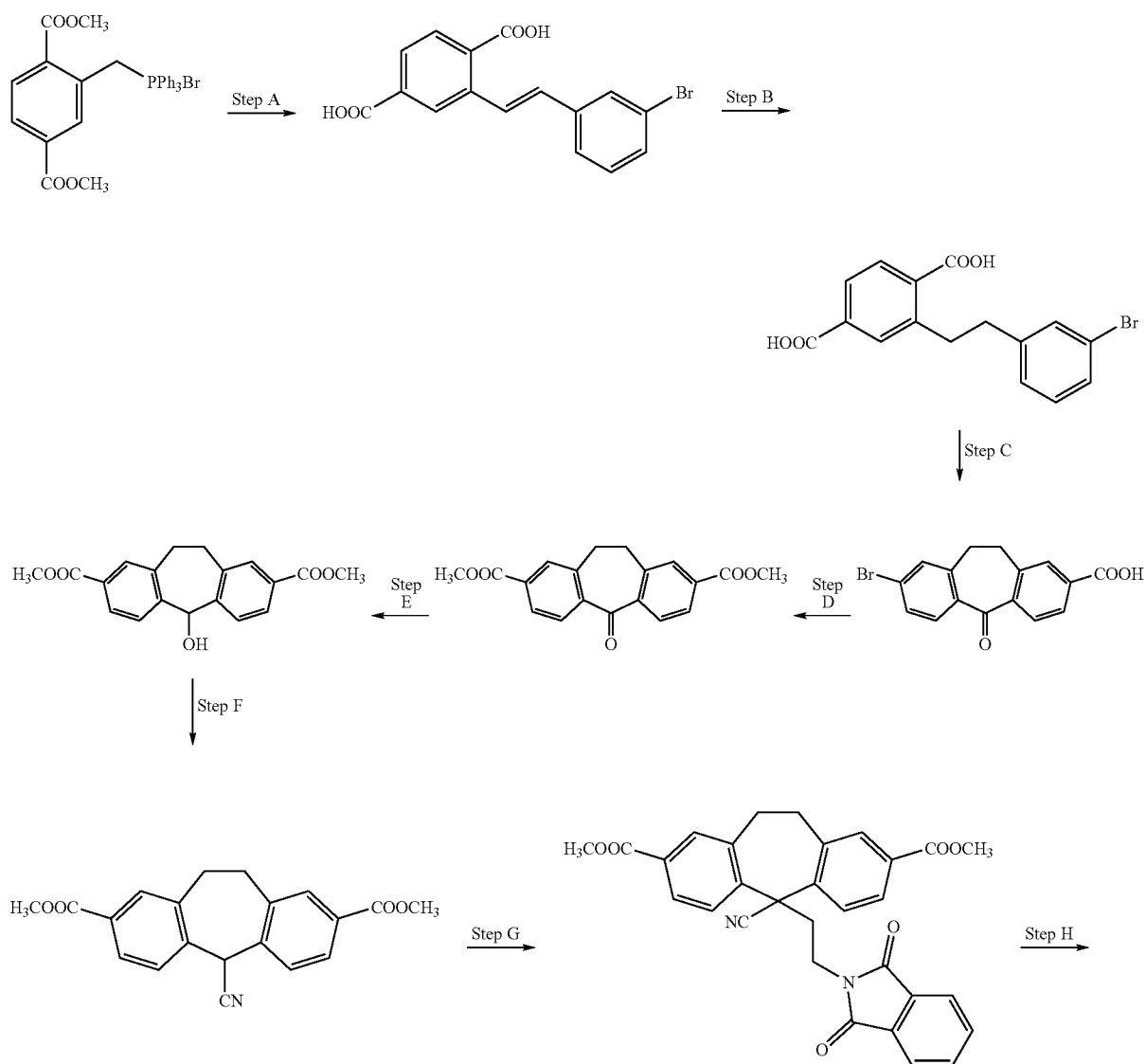
combined organic phase was washed with brine (15 ml), dried over $MgSO_4$ and concentrated to afford the title compound (241 mg; 100%, $MNa^+=489$).

Step B

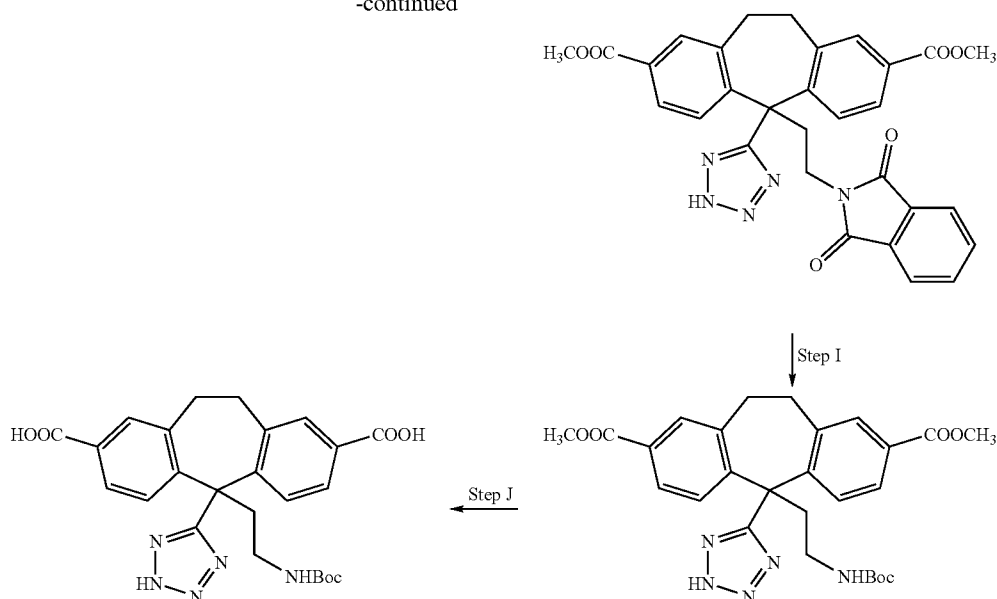
[0433] The title compound from Step A above (240 mg) was suspended/dissolved in $CH_2Cl_2/MeOH$ 4:1 (5 ml) and a 4 M solution of HCl in dioxane (7 ml) added after which a clear solution was obtained. The mixture was stirred at rt for 3 h and concentrated. The residue was partitioned between EtOAc containing 10% THF (25 ml) and 0.01 N HCl (25 ml). The organic phase was extracted with H_2O (25 ml) and 0.01 N HCl (25 ml). The combined aqueous phase was concentrated to afford the title compound (162 mg, 90%, $MH^+=367$).

Preparative Example 54

[0434]



-continued



Step A

[0435] The title compound from Preparative Example 49 Step C (47.6 g) was suspended in CH₃CN (350 ml) and commercially available 3-bromobenzaldehyde (13.9 ml) added. After the addition of DBN (24 ml), the mixture was heated at 100° C. for 1 h. The mixture was cooled and the precipitate collected by filtration to afford the trans-olefin (7.5 g). The mother liquor was concentrated to half its volume and poured into H₂O (300 ml). The mixture was extracted with EtOAc (2×300 ml), the organic phase washed with 5% HCl (2×80 ml), dried over MgSO₄ and concentrated. To this residue was added the trans olefin from above and the mixture was suspended in H₂O (500 ml), MeOH (60 ml) and dioxane (60 ml). After the addition of KOH (47 g), the mixture was heated at 60° C. for 16 h, cooled to rt and washed with CH₂Cl₂ (3×100 ml). The aqueous phase was made acidic (pH~1) by adding conc. HCl, filtered, the precipitate washed with H₂O (150 ml) and air-dried to afford the title compound as a mixture of cis/trans-olefins (26.5 g; 88%; MH⁺=347).

Step B

[0436] The title compound from Step A above (6 g) was dissolved in MeOH (450 ml) and EtOAc (150 ml). After the addition of a suspension of 5% Pt/C (2.5 g) in 10% HCl (5 ml) and MeOH (10 ml), the mixture was hydrogenated for 6 h. The mixture was filtered, the catalyst washed with MeOH (60 ml) and the filtrates evaporated to afford the title compound (5.5 g, 91%).

[0437] ¹HNMR δ (DMSO-d₆) δ 2.81-2.90 (m, 2H), 3.13-3.27 (m, 2H), 7.23-7.32 (m, 2H), 7.39-7.45 (m, 1H), 7.51 (s, 1H), 7.85-7.95 (m, 3H)

Step C

[0438] The title compound from Step B above (4 g) was suspended in sulfolane (9 ml) and treated with polyphosphoric acid (30 g). The mixture was heated under N₂ at 175-180°

C. for 2 h 30 min and poured into ice-water (250 ml). The mixture was stirred at rt overnight and the precipitate collected by filtration to afford the crude title compound (3.56 g; 94%; MH⁺=331).

Step D

[0439] The title compound from Step C above (3.5 g) was dissolved in N-methyl pyrrolidone (25 ml) and CuCN (900 mg) added. The mixture was heated at 200° C. for 8 h, cooled to rt and diluted with H₂O (200 ml) and 1 M HCl (50 ml). The mixture was extracted with EtOAc (3×100 ml) and the combined organic phase washed with H₂O (100 ml) and brine (100 ml). The organic phase was dried over MgSO₄ and evaporated. The residue was dissolved in dioxane (50 ml) and conc. HCl (50 ml) added. The mixture was heated at 90° C. for 18 h and the solvents evaporated. The residue was suspended in MeOH (75 ml), treated with SOCl₂ (1.5 ml) and heated under reflux for 1 h 30 min. The mixture was concentrated to half its volume, diluted with Et₂O (300 ml) and washed with sat. NaHCO₃ (80 ml) and brine (80 ml). The organic phase was separated, dried over MgSO₄ and evaporated. The residue was purified by chromatography on silica (EtOAc/hexane, 1:4) to afford the title compound (1040 mg; 27%; MH⁺=325).

Step E

[0440] The title compound from Step D above (1040 mg) was dissolved in CHCl₃ (15 ml) and MeOH (15 ml) and the NaBH₄ (150 mg) added. The mixture was stirred at rt for 1 h, diluted with ice water (80 ml) and extracted with EtOAc (2×100 ml). The organic phase was dried over MgSO₄ and concentrated. The residue was purified by chromatography on silica (CH₂Cl₂/acetone, 98:2->CH₂Cl₂/acetone, 95:5) to afford the title compound (817 mg, 78%, MN⁺=349).

Step F

[0441] The title compound from Step E above (817 mg) was dissolved in THF (10 ml) and treated with SOCl₂ (0.46

ml). The mixture was stirred at rt overnight and the solvents evaporated. The residue was dissolved in CH₃CN (10 ml) and benzene (5 ml) and added to a suspension of AgCN (406 mg) in CH₃CN (10 ml). The mixture was heated at 90° C. for 5 h, filtered and the salts washed with CH₃CN (10 ml). The filtrates were evaporated and the residue purified by chromatography on silica (CH₂Cl₂/acetone, 98:2) to afford the title compound (572 mg, 68%, MH⁺=336).

Step G

[0442] The title compound from Step F above (676 mg) was suspended in THF (20 ml) and DMF (5 ml) and treated under a N₂ atmosphere with NaH (106 mg). The mixture was heated at ~95° C. for 75 Min, cooled to rt and treated with a solution of 1,2-dibromoethane (0.7 ml) in THF (3 ml). The mixture was then heated at 95° C. for 10 h, cooled to rt and treated with sat. NH₄Cl (15 ml) and EtOAc (100 ml). The organic phase was separated, washed with brine (15 ml), dried over MgSO₄ and concentrated. The residue was dissolved in DMA (8 ml) and treated with potassium phthalimide (554 mg). The mixture was heated at 60° C. overnight, the solvent removed and the residue dissolved in EtOAc (50 ml) and H₂O (15 ml). The organic phase was separated, washed with brine (15 ml) and concentrated. The residue was purified by chromatography on silica (CH₂Cl₂/acetone, 98:2) to afford the title compound (740 mg, 72%, MNH₄⁺=526).

Step H

[0443] The title compound from Step G above (600 mg) was suspended in toluene (5 ml) and treated with dibutyltin oxide (138 mg) and trimethylsilylazide (1.45 ml). The mixture was heated under a N₂ atmosphere at 90-95° C. for 3 d and the solvent evaporated. The residue was suspended in MeOH (10 ml) and the solvent evaporated. The residue was dissolved in EtOAc (30 ml) water (10 ml). The organic phase was separated, dried over MgSO₄ and concentrated. The residue was purified by chromatography on silica (CH₂Cl₂/MeOH, 95:5) to afford the title compound (415 mg, 68%, MH⁺=552).

Step I

[0444] The title compound from Step H above (415 mg) was dissolved in MeOH (6 ml) and triethylamine (0.23 ml). The mixture was cooled to 0° C. and 3-dimethylaminopropylamine (0.23 ml) added. The mixture was stirred at 0° C. for 10 min and at rt overnight. The mixture was concentrated, dissolved in MeOH (10 ml), again concentrated and dried in HV. The residue was dissolved in dioxane (5 ml) and H₂O (5 ml) and the pH adjusted to pH=8-9 by adding 1 M KOH. The mixture was then treated with Boc₂O (870 mg) and stirred overnight. The mixture was adjusted to pH=4 by adding 1 M HCl and diluted with EtOAc (150 ml). The organic phase was separated and the aqueous phase extracted with EtOAc (2×75 ml). The combined organic phase was dried over MgSO₄ and concentrated. The residue was purified by chromatography on silica gel (CH₂Cl₂/MeOH, 95:5→4:1) to afford the title compound (227 mg, 58%, MH⁺=522).

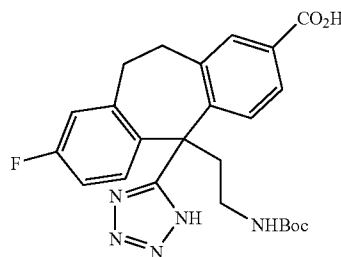
Step J

[0445] The title compound from Step I above (227 mg) was dissolved in dioxane (10 ml) and 1 M KOH (3.75 ml) added. The mixture was stirred at rt overnight and the pH adjusted to pH=4 by adding 1 M HCl. The mixture was extracted with

EtOAc, containing 10% THF (2×150 ml). The organic phase was separated, dried over MgSO₄ and concentrated to afford the title compound (177 mg, 82%; MH⁺=494).

Preparative Example 55

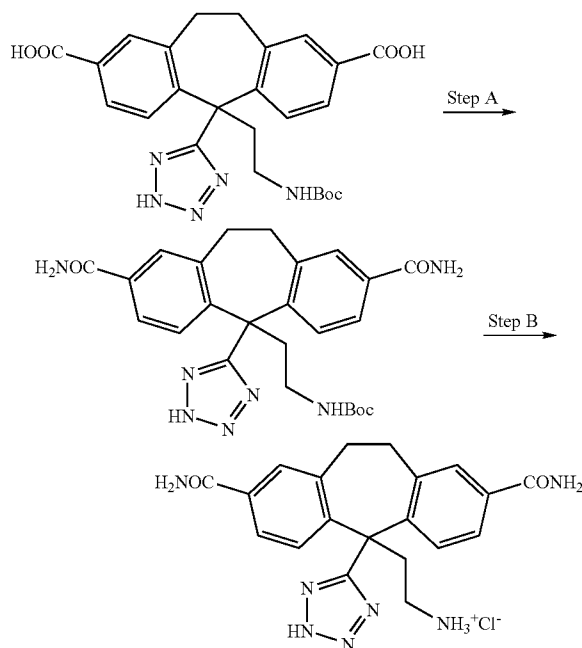
[0446]



[0447] If one were to follow a similar procedure as described in Preparative Example 54, but using 3-fluorobenzaldehyde in Step A and omitting Step D, one would obtain the desired compound.

Preparative Example 56

[0448]



Step A

[0449] The title compound from Preparative Example 54 (177 mg) was dissolved in THF (6 ml) and triethylamine (0.2 ml) added. The precipitate was dissolved/suspended by adding CH₃CN (3 ml). The mixture was cooled to -40° C. and ethylchloroformate (0.1 ml) was slowly added. The mixture was stirred at -25° C. for 1 h and allowed to warm to 0° C. At 0° C. 7 M NH₃/MeOH-solution (7 ml) was added and the

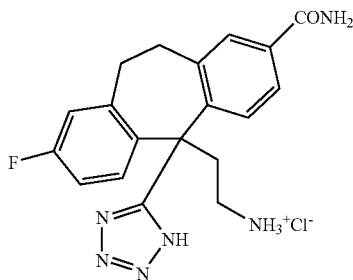
mixture was stirred at 0° C. for 30 min and 1 h at rt. The mixture was concentrated and the residue dissolved in H₂O (10 ml) and THF (2 ml). The pH was adjusted to pH~4.0 by adding 100 mM HCl and the aqueous phase extracted with EtOAc (4×30 ml) containing 10% THF. The organic phase was dried over MgSO₄ and concentrated to afford the title compound (110 mg; 62%, MNa⁺=514).

Step B

[0450] The title compound from Step A above (103 mg) was dissolved in THF (2 ml) and a 4 M solution of HCl in dioxane (5 ml) added. The mixture was stirred at rt for 2 h and concentrated. The residue was dissolved in H₂O (20 ml) and washed with EtOAc (2×8 ml). The aqueous phase was concentrated, the residue dissolved in 50 mM HCl (6 ml) and filtered through a Millex VV (0.1 μM) filter unit. The filtrate was concentrated to afford the title compound (90 mg, 94%, MH⁺=392).

Preparative Example 57

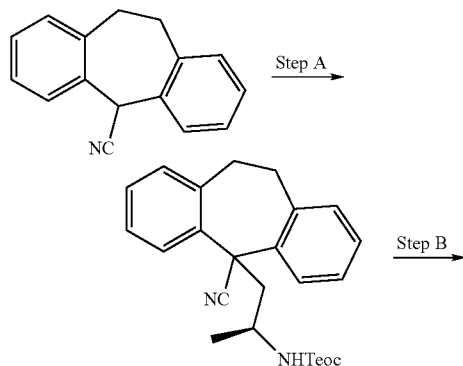
[0451]



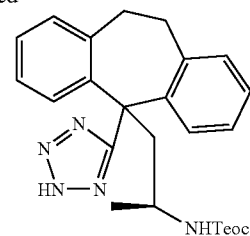
[0452] If one were to follow a similar procedure as described in Preparative Example 56, but using the title compound from Preparative Example 55, one would obtain the desired compound.

Preparative Example 58

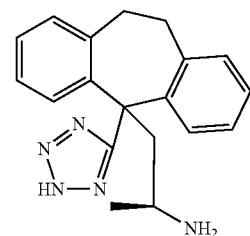
[0453]



-continued



Step C



Step A

[0454] A suspension of NaH (66 mg) in THF (10 ml) was added to a solution of the title compound from Preparative Example 13 Step A (0.57 g) in THF (20 ml) and heated at 65° C. for 1 h. Then the mixture was cooled to 0° C. and a solution of Preparative Example 21 (0.74 g) in THF (10 ml) was added. The suspension was heated at 65° C. for 5 h and then diluted with ethyl acetate. The organic phase was washed with water, brine and dried over MgSO₄. Removal of the solvents and column chromatography (EtOAc/hexane, 1:4) afford the title compound (630 mg, 58%, MH⁺=421).

Step B

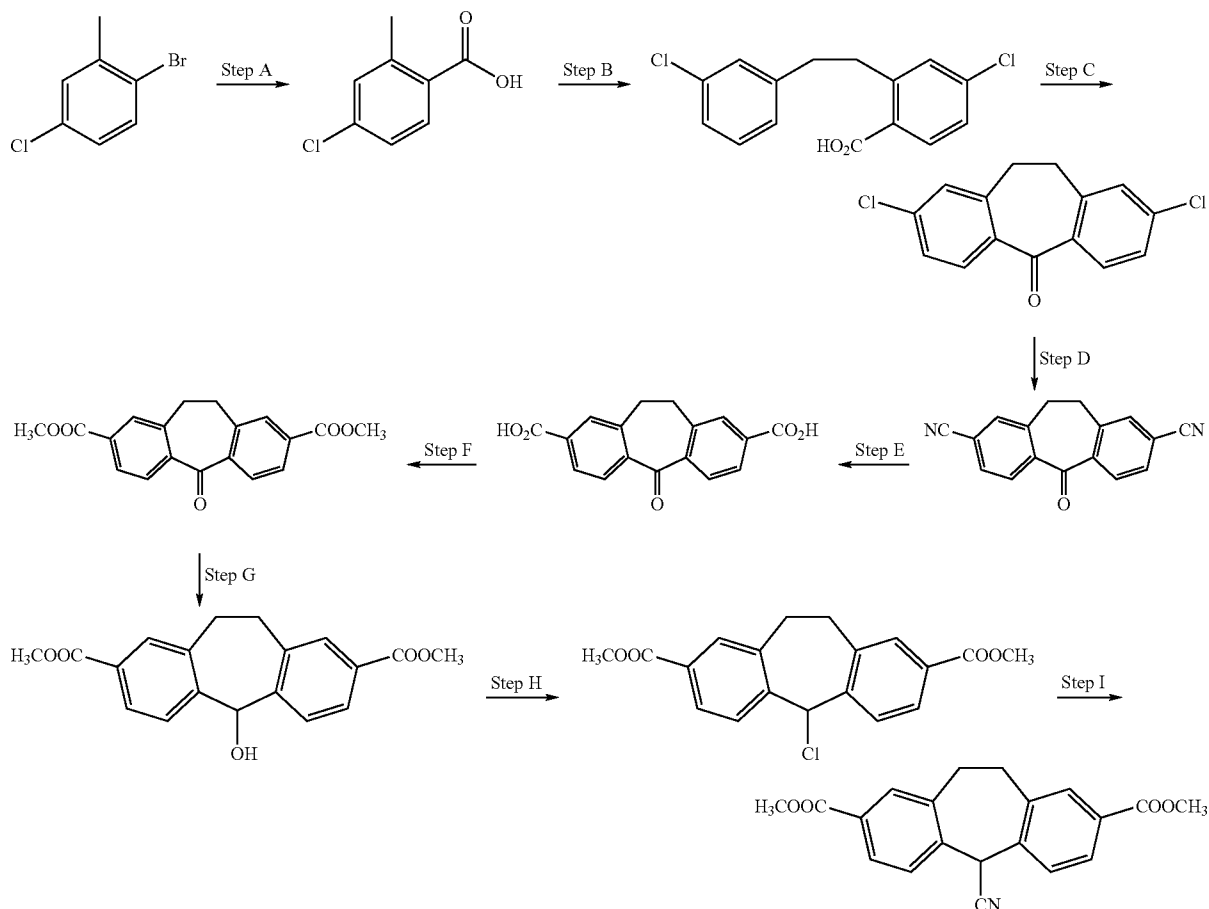
[0455] The title compound from Step A above (632 mg) was dissolved in DMF (10 ml) and treated with NaN₃ (1.2 g) and NH₄Cl (963 mg). The mixture was heated under a N₂ atmosphere at 110° C. for 3 d and the solvent evaporated. Column chromatography (CH₂Cl₂/MeOH, 9:1) afford the title compound (350 mg, 51%, MH⁺=464).

Step C

[0456] The title compound from Step B above (350 mg) was dissolved in THF (10 ml) and treated with TBAF·3H₂O. The mixture was stirred at rt for 4 h and the solvent evaporated. Preparative TLC using CH₂Cl₂/MeOH (4:1) afford the title compound (121 mg, 50%, MH⁺=320).

Preparative Example 59

[0457]



Step A

[0458] Commercially available 2-Brom-5-chlor-toluene (123 g) was diluted with Et₂O (70 ml) and 10% of this solution was added to a mixture of Mg (15.2 g) and iodine (3 crystals) in Et₂O (250 ml). After the Grignard reaction had started, the remaining starting material was added at such a rate to maintain gentle reflux. After the complete addition of the starting material, the mixture was heated at 60° C. oil-bath temperature for 45 Min. The mixture was then cooled to rt and poured onto a mixture of dry-ice in Et₂O (1800 ml). The mixture was allowed to warm to rt over a period of 2 h and the solvent removed. The residue was dissolved with EtOAc (1200 ml) and washed with 3 N HCl (3×1000 ml). The organic phase was separated, dried over MgSO₄, filtered and concentrated to afford the title compound (94.3 g, 92%)

[0459] ¹HNMR δ (DMSO-d₆) 2.51 (s, 3H), 7.33 (dd, 1H), 7.39 (d, 1H), 7.81 (d, 1H), 12.9 (br-s, 1H)

Step B

[0460] The title compound from Step A above (47 g) was dissolved in THF (500 ml) and the mixture cooled to -60° C. At -60° C. a 1.3 M solution of sec-BuLi (455 ml) in hexane

was slowly added as to keep the internal temperature below -30° C. The precipitate began to dissolve after the addition of more than half of the sec-BuLi solution. After the complete addition of sec-BuLi, the deep red solution was stirred at -50° C. for 1 h. The anion solution was then transferred via canula to a cooled (-40° C.) solution of commercially available 3-chlor-benzylbromide (62.3 g) in THF (150 ml). The addition of the anion was at such a rate as to maintain -40° C. during the addition. After the addition of the anion was completed, the mixture was stirred at -40° C. for 1 h and was then allowed to warm to rt over a period of 3 h. The reaction was quenched by adding 2 M NaOH (1000 ml) and the THF removed in vacuo. The remaining solution was extracted with cyclohexane (2×500 ml) and the aqueous phase acidified to PH=1 by adding conc. HCl. The mixture was extracted with EtOAc (3×400 ml), the organic phase dried over MgSO₄, filtered and concentrated to afford the title compound (71 g, 87%).

[0461] ¹HNMR δ (acetone-d₆) 2.83-2.91 (m, 2H), 3.22-3.31 (m, 2H), 7.13-7.40 (m, 6H), 7.98 (d, 1H).

Step C

[0462] The title compound from Step B above (71 g) was suspended in sulfolane (250 ml) and PPA (700 g) added. The

mixture was stirred with a mechanical stirrer and heated at 170° C. oil-bath temperature for 9 h. The hot mixture (~120° C.) was then poured onto crushed-ice (4000 g) and stirred overnight. The precipitate was allowed to settle for 30 Min and the aqueous phase decanted. The residue was dissolved in Et₂O (1500 ml) and washed with 1 M NaOH (2×500 ml). The organic phase was dried over MgSO₄, filtered and concentrated to afford the title compound (50 g, 75%).

[0463] ¹HNMR δ (CDCl₃) 3.16 (s, 4H), 7.23 (d, 2H), 7.32 (dd, 2H), 8.0 (d, 2H)

Step D

[0464] The title compound from Step C above (25 g) was dissolved in toluene (160 ml) and added to a mixture of KCN (11.7 g), dipiperidinomethane (7.26 ml), sulfolane (2 ml) and 1,4-Bis-(diphenylphosphino)-butane (6 g). The mixture was degassed by sonication under a stream of nitrogen and then palladium(II)-acetate (1.6 g) was added. The mixture was then heated in a sealed glass reaction vessel at 160° C. oil-bath temperature for 18 h. The mixture was cooled to rt, diluted with CH₂Cl₂ (800 ml) and washed with H₂O (300 ml) and brine (300 ml). The organic phase was separated, dried over MgSO₄, filtered and concentrated. The residue was diluted with EtOAc (90 ml) and sonicated. The suspension was then treated with cyclohexane (400 ml) and allowed to stand for 30 Min. The precipitate was collected by filtration and air-dried to afford the title compound (18 g, 77%, MH⁺=259).

Step E

[0465] The title compound from Step D above (18 g) was suspended in EtOH (75 ml) and H₂O (20 ml) and the KOH (19.3 g) added. The mixture was heated at 100° C. oil-bath temperature for 12 h, concentrated and the residue dissolved in H₂O (500 ml). The aqueous phase was acidified to pH=1 by adding conc. HCl and the precipitate collected by filtration and air-dried to afford the title compound (19.5 g, 95%, MH⁺=297).

Step F

[0466] The title compound from Step E above (19.5 g) was suspended in MeOH (600 ml) and treated with thionyl chloride (29 ml). The mixture was then heated at 90° C. oil-bath temperature for 3 h, the hot mixture filtered and concentrated. The residue was dissolved in CH₂Cl₂ (800 ml) and washed with sat. NaHCO₃ (200 ml). The organic phase was separated, dried over MgSO₄, filtered and concentrated to afford the title compound (18.8 g, 88%, MH⁺=325).

Step G

[0467] The title compound from Step F above (18.8 g) was dissolved in CHCl₃ (250 ml) and MeOH (250 ml). The mixture was then treated with NaBH₄ (2.47 g) in small portions. After the complete addition of the reducing agent, the mixture was stirred at rt for 1 h. The mixture was poured into ice-water (800 ml), the organic phase separated and the aqueous phase extracted with EtOAc (300 ml). The combined organic phase was dried over MgSO₄, filtered and concentrated. The residue was purified by chromatography on silica (CH₂Cl₂ to CH₂Cl₂/acetone, 98:2 to CH₂Cl₂/acetone, 95:5) to afford the title compound (11.9 g, 63%, MNa⁺=349).

Step H

[0468] The title compound from Step G above (11.9 g) was dissolved in THF (150 ml) and the mixture cooled to 0° C. At

0° C. thionyl chloride (6.5 ml) was added and the mixture was allowed to warm to rt overnight. The solvent was then removed in vacuo to afford the crude title compound.

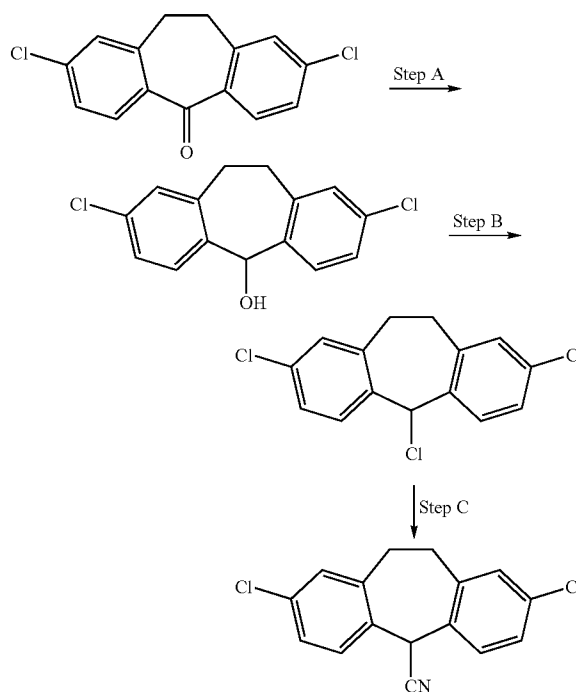
[0469] ¹HNMR δ (CDCl₃) 2.93-3.05 (m, 2H), 3.70-3.80 (m, 2H), 3.90 (s, 6H), 6.10 (s, 1H), 7.40 (d, 2H), 7.78-7.86 (m, 4H).

Step I

[0470] The title compound from Step H above was dissolved in CH₃CN (300 ml) and benzene (95 ml). After the addition of AgCN (5.9 g) the mixture was heated at 95° C. oil-bath temperature for 2 h 45 Min. The mixture was filtered while hot and the salts washed with CH₂Cl₂ (100 ml). The filtrate was concentrated and the residue purified by chromatography on silica (CH₂Cl₂/acetone, 98:2) to afford the title compound (11.3 g, 92%, MH⁺=336).

Preparative Example 60

[0471]



Step A

[0472] The title compound from Preparative Example 59 Step C (9.5 g) was dissolved in CHCl₃ (100 ml) and MeOH (60 ml) at 0° C. The mixture was then treated with NaBH₄ (1.64 g) in small portions. After the complete addition of the reducing agent, the mixture was stirred at rt for 3 h. Water (50 ml) was added and the mixture was concentrated to half of its volume and extracted with EtOAc (2×150 ml). The combined organic layers were washed with water (50 ml), brine (50 ml), dried over MgSO₄ and concentrated. The crude product was used without further purification (9 g, 90%, MNa⁺=301).

Step B

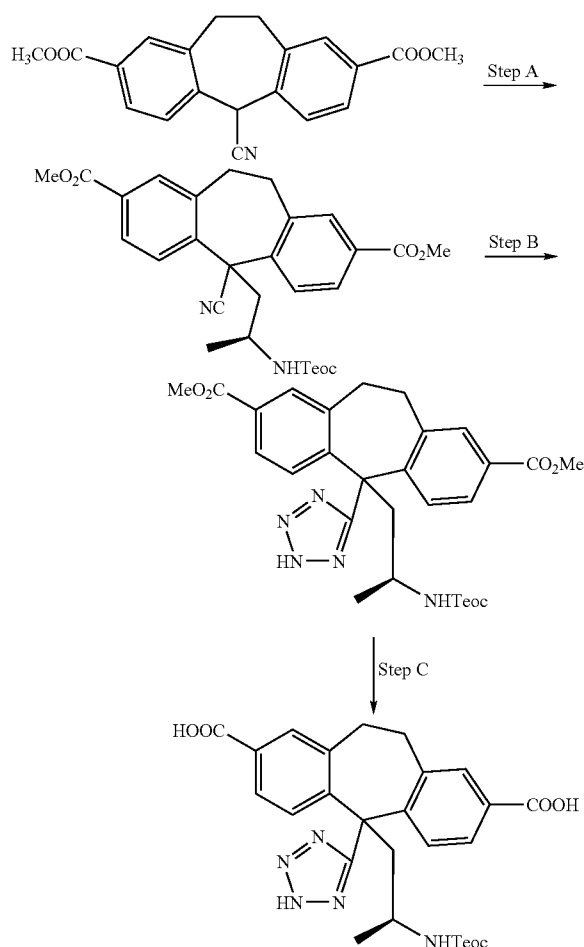
[0473] The crude title compound from Step A above (9 g) was dissolved in THF (100 ml) and the mixture was cooled to 0° C. At 0° C. thionyl chloride (7.1 ml) was added and the mixture was allowed to warm to rt overnight. The solvent was then removed in vacuo to afford the title compound (9.2 g).

Step C

[0474] The title compound from Step B above (9.2 g) was dissolved in CH₃CN (180 ml) and benzene (60 ml). After the addition of solid AgCN (5.2 g) the mixture was heated at 90° C. oil-bath temperature for 2.5 h. The mixture was filtered while hot through celite and the salts washed with CH₂Cl₂ (200 ml). The filtrate was concentrated to give the crude title compound (8.66 g, 93%, MH⁺=288).

Preparative Example 61

[0475]



Step A

[0476] The title compound from Preparative Example 59 (3.8 g) was suspended in THF (50 ml) and DMF (35 ml). The mixture was treated under a N₂ atmosphere with NaH (408 mg) and the mixture was heated at 95° C. oil-bath temperature for 90 Min, cooled to rt and treated with the title compound from Preparative Example 21 (4.78 g). The mixture was then heated at 90-95° C. for 4 h, cooled to rt and quenched with sat. NH₄Cl (75 ml) and brine (90 ml). The organic phase was separated and the aqueous layer extracted with EtOAc (2×50 ml). The combined organic phase was dried over MgSO₄ and concentrated. The residue was purified by chromatography on silica (CH₂Cl₂/MeOH, 95:5) to afford the title compound (5 g, 82%, MH⁺=537).

Step B

[0477] The title compound from Step A above (5 g) was dissolved in DMA (90 ml) and treated with NaN₃ (5.9 g) and NH₄Cl (4.8 g). The mixture was heated under a N₂ atmosphere at 100-105° C. for 50 h. The cooled mixture concentrated and the residue dissolved in EtOAc (600 ml) and H₂O (200 ml). The aqueous layer was acidified to pH=4 by adding 1 M HCl and the organic phase separated. The aqueous phase was extracted with EtOAc (2×80 ml) and the combined organic extracts washed with 100 mM HCl (200 ml) and brine (200 ml). The organic phase was separated, dried over MgSO₄, filtered and concentrated. The residue was purified by chromatography on silica (CH₂Cl₂/MeOH 9:1→4:1) to afford the title compound (4 g, 74%, MH⁺=580).

Step C

[0478] The title compound from Step B above (4 g) was dissolved in dioxane (153 ml). After the addition of 1 M KOH (42.5 ml), the mixture was stirred at rt overnight. The mixture was concentrated and then 43 ml 1 M HCl added. The precipitate was dissolved in EtOAc (100 ml) and H₂O (100 ml) and the organic phase separated. The aqueous phase was extracted with EtOAc (100 ml) and the organic phase combined. The solvent was then removed to afford the title compound (3.9 g, quanta, MH⁺=552).

Preparative Example 62-64

[0479] Following a similar procedure as that described in Preparative Example 61 but using the sulfamides and compounds from the Preparative Examples as indicated in the Table below, the title compounds were obtained.

Preparative Example	Preparative Example	Sulfamide	Title compound	MH ⁺
62	59			538

-continued

Preparative Example	Preparative Example	Sulfamidate	Title compound	MH ⁺
63	59			566
64	60			475

Preparative Example 65

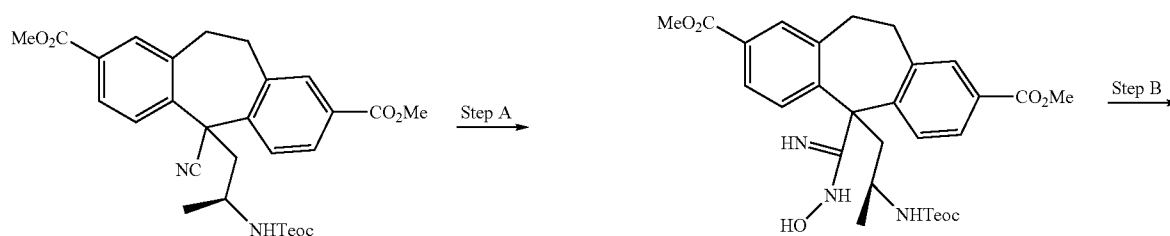
[0480] If one were to treat the title compound from Preparative Example 59 according to the procedures described in Preparative Example 61, but using the sulfamidate as indicated in the table below, one would obtain the title compound.

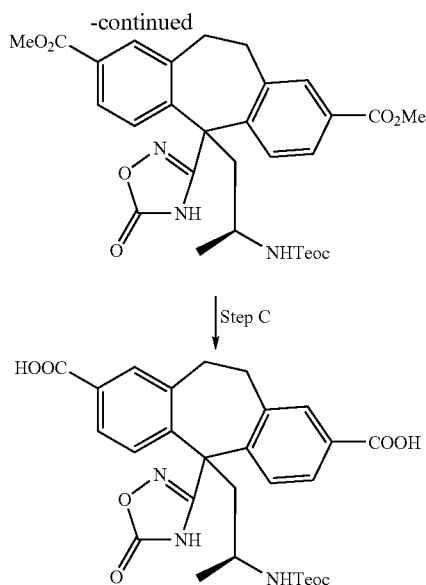
Preparative Example	Preparative Example	Sulfamidate	Title compound
65	59		

Preparative Example 66

[0481]

-continued





Step A

[0482] The title compound from Preparative Example 61 Step A (1000 mg) was suspended in MeOH (10 ml) and hydroxylamine hydrochloride (517 mg) and a 5.5 M solution of sodium methoxide in MeOH (1.4 ml) added. The mixture was heated in a pressure bottle at 110° C. for 12 h and then the solvent removed. The residue was purified by chromatography on silica (cyclohexane/EtOAc 1:3→1:1) to afford the title compound (210 mg, 20%, $MH^+=570$).

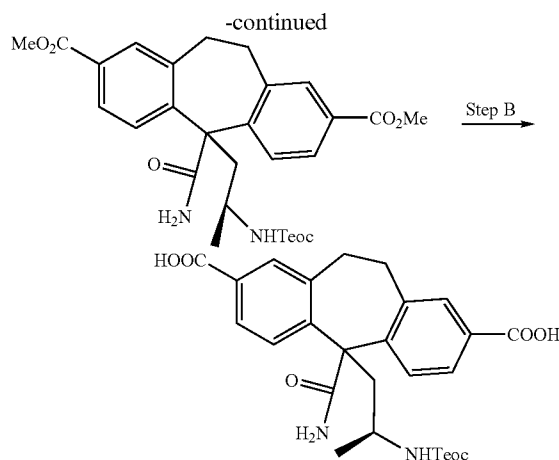
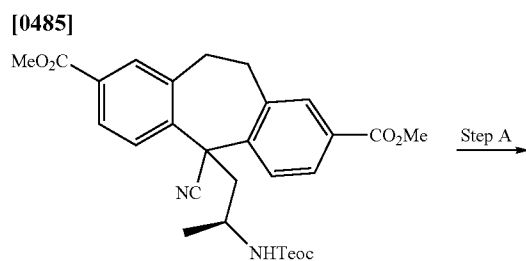
Step B

[0483] The title compound from Step A above (180 mg) was dissolved in MeOH (10 ml) and sodium methoxide (233 mg) and diethyl carbonate (1130 mg) added. The mixture was heated at 110° C. in a pressure bottle overnight. The solvent was removed and the residue purified by chromatography on silica ($CHCl_3$) to afford the title compound (110 mg, 58%, $M^+-27=568$).

Step C

[0484] The title compound from Step B above (110 mg) was dissolved in THF (25 ml) and treated with 1M KOH (6 ml). After stirring at rt overnight, 1M HCl (2.8 ml) was added and the solvents removed to afford the crude title compound (105 mg, quant., $M^+-27=540$).

Preparative Example 67



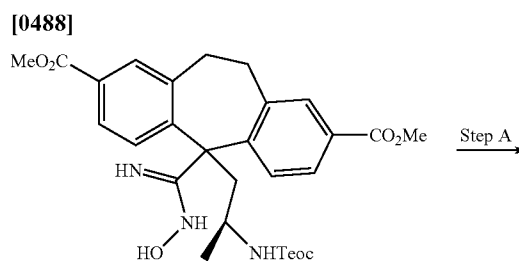
Step A

[0486] Hydroxylamine hydrochloride (401 mg) was suspended in anhydrous MeOH (14 ml) and a 5.5 M solution of sodium methoxide in MeOH (0.946 ml) added. This mixture was stirred at rt for 45 min and the title compound from Preparative Example 61 Step A (1400 mg) was added. The resulting mixture was heated in a closed vessel at 100° C. overnight and subsequently allowed to cool down to rt. Due to incomplete conversion, hydroxylamine hydrochloride (401 mg) and a 5.5 M solution of sodium methoxide in MeOH (0.946 ml) were added and the mixture was heated again at 100° C. for 20 h. After cooling down to rt, the salts were filtered off and washed with EtOAc (15 ml) and $CHCl_3$ (15 ml). The united organic phases were evaporated and the residue purified by chromatography on silica (cyclohexane/EtOAc 8:2→6:4) to afford the title compound from Preparative Example 66 Step A (300 mg, 20%, $MH^+=570$) and the title compound (1130 g, 74%, $MNa^+=577$).

Step B

[0487] The title compound from Step A above (1380 g) was dissolved in THF (30 ml) and treated with 1M KOH (9 ml). After stirring at rt overnight, 1M KOH (9 ml) was added and stirring continued for 22 h. The reaction mixture was acidified with 4 M HCl to pH 2-3, extracted with EtOAc/THF 10/1 (4×40 ml) and the combined organic extracts washed with brine (20 ml). The organic phase was separated, dried over $MgSO_4$, filtered and concentrated to afford the title compound (1220 mg, quant., $M^+-27=499$, $MNa^+=549$).

Preparative Example 68



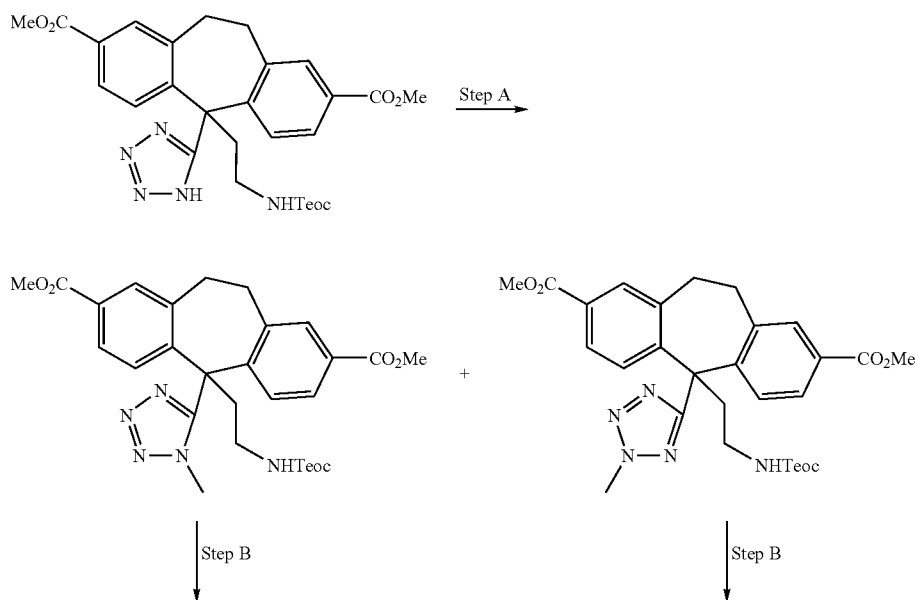
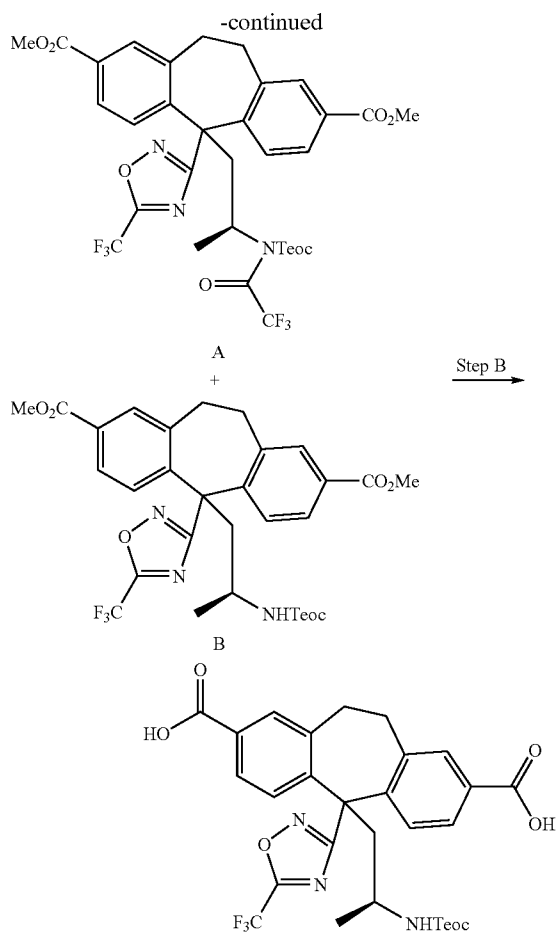
Step A

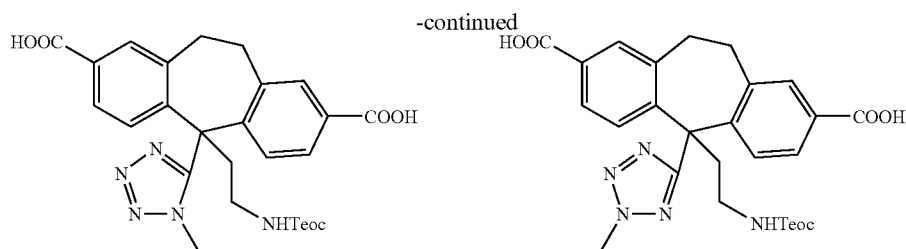
[0489] The N-hydroxyamidine product from Preparative Example 66 Step A (300 mg) was dissolved in anhydrous dichloromethane (5 ml), the solution cooled down to 0° C. and triethylamine (147 μ l) and trifluoroacetic anhydride (103 μ l) added. The reaction mixture was stirred at rt overnight. Due to incomplete conversion, triethylamine (221 μ l) and trifluoroacetic anhydride (155 μ l) were added at 0° C. and stirring was continued at rt for 3 d. Dichloromethane (9 ml) and water (10 ml) were added to the stirred mixture. After 5 min, the separated organic phase was washed with brine (5 ml), dried over MgSO_4 , filtered and concentrated. The residue was purified by chromatography on silica (cyclohexane/EtOAc 8:2- \rightarrow 7:3) to afford the title compounds A (267 mg, 68%, $\text{MNa}^+=766$) and B (36 mg, 10%, $\text{MNa}^+=670$).

Step B

[0490] The title compounds A (267 mg; $\text{MNa}^+=766$) and B (36 mg, $\text{MNa}^+=670$) from Step A above were dissolved in dioxane (11 ml) and water added (11 ml). The resulting suspension was treated with 1M NaOH (3.6 ml). After stirring at rt overnight, the reaction mixture was acidified with 1M HCl to pH 2-3, extracted with EtOAc (4 \times 40 ml) and the combined organic phases dried over MgSO_4 , filtered and concentrated to afford the title compound (282 mg, quant., $\text{MNa}^+=642$).

Preparative Example 69

[0491]



Step A

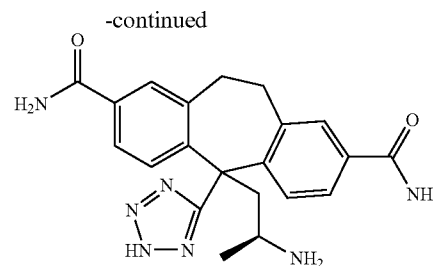
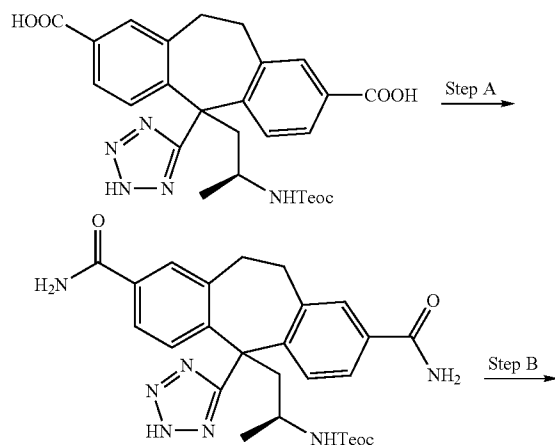
[0492] To the title compound of Preparative Example 61 Step A (500 mg) in anhydrous DMF (10 ml) was added K_2CO_3 (123 mg). After cooling down to $0^\circ C.$, methyl iodide (75 μl) was added dropwise to the stirred mixture. After 10 min, the mixture was allowed to rt and stirred overnight. The reaction mixture was cooled down to $0^\circ C.$, diluted with acidified saturated aq. NaCl solution (pH 2-3) and added to stirred EtOAc (150 ml). The separated organic phase was washed with brine (2x25 ml), dried over $MgSO_4$, filtered and concentrated. The residue was purified by chromatography on silica (cyclohexane/EtOAc 8:2- \rightarrow 7:3) to afford the title compounds: the 1-Me-tetrazole (170 mg, 33%, $MH^+=580$) and the 2-Me-tetrazole (163 mg, 32%, $MH^+=580$).

Step B

[0493] The title compounds from Step A above (170 mg of the 1-Me-tetrazole and 163 mg of the 2-Me-tetrazole) were separately dissolved in dioxane (5.5 ml) and treated with 1M KOH (1.5 ml) each. After stirring at rt for 3 h, the reaction mixtures were concentrated to $\frac{1}{3}$ of their volumes and the pH adjusted to 3 with 1M HCl. The resulting aq. suspension was extracted with EtOAc (3x25 ml) and the combined organic phases dried over $MgSO_4$, filtered and concentrated to afford the title compounds: the 1-Me-tetrazole (171 mg, quant., $M^+-27=524$) and the 2-Me-tetrazole (172 mg, quant., $M^+-27=524$).

Preparative Example 70

[0494]



Step A

[0495] The title compound from Preparative Example 61 (2 g) was dissolved in THF (75 ml) and CH_3CN (75 ml) and triethylamine (4 ml) added. The mixture was cooled to $-40^\circ C.$ and ethylchloroformate (2.3 ml) was slowly added. The mixture was stirred at $-25^\circ C.$ for 1 h, filtered and the salts washed with 35 ml THF. The filtrate was placed in a cooling bath ($-20^\circ C.$) and a 33%-solution of NH_4OH (30 ml) was added. The mixture was stirred at $-20^\circ C.$ for 30 min and 15 min at rt. Since LC-MS indicated that the conversion was not complete, the mixture was concentrated. The reaction was repeated using the same reaction conditions. After the second run LC-MS indicated that the reaction was completed. The mixture was concentrated to afford the crude title compound together with salts from the reaction ($MNa^+=572$).

Step B

[0496] The crude title compound from Step A above was suspended in $CHCl_3$ (25 ml) and the mixture cooled to $0^\circ C.$ At $0^\circ C.$ TFA (25 ml) was added and stirring at $0^\circ C.$ was continued for 2 h. The mixture was concentrated and the residue dissolved in H_2O (15 ml). The pH was adjusted to pH=7.0 by adding 10% NaOH and the neutral solution loaded onto a RP-column (Merck; silica gel 60 RP-18, 40-63 μm). The column was washed with H_2O to remove the salts, followed by CH_3CN/H_2O (1:1) to elute the title compound (1.3 g, 88%, $MH^+=406$).

Preparative Example 71-87

[0497] Treating the compounds from the Preparative Examples with the amines as indicated in the Table below, according to a modified procedure as described in Preparative Example 70, the title compounds were obtained as HCl-salts.

[0498] Modifications:

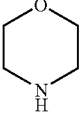
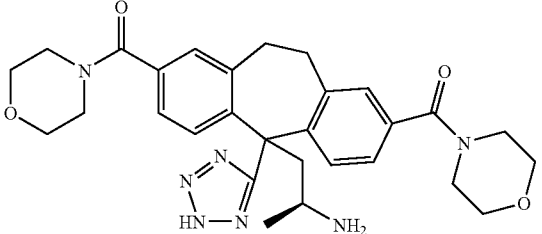

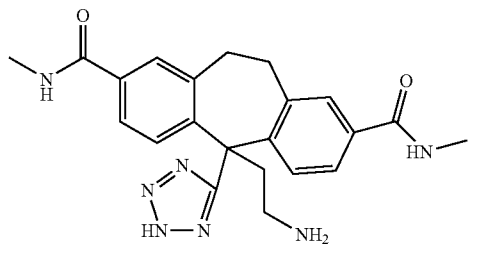

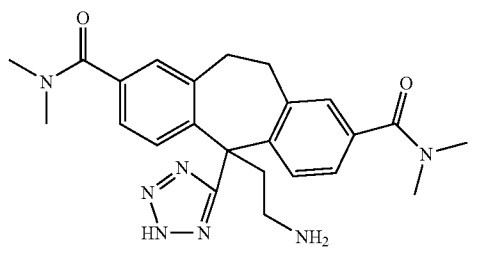

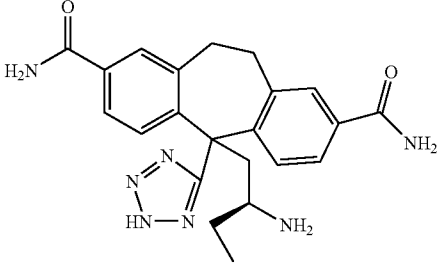

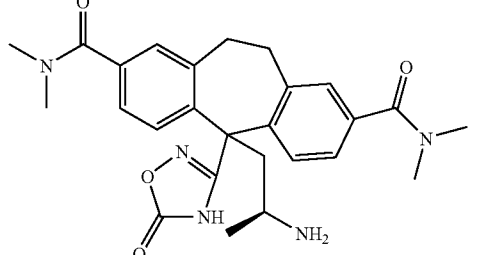
[0499] Step A The crude mixture from Step A was dissolved in H_2O and the pH adjusted to pH=4.0 by adding 1 M HCl. The mixture was then extracted with EtOAc, the organic phase separated, dried over $MgSO_4$, filtered and the solvents removed.

[0500] Step B The residue after removal of the Teoc protecting group was diluted with 1M HCl and the aqueous


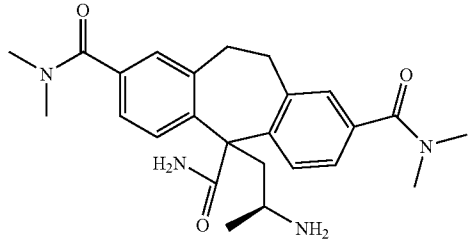

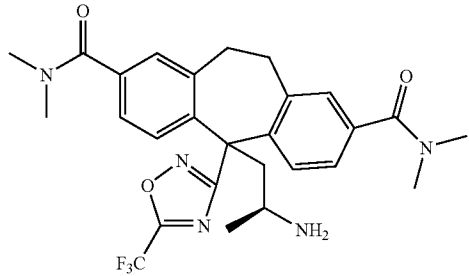

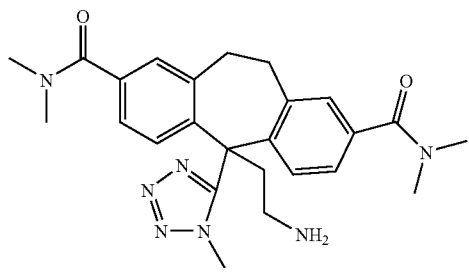

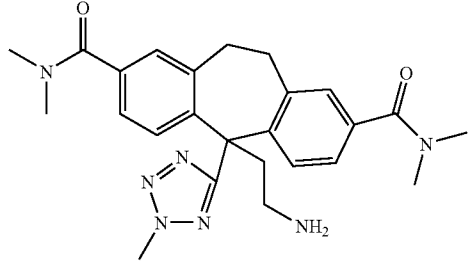
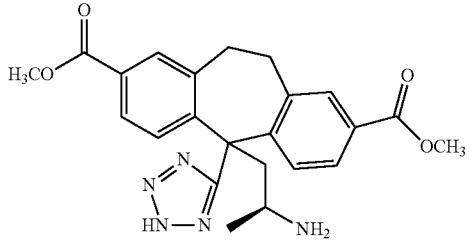
phase washed with EtOAc. Concentration of the aqueous phase afforded the title compound as HCl-salt.

Preparative Example	Preparative Example	Amines	Title compound	MH ⁺
71	61			462
72	61			434
73	61			462
74	61			490
75	61			486

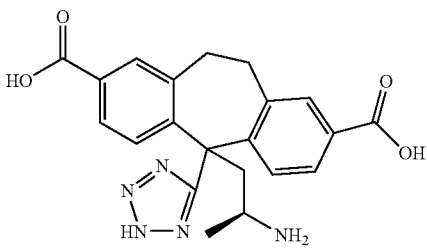
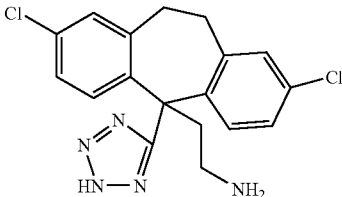
-continued

Preparative Example	Preparative Example	Amines	Title compound	MH ⁺
76	61			546
77	62			420
78	62			447
79	63			420
80	66			478

-continued

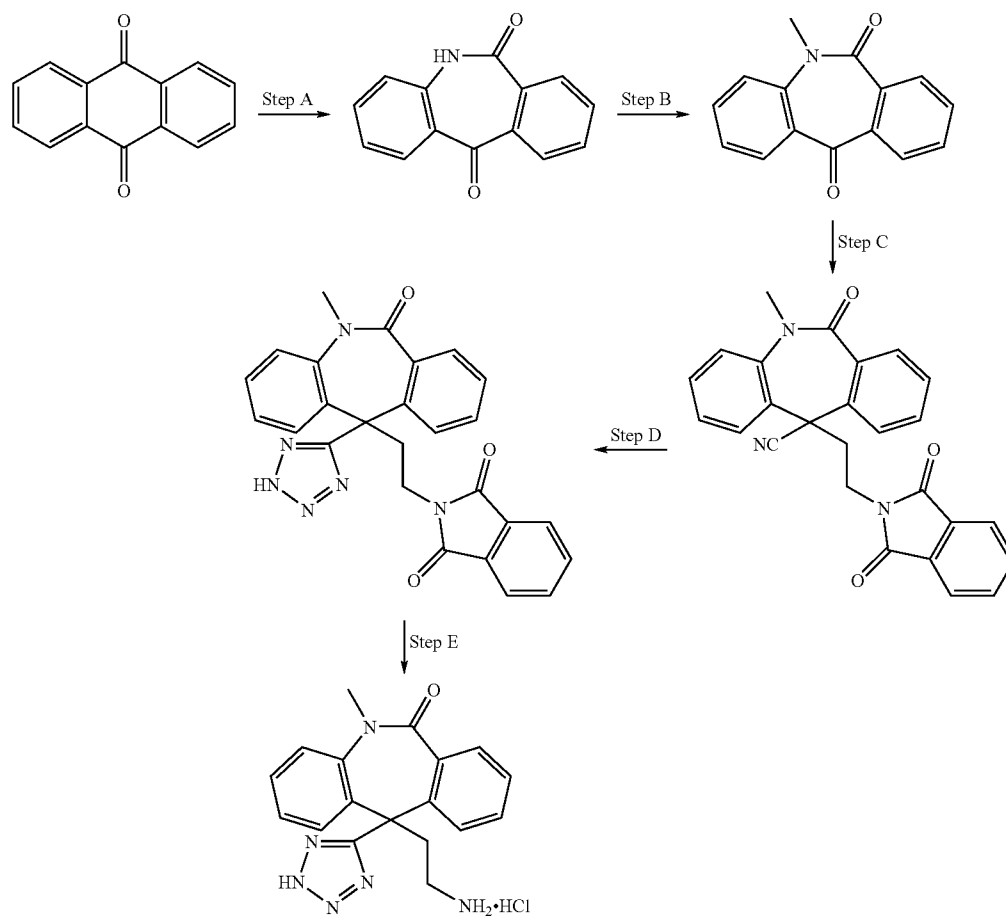
Preparative Example	Preparative Example	Amines	Title compound	MH ⁺
81	67			437
82	68			530
83	69 1-Me-tetrazole			406
84	69 2-Me-tetrazole			406
85	61 Step B	none		436

-continued

Preparative Example	Preparative Example	Amines	Title compound	MH ⁺
86	61	none		408
87	64	none		374

Preparative Example 88

[0501]



Step A

[0502] Commercially available anthraquinone (8.0 g) was suspended in CHCl_3 (100 ml) and conc. H_2SO_4 (20 ml) was added. The resulting biphasic system was rapidly stirred and NaN_3 (3.1 g) was added in portions at rt. The mixture was stirred for 1 h at rt and at 30–40° C. (water bath) for another 3 h. After the addition of ice water (80 ml), the precipitate was collected by filtration and dried to afford the title compound (8.40 g; 97%; $\text{MH}^+=224$).

Step B

[0503] The title compound from Step A above (8.0 g) was dissolved in DMSO (140 ml) under N_2 at 10° C. After the addition of KOTBu (5.7 g), the mixture was stirred for 15 min at that temperature. After the addition of CH_3I (4.2 ml), the mixture was allowed to warm to rt and stirred for 2 h. After the addition of 1 M HCl (130 ml) and EtOAc (100 ml), the organic phase was separated and the aqueous phase extracted with EtOAc (2×50 ml). The combined organic phase was washed with H_2O (50 ml), brine (50 ml), dried over MgSO_4 and concentrated. The residue was purified by chromatography on silica ($\text{EtOAc}/\text{cyclohexane}$) to afford the title compound (4.88 g; 61%; $\text{MH}^+=238$).

Step C

[0504] Tosylmethyl isocyanide was dissolved in DMSO (10 ml) under N_2 at 10° C. and KOTBu (1.36 g) was added. The mixture was stirred for 5 min and MeOH (0.173 ml) was added. The title compound from Step B above (0.8 g) was immediately added to the mixture. After 10 min dibromomethane (1.51 ml) was added and stirring was continued for 1 h at rt. The mixture was diluted with EtOAc (10 ml) and sat. NH_4Cl (30 ml) was added. The organic phase was separated and the aqueous phase was extracted with EtOAc (2×50 ml). The combined organic phase was washed with H_2O (50 ml), brine (50 ml), dried over MgSO_4 and concentrated. The resi-

due was dissolved in DMF (40 ml) and potassium phthalimide (3.13 g) added. The resulting mixture was heated to 60° C. for 3 h and concentrated. The residue was suspended in CHCl_3 and filtered. The filtrate was concentrated and the residue purified by chromatography on silica ($\text{EtOAc}/\text{cyclohexane}$) to afford the title compound (612 mg; 43%; $\text{MH}^+=422$).

Step D

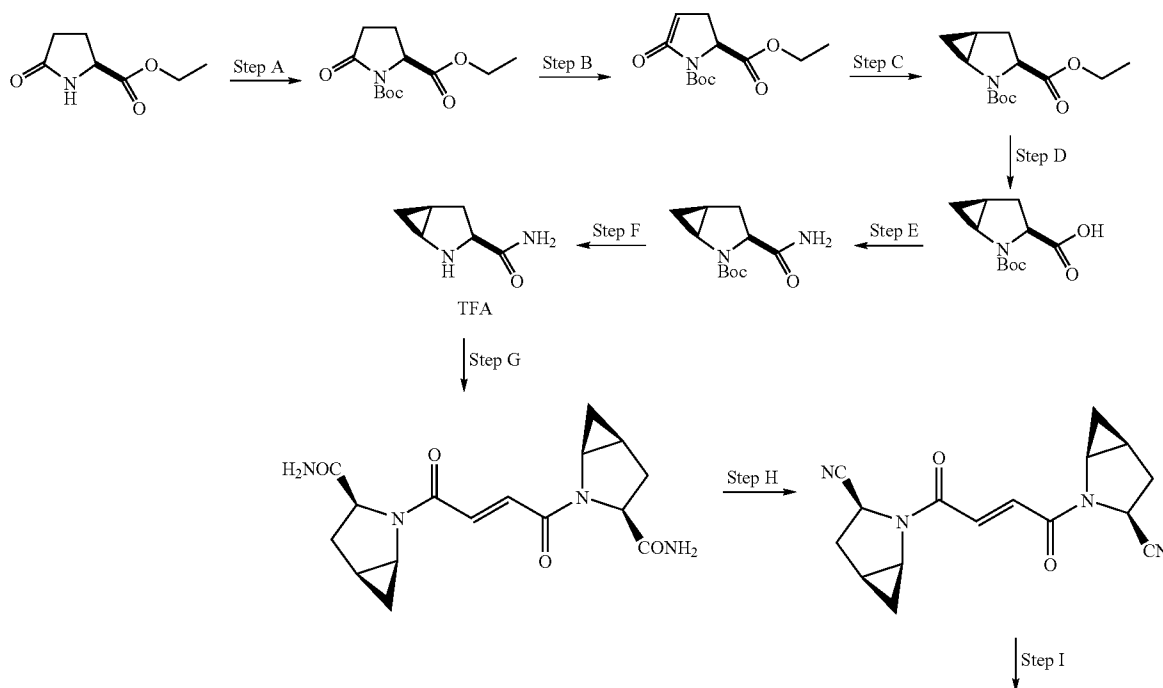
[0505] The title compound from Step C above (0.6 g) was dissolved in toluene (30 ml) under N_2 and dibutyltin oxide (1.68 g) and trimethylsilylazide (8.9 ml) were added. The mixture was then heated at 75° C. for 24 h. The mixture was concentrated, the residue suspended in EtOAc (40 ml) and 1 M HCl (40 ml) and stirred for 2 h at rt. MeOH (10 ml) was added and the organic phase was separated. The aqueous phase was extracted with EtOAc (3×20 ml) and the combined organic phase was washed with brine (20 ml), dried over MgSO_4 and evaporated. The residue was purified by chromatography on silica ($\text{MeOH}/\text{CH}_2\text{Cl}_2$) to afford the title compound (565 mg; 84%; $\text{MH}^+=465$).

Step E

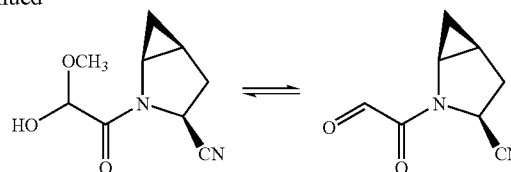
[0506] The title compound from Step D above (0.22 g) was dissolved in EtOH (7 ml) and CHCl_3 (3 ml) and the mixture was heated to 80° C. Hydrazine monohydrate (0.108 g) was added and the mixture was stirred at 80° C. for 1 h. The mixture was allowed to cool to rt within 1 h. The precipitate was removed by filtration and washed with EtOH . The filtrate was concentrated and dissolved in CHCl_3 (20 ml) and 1 M HCl (10 ml). The aqueous phase was separated, filtered and evaporated to afford the title compound (85 mg; 48%; $\text{MH}^+=335$).

Preparative Example 89

[0507]



-continued



Step A

[0508] To a solution of the commercially available L-pyrogutamic acid ethylester (15.7 g) in methylene chloride (90 ml) was sequentially added at rt di-tert-butyl dicarbonate (24 g) and a catalytic amount of DMAP (120 mg). After stirring for 6 h at rt the reaction mixture was quenched with saturated brine and extracted with methylene chloride. (3×30 ml). The organic phase was dried over MgSO_4 , concentrated and the residue purified by flash chromatography on silica (CH_2Cl_2) to afford the title compound (16.3 g, 63%, $\text{MNa}^+=280$).

Step B

[0509] A solution of the title compound from Step A above (16.3 g) in toluene (100 ml) was cooled to -78°C . and triethylborohydride (67 ml of a 1.0 M solution in THF) was added dropwise over 90 minutes. After 3 h, 2,6 lutidine (43 ml) was added dropwise followed by DMAP (20 mg). To this mixture was added TFAA (11 ml) and the reaction was allowed to come to ambient temperature over 2 h. The mixture was diluted with ethyl acetate and water and the organics were washed with 3 N HCl, water, aqueous bicarbonate and brine. The organic phase was dried over MgSO_4 , filtered and concentrated. The residue was purified by chromatography on silica (cyclohexane/EtOAc 5:1) to afford the title compound (10.9 g, 72%, $\text{MNa}^+=264$).

Step C

[0510] A solution of the title compound from Step B above (3.5 g) in 1,2 dichloroethane (75 ml) was cooled to -15°C . and Et_2Zn (25 mL of a 1.0 M solution in THF) was added dropwise. To this mixture was added drop wise ClCH_2I (4.5 ml) over 30 minutes. After stirring for 18 h at -15°C . the mixture was quenched with saturated aqueous bicarbonate and the solvent was evaporated and the reaction was taken up in ethyl acetate and washed with brine. The organic phase was dried over MgSO_4 , filtered and concentrated. The residue was purified by chromatography on silica (cyclohexane/EtOAc 4:1) to afford the diastereomerically pure title compound (1.5 g, 41%, $\text{MNa}^+=278$).

Step D

[0511] A solution of the title compound from Step C above (1.4 g) in MeOH (40 ml) and THF (20 ml) was treated with 1 N LiOH (10 ml) and stirred overnight at rt. The reaction mixture was acidified to pH 4.5 with 2 N HCl and stirred for 15 min at rt. The mixture was then extracted with EtOAc, the organic phase washed with brine, dried over MgSO_4 and evaporated to afford the title compound (1.2 g, 96%, $\text{MNa}^+=250$).

Step E

[0512] To a solution of the title compound from Step D above (1.2 g) in THF (20 ml) was added at -15°C . 4-meth-

ylmorpholine (710 μl) and then isobutyl chloroformate (780 μl) over 5 minutes and stirred then for 30 minutes. The reaction mixture was cooled to -30°C . and treated with a solution of NH_3 in dioxane (25 ml, 0.5 M in dioxane). The reaction mixture was stirred for 30 minutes, warmed to rt and stirred overnight. The reaction mixture was acidified to pH 4.5 with 10% aqueous citric acid and extracted with ether (3×50 ml). The organic phase was dried over MgSO_4 , filtered and concentrated. The residue was purified by chromatography on silica (cyclohexane/EtOAc 1:10) to afford the title compound (1.0 g, 84%, $\text{MNa}^+=248$).

Step F

[0513] To a stirred solution of the title compound from Step E above (0.9 g) in methylene chloride (5 ml) was sequentially added at 0°C . TFA (5 ml). After stirring for 12 h at 0°C . the reaction mixture was concentrated under reduced pressure to afford the title compound (0.9 g, 100%, $\text{MH}^+=127$).

Step G

[0514] The title compound from Step F above (450 mg) was dissolved in CH_2Cl_2 (12 ml) and triethylamine (0.4 ml). The mixture was cooled to 0°C . and DMAP (25 mg) was added followed by fumarylchloride (0.099 ml). The mixture was stirred at 0°C . and allowed to warm to rt overnight. The mixture was concentrated to afford the crude title compound ($\text{MH}^+=333$).

Step H

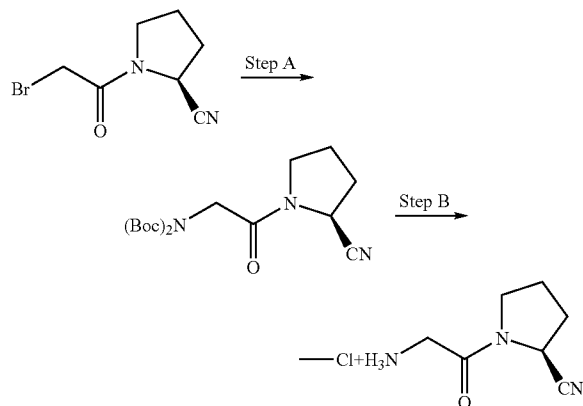
[0515] To a cooled (0°C .) solution of DMF (4 ml) was carefully added oxalylchloride (0.32 ml). After the addition was completed, the mixture was stirred at 0°C . for 5 min. Then pyridine (0.6 ml) was added followed by a solution of the crude title compound from Step G above in DMF (2 ml) and CH_2Cl_2 (4 ml). The mixture was then stirred at 0°C . for 2 h. The mixture was concentrated and the residue partitioned between EtOAc (50 ml) and brine (25 ml). The organic phase was separated and the aqueous phase extracted with EtOAc (2×25 ml). The combined organic phase was dried over MgSO_4 , filtered and concentrated. The residue was purified by chromatography on silica ($\text{CH}_2\text{Cl}_2/\text{MeOH}$, 95:5) to afford the title compound (250 mg, 92%, $\text{MH}^+=297$).

Step I

[0516] The title compound from Step H above (328 mg) was dissolved in CHCl_3 (3 ml) and MeOH (3 ml). The mixture was then treated with ozone according to Preparative Example 2 Step C to afford the title compound (350 mg, 80%, $\text{MH}^+=165$ (aldehyde); $\text{MH}^+=219$ (hemiacetal)).

Preparative Example 90

[0517]



Step A

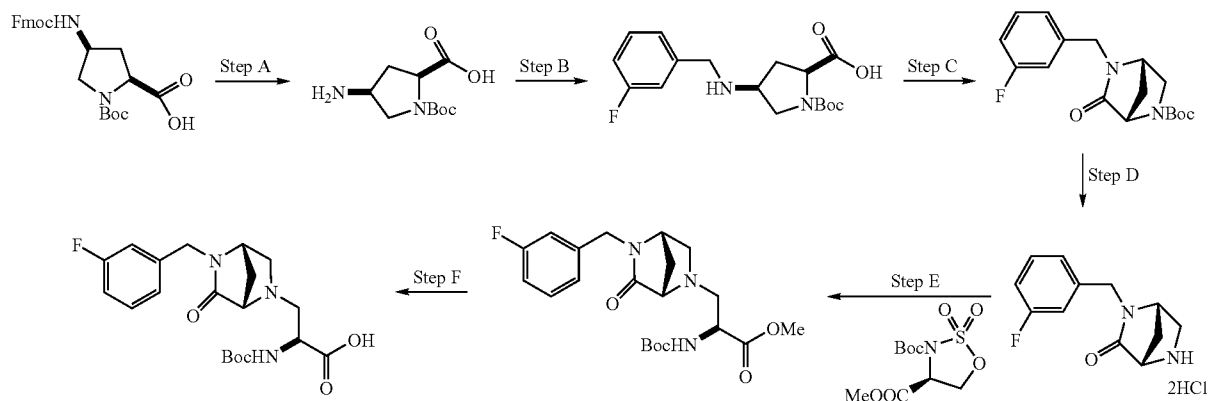
[0518] To a stirred solution of potassium hydroxide (1.2 g) in ethanol (10 mL) was sequentially added at rt the commercial available bis(tert.-butyldicarbonyl)amine (4.5 g). After stirring for 1 h at rt the reaction mixture was quenched with ether and the precipitate was filtered and washed with ether (3×10 mL) to afford the title compound (3.4 g)

Step B

[0519] The title compound from Step A above (95 mg) was dissolved in CHCl_3 (2.25 mL) and 1,3-dimethoxybenzene (0.18 mL) added. To the mixture was then added TFA (0.75 mL) and the mixture was stirred at rt for 1 h 30 min. The mixture was concentrated, dissolved in CH_3CN (3 mL) and concentrated again. The residue was dissolved in 100 mM HCl (3 mL) and EtOAc (3 mL). The aqueous phase was separated, washed with EtOAc (2 mL) and concentrated. The residue was suspended in CH_3CN (1.5 mL), sonicated for 1 min and the CH_3CN removed by syringe. The residue was then dried in HV to afford the title compound (42 mg, 84%, $\text{MH}^+=154$).

Preparative Example 91

[0520]



Step A

[0521] To a solution of the commercial available Boc-Fmoc-protected amino acid (1.05 g) in methanol (25 mL) was added diethyl amine (1.5 mL). After stirring for 2.5 h at room temperature the reaction mixture was concentrated, and the residue was dissolved in water (50 mL) and Et_2O (50 mL). The organic phase was extracted with water (3×50 mL) and the combined aqueous extracts were concentrated. The residue was used for the next step without any further purification.

Step B

[0522] To a solution of the title compound from Step A above (530 mg) and 3-fluorobenzaldehyde (245 μL) in 15 mL of methanol was added NaBH_3CN (150 mg), and the mixture was stirred at 25° C. overnight. The mixture was concentrated, and the residue was dissolved in EtOAc (50 mL). The organic layer was extracted with water (3×50 mL) and the combined aqueous extracts were concentrated. The residue was used for the next step without any further purification.

Step C

[0523] To a stirring solution of the title compound from Step B above (760 mg) in DMF (20 mL) was added HOBt (470 mg) followed by EDCI (670 mg) and DMAP (30 mg). N-methyl morpholine (440 μL) was added and stirring was continued at rt overnight. The solvent was removed in vacuo, the residue diluted with EtOAc and then washed with saturated aqueous NaHCO_3 . The organic phase was dried over MgSO_4 , concentrated and the residue purified by flash chromatography on silica (CH_2Cl_2 /acetone, 9:1) to afford the title compound (430 mg, 60% over 3 steps, $\text{MH}^+=321$).

Step D

[0524] The title compound from Step C above (760 mg) was dissolved in EtOAc (6 mL) and a solution of 4 M HCl in dioxane (6 mL) was added. After 2 h the mixture was triturated with aqueous NaHCO_3 to pH 7.5 and stirred for 15 min at rt. After evaporation of the solvent, the crude product was purified by flash chromatography on silica (CH_2Cl_2 /MeOH, 9:1) to afford the title compound (420 mg, 80%, $\text{MH}^+=221$).

Step E

[0525] To a solution of the title compound from Step D above (85 mg) in THF (5 mL) was added triethylamine (80 μL)

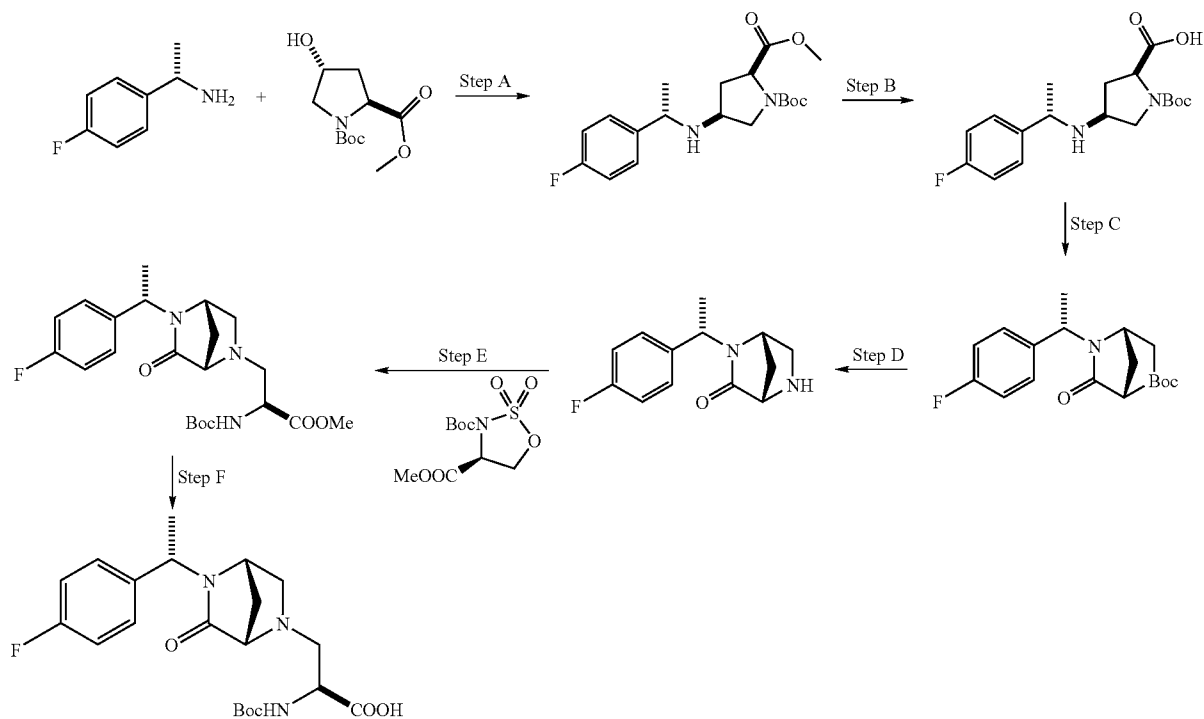
and the mixture was stirred for 1 h at 50° C. Then the sulfamate (240 mg.), prepared according to WO 03/037327, was added in one portion at -15° C. and the mixture was stirred at ambient temperature over 2 d. After the addition of 1 M NH_4HCO_3 solution (5 ml), the mixture was stirred for 30 min. Then an excess saturated NaHCO_3 solution was added and stirring was continued for another 15 min. The mixture was then partitioned between EtOAc and water and the aqueous phase extracted with EtOAc. The combined organic phase was dried over MgSO_4 and concentrated in vacuo. The residue was purified by column chromatography on silica (CH_2Cl_2 /acetone, 9:1) to afford the title compound (135 mg, 79%, $\text{MH}^+=422$).

Step F

[0526] A solution of the title compound from Step E above (135 mg) in MeOH (2.5 ml) and THF (5 ml) was treated with 1 N LiOH (1.5 ml) and stirred overnight at rt. The reaction mixture was acidified to pH 4.5 with 2 N HCl and stirred for 15 min at rt. The mixture was then extracted with EtOAc, the organic phase washed with brine, dried over MgSO_4 and evaporated to afford the title compound (125 mg, 96%, $\text{MH}^+=408$).

Preparative Example 92

[0527]



Step A

[0528] A solution of commercially available N-Boc-trans-4-hydroxy-L-proline ester (2.93 g) in CH_2Cl_2 (20 ml) was cooled to -30° C. and treated with DIEA (4.8 ml). After the addition of triflic anhydride (2.2 ml), the mixture was stirred at -30° C. for 60 min and then treated with a solution of the

commercially available amine in CH_2Cl_2 (20 ml). The mixture was allowed to warm to rt overnight. The mixture was diluted with CH_2Cl_2 (20 ml), washed with 0.5 M Na_2CO_3 (2x50 ml) and brine (50 ml). The organic phase was dried over MgSO_4 and concentrated to leave a residue, which was purified by chromatography on silica (CH_2Cl_2 /acetone, 4:1) to afford the title compound (2.22 g, 75%, $\text{MH}^+=367$).

Step B

[0529] A solution of the title compound from Step A above (700 mg) in MeOH (24 ml) and THF (12 ml) was treated with 1 N LiOH (6 ml) and stirred overnight at rt. The reaction mixture was acidified to pH 4.5 with 1 N HCl and stirred for 15 min at rt. The mixture was then extracted with EtOAc, the organic phase washed with brine, dried over MgSO_4 and evaporated to afford the title compound (665 mg, 95%, $\text{MH}^+=353$).

Step C

[0530] To a stirring solution of the title compound from Step B above (665 mg) in DMF (15 ml) was added HOBt (390 mg) followed by EDCI (560 mg) and DMAP (30 mg). N-methyl morpholine (420 μl) was added and stirring was continued at rt overnight. The solvent was removed in vacuo, the residue diluted with EtOAc and then washed with saturated aqueous NaHCO_3 . The organic phase was dried over MgSO_4 ,

concentrated and the residue purified by flash chromatography on silica (CH_2Cl_2 /acetone, 9:1) to afford the title compound (556 mg, 87%, $\text{MH}^+=335$).

Step D

[0531] The title compound from Step C above (760 mg) was dissolved in EtOAc (4 ml) and a solution of 4 M HCl in

dioxane (4 ml) was added. After 2 h the mixture was triturated with aqueous NaHCO_3 to pH 7.5 and stirred for 15 min at rt. After evaporation of the solvent, the crude residue was purified by flash chromatography on silica ($\text{CH}_2\text{Cl}_2/\text{MeOH}$, 9:1) to afford the title compound (300 mg, 77%, $\text{MH}^+=235$).

Step E

[0532] To a solution of the title compound from Step D above (290 mg) in THF (5 ml) was added triethyl amine (280 μl) and the mixture was stirred for 1 h at 50°C . Then the sulfamidate (590 mg), prepared according to WO 03/037327, was added in one portion at -15°C . and the mixture was stirred at ambient temperature over 2 d. After the addition of 1 M NH_4HCO_3 solution (5 ml), the mixture was stirred for 30 min. Then an excess saturated NaHCO_3 solution was added and stirring was continued for another 15 min. The mixture was then partitioned between EtOAc and water and the aqueous phase extracted with EtOAc. The combined organic phase was dried over MgSO_4 and concentrated in vacuo. The residue was purified by column chromatography on silica ($\text{CH}_2\text{Cl}_2/\text{acetone}$, 4:1) to afford the title compound (163 mg, 30%, $\text{MH}^+=436$).

Step F

[0533] A solution of the title compound from Step E above (163 mg) in MeOH (2.5 ml) and THF (5 ml) was treated with 1 N LiOH (1.5 ml) and stirred overnight at rt. The reaction mixture was acidified to pH 4.5 with 2 N HCl and stirred for 15 min at rt. The mixture was then extracted with EtOAc, the organic phase washed with brine, dried over MgSO_4 and evaporated to afford the title compound (140 mg, 96%, $\text{MH}^+=422$).

Preparative Example 93

[0534]

hydrochloride (15 mg) was added after 1 h, followed by N-methyl morpholine (20 μl). The mixture was stirred at rt overnight, the solvent removed in vacuo, and the residue was diluted with EtOAc. The mixture was washed with saturated aqueous NaHCO_3 , separated, dried over MgSO_4 and concentrated. The residue was purified by flash chromatography on silica ($\text{CH}_2\text{Cl}_2/\text{acetone}$, 9:1) to afford the title compound (17 mg, 59%, $\text{MH}^+=486$).

Step B

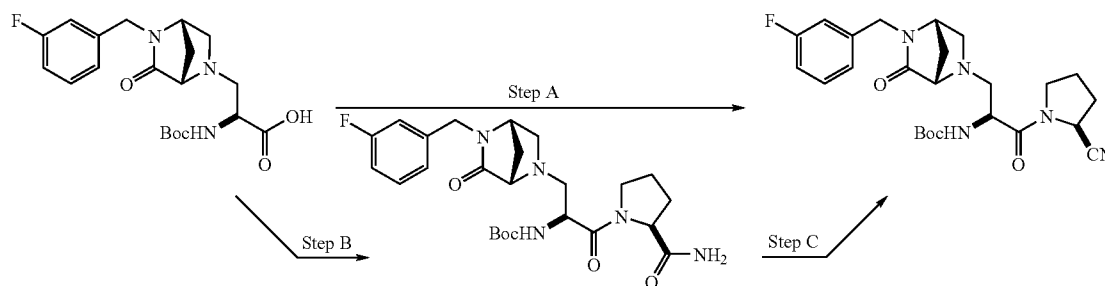
[0536] To a stirring solution of the title compound Preparative Example 91 (125 mg) in DMF (5 ml) was HOBt (46 mg), followed by EDCI (65 mg) and DMAP (5 mg). After 1 h commercially available L-proline amide (68 mg) and N-methyl morpholine (100 μl) were added and stirring was continued at rt overnight. The solvent was removed in vacuo, the residue diluted with EtOAc and washed with saturated aqueous NaHCO_3 . The organic phase was separated, dried over MgSO_4 and concentrated. The residue was purified by flash chromatography on silica ($\text{CH}_2\text{Cl}_2/\text{acetone}$, 4:1) to afford the title compound (137 mg; 88%; $\text{MH}^+=504$).

Step C

[0537] To a solution of the title compound from Step B above (137 mg) in pyridine (7 ml) was added imidazole (41 mg). At -30°C . POCl_3 (102 μl) was slowly added to the mixture and the mixture was allowed to reach rt over a period of 1 h. Then the solvent was removed and the residue diluted with 1 N HCl and Et₂O. The organic phase was separated, dried over MgSO_4 and evaporated. The residue was purified by column chromatography on silica ($\text{CH}_2\text{Cl}_2/\text{acetone}$, 4:1) to afford the title compound (72 mg, 55%, $\text{MH}^+=486$).

Preparative Example 94-108

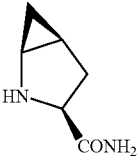
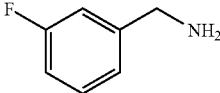
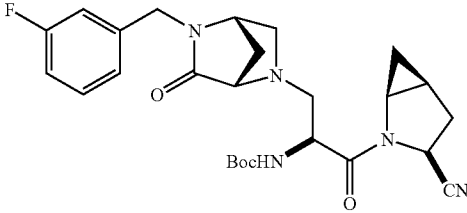
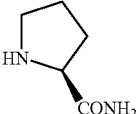
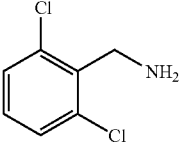
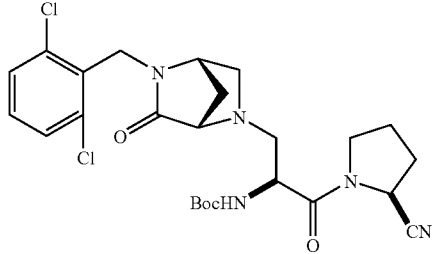

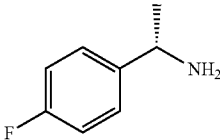
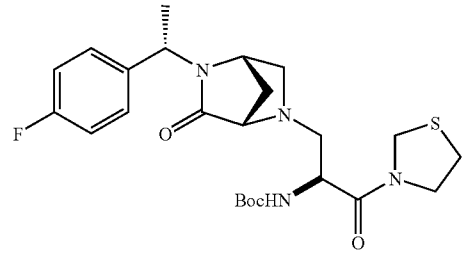
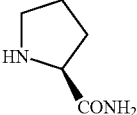
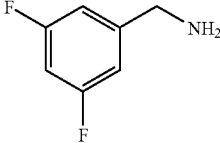
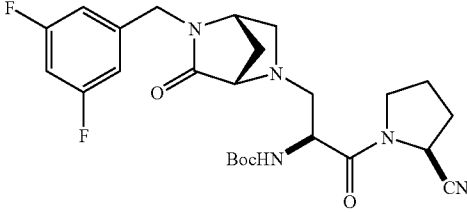
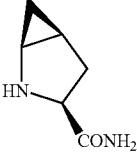
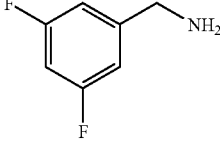
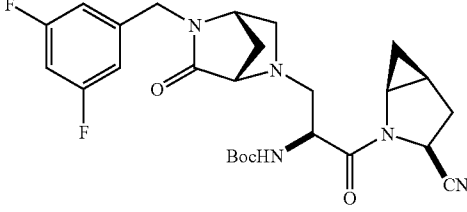
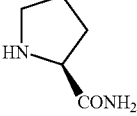
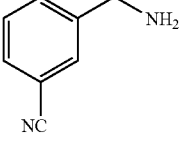
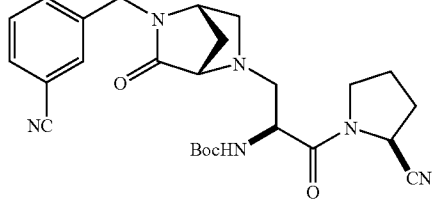
[0538] Following a similar procedure as that described in Preparative Examples 92 and 93, except using the amines and



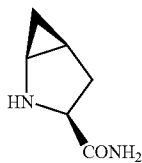
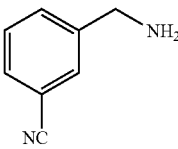
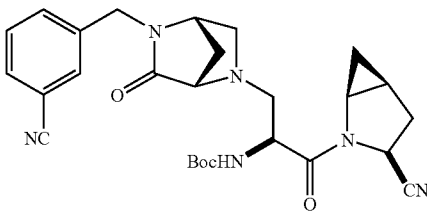
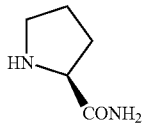
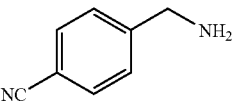
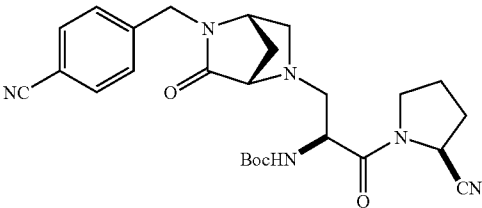
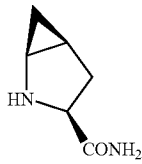
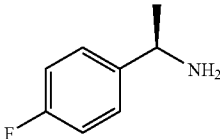
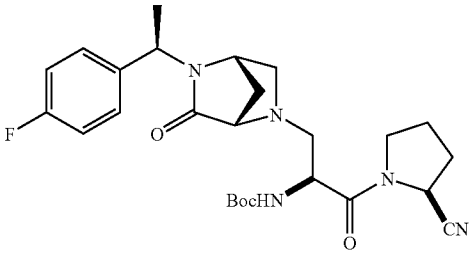
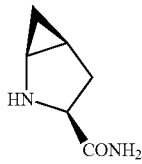
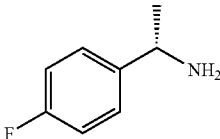
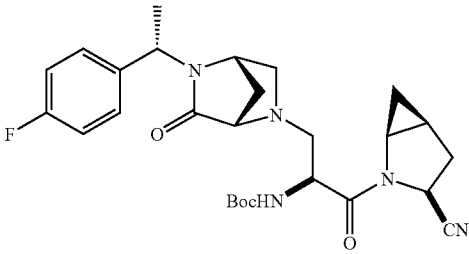
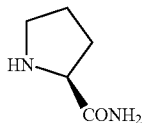
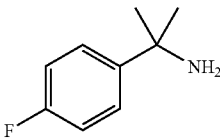
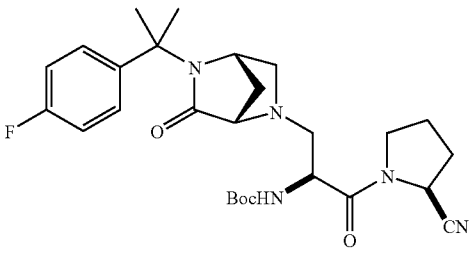
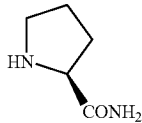
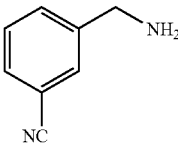
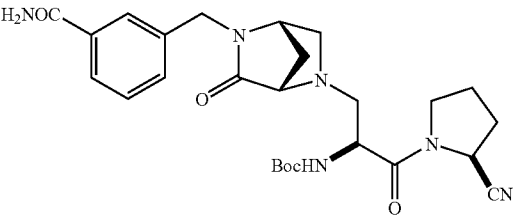
Step A

[0535] To a stirring solution of the title compound from Preparative Example 91 (25 mg) in DMF (3 ml) was added HOBt (15 mg), followed by EDCI (20 mg) and DMAP (3 mg). Commercially available (S)-Pyrrolidine-2-carbonitrile

amides as indicated in the Table below, the following compound were prepared. For Preparative Examples 105 and 106 the conversion of the nitrile to the carboxamide with subsequent saponification of the ester moiety was done according to Preparative Example 91 Step F with 3M Na_2CO_3 and H_2O_2 .

Preparative Example	Amide	Amine	Product	1. Yield 2. MH ⁺
94				1. 55% 2. 498
95				1. 90% 2. 537
96				1. 71% 2. 493
97				1. 70% 2. 504
98				1. 73% 2. 516
99				1. 65% 2. 493

-continued

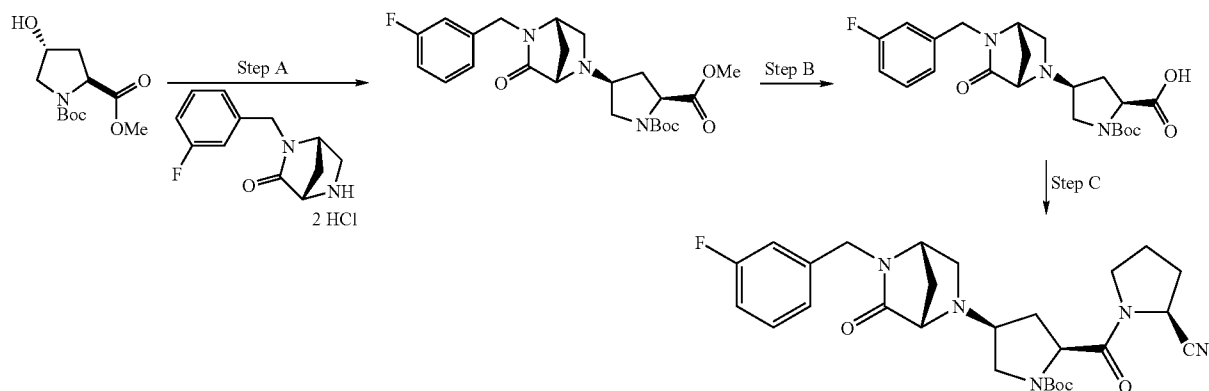
Preparative Example	Amide	Amine	Product	1. Yield 2. MH ⁺
100				1. 54% 2. 505
101				1. 78% 2. 493
102				1. 56% 2. 500
103				1. 65% 2. 512
104				1. 71% 2. 514
105				1. 68% 2. 511

-continued

Preparative Example	Amide	Amine	Product	1. Yield 2. MH ⁺
106				1. 56% 2. 511
107				1. 62% 2. 526
108				1. 2.

Preparative Example 109

[0539]



Step A

[0540] A solution of commercially available N-Boc-trans-4-hydroxy-L-proline methyl ester (370 mg) in CH_2Cl_2 (2 ml) was cooled to -30°C . and treated with DIEA (600 μl). After the addition of triflic anhydride (280 μl), the mixture was stirred at -30°C . for 60 min and then treated with a solution of the title compound from Preparative Example 91 Step D in

CH_2Cl_2 (2 ml). The mixture was allowed to warm to rt overnight. The mixture was diluted with CH_2Cl_2 (10 ml), washed with 0.5 M Na_2CO_3 (2×10 ml) and brine (10 ml). The organic phase was dried over MgSO_4 and concentrated to leave a residue, which was purified by chromatography on silica ($(\text{CH}_2\text{Cl}_2/\text{acetone}, 4:1, 4:1)$) to afford the title compound (225 mg, 33%, $\text{MH}^+=448$).

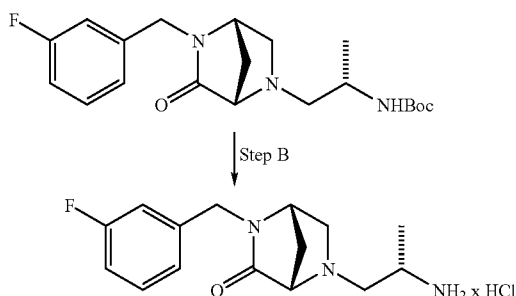
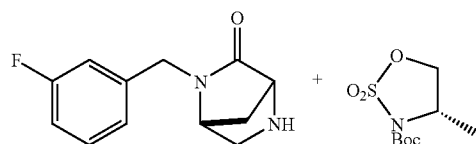
Step B

[0541] A solution of the title compound from Step A above (225 mg) in MeOH (4 ml) and THF (8 ml) was treated with 1 N LiOH (2 ml) and stirred overnight at rt. The reaction mixture was acidified to pH 4.5 with 1 N HCl and stirred for 15 min at rt. The mixture was then extracted with EtOAc, the organic phase washed with brine, dried over MgSO_4 and evaporated to afford the title compound (91 mg, 40%, $\text{MH}^+=434$).

Step C

[0542] To a stirring solution of the title compound from Step B above (91 mg) in DMF (3 ml) was added HOBt (40 mg), followed by EDCI (60 mg) and DMAP (10 mg). Commercially available (S)-Pyrrolidine-2-carbonitrile hydrochloride (35 mg) was added after 1 h, followed by N-methyl morpholine (66 μl). The mixture was stirred at rt overnight, the solvent removed in vacuo, and the residue was diluted with EtOAc. The mixture was washed with saturated aqueous NaHCO_3 , separated, dried over MgSO_4 and concentrated. The residue was purified by flash chromatography on silica (CH_2Cl_2 /acetone, 1:1) to afford the title compound (50 mg, 47%, $\text{MH}^+=512$).

Preparative Example 110

[0543]

Step A

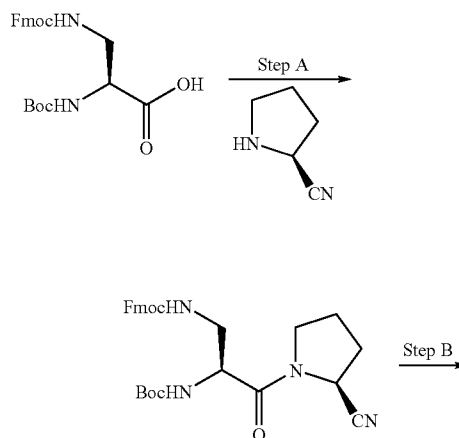
[0544] The title compound from Preparative Example 91 Step D (305 mg) was dissolved in THF (2 ml) and triethyl amine (63 μl) was added and the mixture was stirred for 1 h at 50°C . Then the title compound from Preparative Example 19 (100 mg) was added in one portion at -15°C . and the mixture was stirred at ambient temperature overnight. After the addition of 1 M NH_4HCO_3 solution (5 ml), the mixture was stirred for 30 min. Then an excess saturated NaHCO_3 solution was added and stirring was continued for another 15 min. The mixture was then partitioned between EtOAc and water and the aqueous phase extracted with EtOAc. The combined organic phase was dried over MgSO_4 and concentrated in vacuo. The residue was purified by column chromatography on silica (CH_2Cl_2 /acetone, 4:1) to afford the title compound (58 mg, 57%, $\text{MH}^+=378$).

Step B

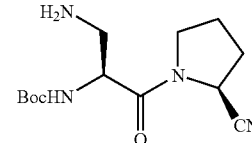
[0545] The title compound from Step A above (58 mg) was dissolved in EtOAc (2 ml) and a solution of 4 M HCl in

dioxane (2 ml) was added. After 2 h the mixture was evaporated to afford the title compound (48 mg, quant., $\text{MH}^+=278$).

Preparative Example 111

[0546]

-continued



Step A

[0547] Commercially available N-cyclohexylcarbodiimide-N'-methyl polystyrene resin (1.9 g) was suspended in 5 ml dichloromethane and agitated for 5 min. The commercially available amino acid (468 mg) and amine (86 mg), prepared from the commercially available hydrochloride by adding 1 eq. pyridine, were dissolved in 1.5 ml dimethylformamide and added to the above resin. The mixture was agitated for 16 h, filtered and the resin washed with 2×5 ml dichloromethane and 5 ml methanol. The combined filtrates were concentrated

and the residue purified by flash chromatography (silica, $\text{CH}_2\text{Cl}_2/\text{MeOH}$, 9:1) to afford the title compound (500 mg; 91%).

[0548] $^1\text{H-NMR}$ (CDCl_3): δ 1.45 (9H, s), 2.05-2.30 (4H, m), 3.25-3.40 (1H, m), 3.50-3.70 (2H, m), 3.80-3.90 (1H, m), 4.15-4.25 (1H, m), 4.30-4.40 (2H, m), 4.55-4.65 (1H, m), 4.70-4.80 (1H, m), 5.50-5.60 (2H, m), 7.25-7.40 (4H, m), 7.55-7.65 (2H, m), 7.70-7.80 (2H, m).

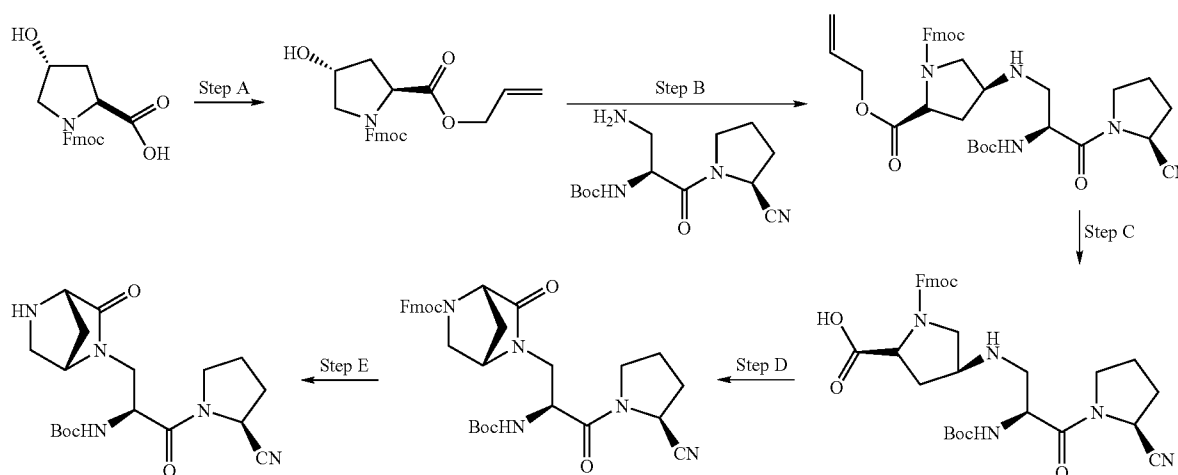
Step B

[0549] The title compound from Step A above (500 mg) was dissolved in dichloromethane (10 ml) and treated with diethylamine (10 ml). After 2 h the mixture was concentrated and the residue was purified by flash chromatography (silica, $\text{CH}_2\text{Cl}_2/\text{MeOH}$, 4:1) to afford the title compound (224 mg; 80%).

[0550] $^1\text{H-NMR}$ (CDCl_3): δ 1.45 (9H, s), 1.70 (2H, s), 2.05-2.30 (4H, m), 2.95-3.05 (2H, m), 3.70-3.85 (2H, m), 4.35-4.50 (1H, m), 4.75-4.85 (1H, m), 5.50-5.60 (1H, m).

Preparative Example 112

[0551]



Step A

[0552] A solution of commercially available N-Fmoc-trans-4-hydroxy-L-proline (4.5 g) in aqueous ethanol (80%, 45 ml) was titrated with a solution of Cs_2CO_3 (2.3 g) in water (18 ml) to pH 7. The solvents were evaporated and the residue dried in vacuo. The caesium salt was suspended in dry DMF (45 ml), cooled to 0°C . and treated with allyl bromide (11.5 ml) by dropwise addition over 10 min. After 30 min the solution was allowed to reach rt and stirring was continued for another 3 h. The reaction mixture was filtered and concentrated. The residue was purified by chromatography on silica ($\text{EtOAc}/\text{cyclohexane}$) to afford the title compound (4.5 g, 90%, $\text{MH}^+=394$).

Step B

[0553] The title compound from Step A above (2.5 g) in CH_2Cl_2 (60 ml) was cooled to -30°C . and treated with DIEA

(2.5 ml). After the addition of triflic anhydride (1.2 ml), the mixture was stirred at -30°C . for 60 min and then treated with a solution of Preparative Example 84 (1.17 g) in CH_2Cl_2 (15 ml). The mixture was allowed to warm to 0°C ., stirred at 0°C . for 12 h and refluxed for additional 4 h. The mixture was diluted with CH_2Cl_2 (50 ml), washed with 0.5 M Na_2CO_3 (2×25 ml) and brine (25 ml). The organic phase was dried over MgSO_4 and concentrated to leave a residue, which was purified by chromatography on silica ($\text{EtOAc}/\text{cyclohexane}$, 7:3) to afford the title compound (1.41 g, 50%, $\text{MH}^+=658$).

Step C

[0554] To the title compound from Step B above (1.8 g) in THF (120 ml) was added dimedone (1.27 g) and $\text{Pd}(\text{PPh}_3)_4$ (422 mg). The reaction mixture was stirred at room temperature for 19 h. Following removal of the solvent under reduced pressure, chromatography on silica ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 9:1) afforded the title compound (1.42 g, 84%, $\text{MH}^+=618$).

Step D

[0555] To a solution of the title compound from Step C above (1.42 g) in CH_2Cl_2 (70 ml) was added HOBT (405 mg)

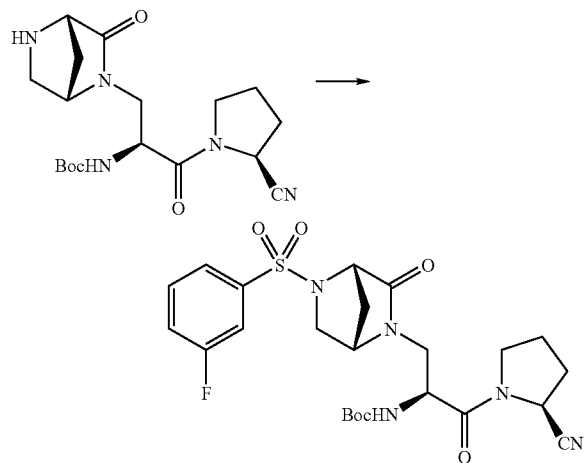
followed by EDCI (575 mg) and N-methyl-morpholine (0.33 ml). After being stirred at ambient temperature for 24 h, the solvent was evaporated to give a viscous residue, which was partitioned between EtOAc and ammonium acetate buffer (pH 6). The aqueous phase was extracted with ethyl acetate (3×100 ml) and the combined organic phase dried over MgSO_4 and concentrated to afford the title compound (1.35 g, $\text{MNH}_4^+=617$).

Step E

[0556] To a solution of the title compound from Step D above (1.35 g) in acetonitrile (100 ml) was added diethylamine (10 ml). After stirring for 2.5 h at rt, the reaction mixture was concentrated. The residue was purified by chromatography on silica ($\text{CH}_2\text{Cl}_2/\text{MeOH}$, 9:1) to afford the title compound (712 mg; 85%, $\text{MH}^+=378$).

Preparative Example 113

[0557]



[0558] To a solution of the title compound from Preparative Example 112 (13 mg) in CH_2Cl_2 (0.8 ml) was added piperidino methyl polystyrene resin (65 mg) and 3-fluorobenzene-1-sulfonyl chloride (5.5 μl). After shaking at rt for 3 h, tris-(2-aminoethyl)amine polystyrene resin (30 mg) was added and agitated for additional 1 h at rt. The mixture was filtered, the resin washed with CH_2Cl_2 (5 ml) and methanol (1 ml) and the combined filtrates evaporated. Purification by chromatography on silica ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 9:1) afforded the title compound (13 mg, 71%, $\text{MNH}_4^+=553$).

Preparative Example 114-116

[0559] Following a similar procedure as that described in Preparative Example 113, except using the sulfonic acid chlorides as indicated in the Table below, the following compounds were prepared.

Preparative Example	Sulfonic acid chloride	Product	1. Yield 2. MH^+
114			1. 69 2. 541 (MNH_4^+)
115			1. 92 2. 546 (MNa^+)
116			1. 89 2. 604 (MNa^+)

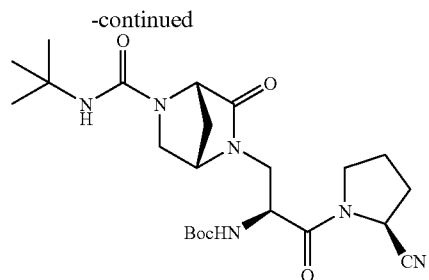
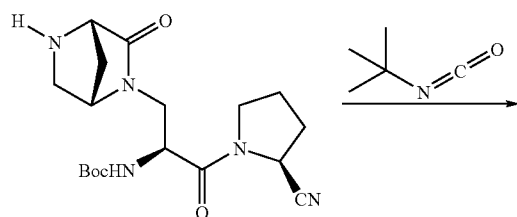
Preparative Example 117-119

[0560] Following a similar procedure as that described in Preparative Example 113, except using the acid chlorides as indicated in the Table below, the following compounds were prepared.

Preparative Example	Acid chloride	Product	1. Yield 2. MH^+
117			1. 100 2. 488 (MH^+)
118			1. 49 2. 519 (MNH_4^+)
119			1. 70 2. 506 (MNa^+)

Preparative Example 120

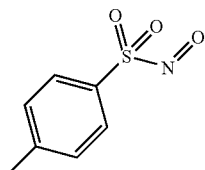
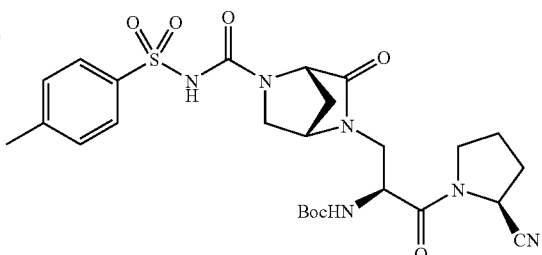
[0561]



[0562] To a solution of the title compound from Preparative Example 112 (20 mg) in CH_2Cl_2 (0.8 ml) was added tert-butyl isocyanate (5.8 mg). After stirring at room temperature for 3 h the solvent was evaporated. Purification by chromatography (CH_2Cl_2 /acetone 1:1) afford the title compound (16 mg, 63%, $MH^+=477$).

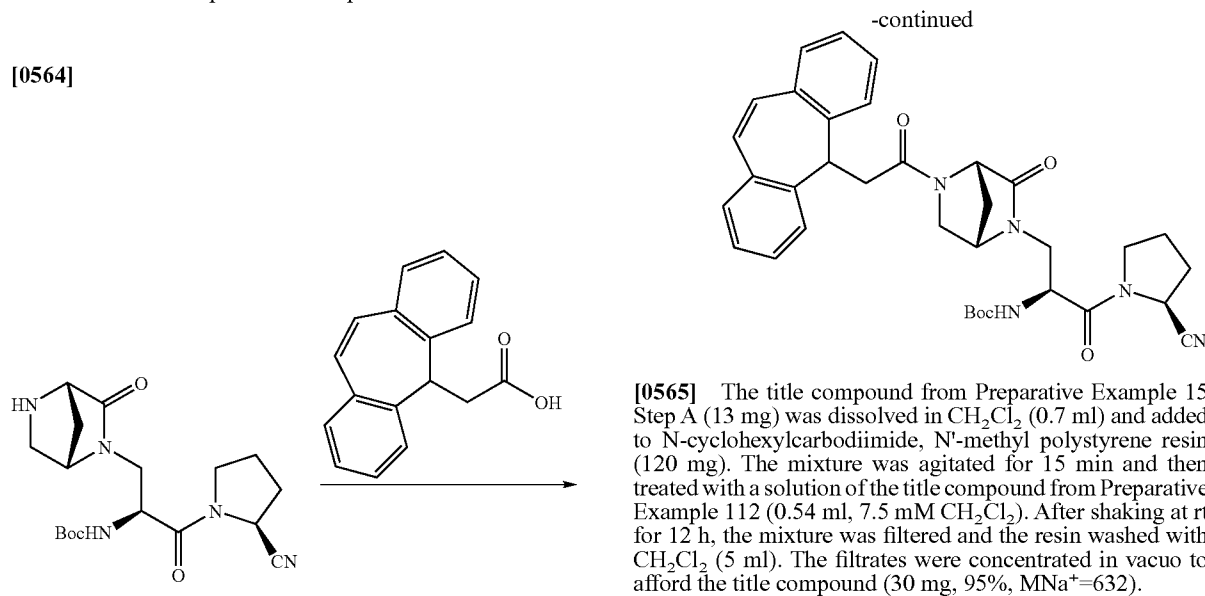
Preparative Example 121

[0563] Following a similar procedure as that described in Preparative Example 120, except using the isocyanate as indicated in the Table below, the following compound was prepared.

Preparative Example	Isocyanate	Product	1. Yield 2. MH ⁺
121			1. 69 2. 592 (MNH ₄ ⁺)

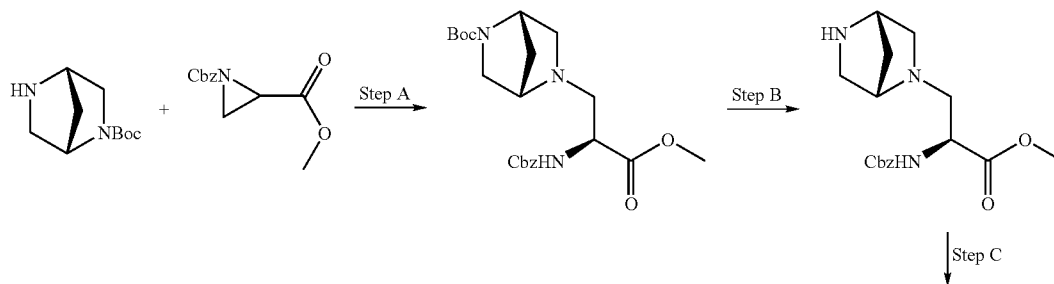
Preparative Example 122

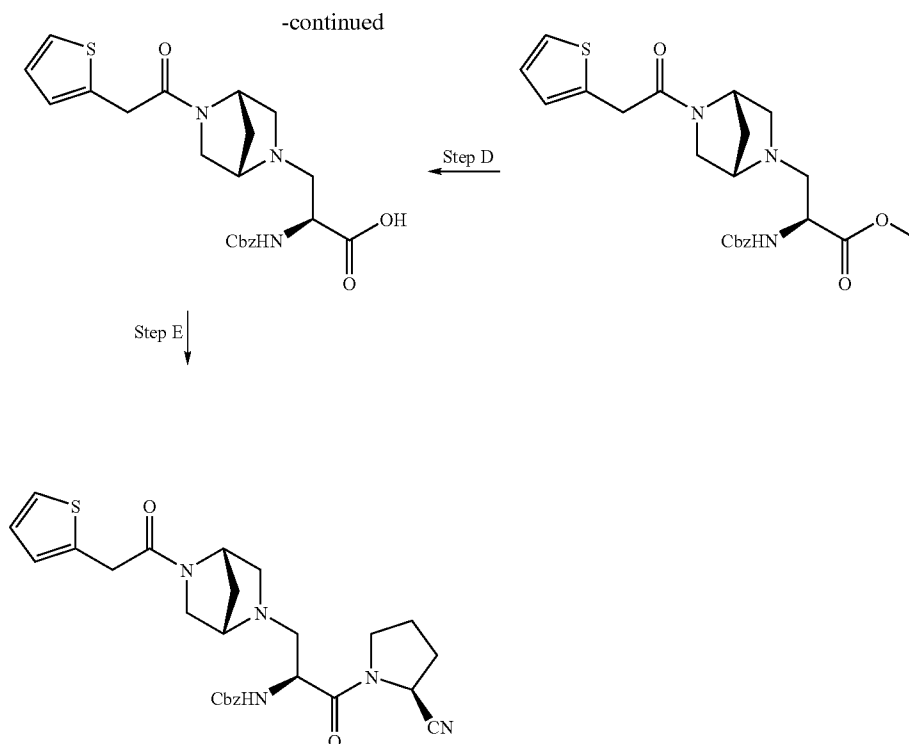
[0564]



Preparative Example 123

[0566]





Step A

[0567] Commercially available 2,5-diaza-bicyclo[2.2.1]heptane-2-carboxylic acid tert-butyl ester (400 mg) and aziridine-1,2-dicarboxylic acid 1-benzyl ester 2-methyl ester (431 mg) were dissolved in toluene (5 ml). The mixture was stirred at rt overnight and then for 5 h at 80° C. The solvent was removed and the residue purified by chromatography on silica (CH₂Cl₂/acetone 9:1) to afford the title compound (468 mg, 58%, MH⁺=434).

Step B

[0568] The title compound from Step A above (245 mg) was dissolved in dioxane (5 ml) and a solution of 4 M HCl in dioxane (5 ml) was added. The mixture was stirred for 2 h at rt and the solvents removed to afford the title compound (208 mg, 100%, MH⁺=334).

Step C

[0569] To the title compound from Step B above (130 mg) were added CH₂Cl₂ (10 ml) and pyridine (1 ml). After the addition of commercially available thiophen-2-yl-acetyl chloride (61 mg) the reaction mixture was stirred at rt overnight. The solvent was removed and the residue purified by chromatography on silica (CH₂Cl₂/acetone 9:1) to afford the title compound (90 mg, 57%, MH⁺=458).

Step D


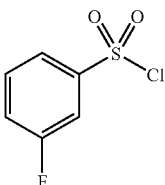
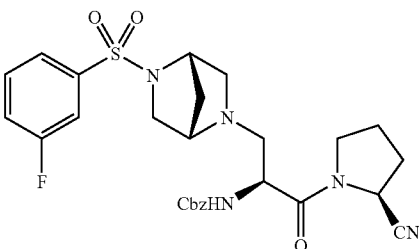
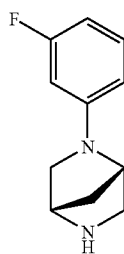
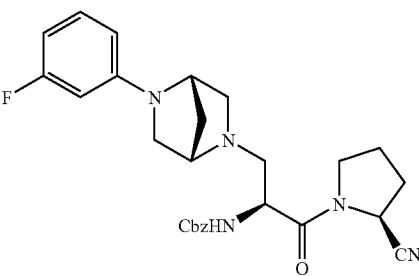
[0570] The title compound from Step C above (130 mg) was dissolved in THF (4 ml) and methanol (2 ml). After the addition of 1 M aqueous LiOH-solution (1 ml), the mixture was stirred for 4 h at rt. The solvents were removed and the residue dissolved in water and acidified with 1 M HCl to pH~4. The mixture was extracted with EtOAc, the organic phase washed with brine, dried over MgSO₄ and concentrated to yield the title compound (75 mg, 86%, MH⁺=444).

Step E

[0571] The title compound from Step D above (75 mg) was dissolved in DMF (5 ml). After the addition of EDCI (38 mg), HOBt (27 mg), N-methylmorpholine (0.15 ml) and DMAP (10 mol %), the mixture was stirred for 1 h at rt. Then commercially available 2-(S)-cyanopyrrolidine hydrochloride was added and the mixture was stirred overnight at rt. The solvent was removed and the residue dissolved in EtOAc, washed with brine, dried over MgSO₄, and concentrated. The residue was purified by chromatography on silica (cyclohexane/EtOAc, 7:3) to afford the title compound (27 mg, 30%, MH⁺=522).

Preparative Example 124-125

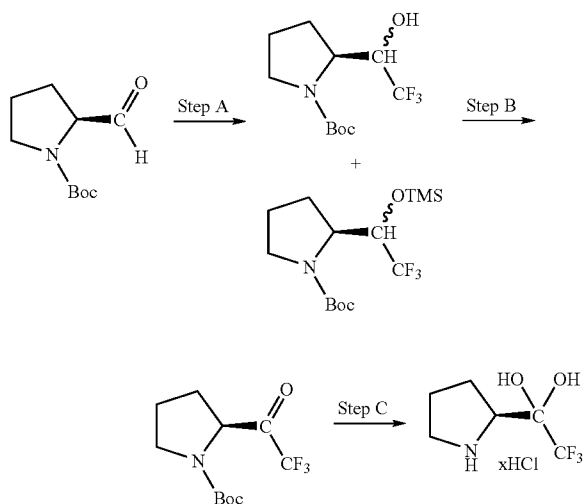
[0572] Following a similar procedure as that described in Preparative Example 123, except using the piperazine derivatives and sulfonic acid chlorides as indicated in the Table below, the following compounds were prepared.

Example	Piperazine derivative	Sulfonic Acid chloride	Product	1. Yield 2. MH ⁺
124				1. 73% 2. 556
125		none		1. 27% 2. 492

[0573] Preparative Examples 126-129 have been intentionally excluded.

Preparative Example 130

[0574]



Step A

[0575] Commercially available 2-formylpyrrolidine-1-carboxylic acid tert-butyl ester (330 mg) in anhydrous THF (5 ml) was cooled to 0° C. and trimethyl-trifluoromethylsilane (300 μ l) added, followed by addition of tetrabutylammoniumfluoride (60 μ l; 1 M in THF). The reaction mixture was allowed to warm to rt and then stirred for 1 h. After dilution

with diethyl ether, the organic phase was washed with brine and the aqueous phase extracted with diethyl ether. The combined organic phases were dried (MgSO₄) and evaporated to afford the title compounds as a 1:1 mixture of alcohol and TMS ether (490 mg, 97%, [MH-Boc]⁺=242 (TMS ether); [MH-Boc]⁺=170 (alcohol)).

Step B

[0576] The title compounds from Step A above (721 mg) in dichloromethane (5 ml) were added to Dess Martin periodinane (2.32 g) in dichloromethane (15 ml) with stirring. Trifluoroacetic acid (410 μ l) was added dropwise and the turbid reaction mixture stirred for 17 h at rt, after which it was directly coated on silica and purified by column chromatography (silica, cyclohexane/EtOAc 90:10→80:20) to afford the title compound (301 mg, 45%, [MH-Boc]⁺=168).

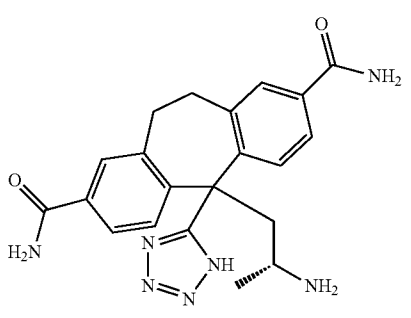
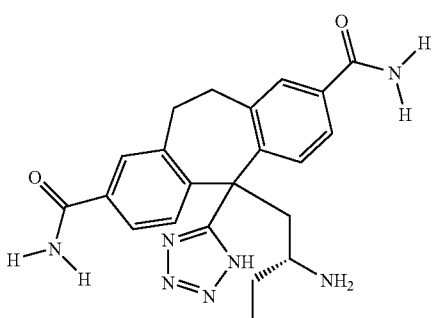
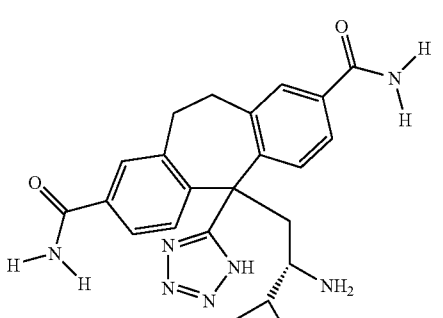
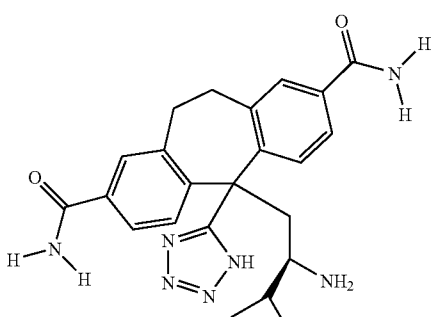
Step C

[0577] To the title compound from Step B above (106 mg) in dioxane (500 μ l) was added 4 M HCl in dioxane (500 μ l) and the resulting mixture stirred for 16 h at rt. Diethyl ether was added (2 ml) and the suspension filtered. The precipitate was dried and the title compound obtained as its HCl salt (81 mg, 91%, MH⁺=186).

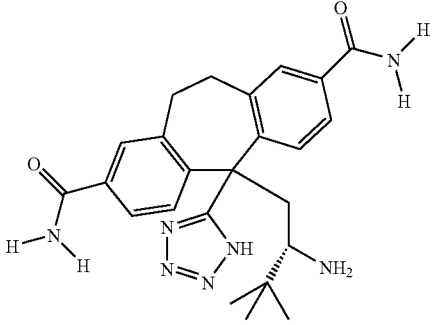
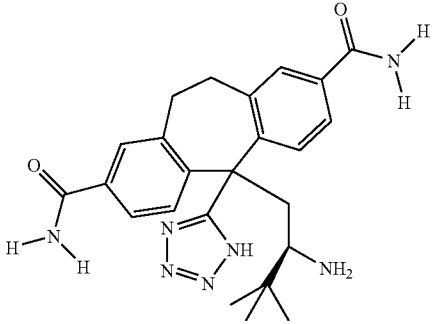
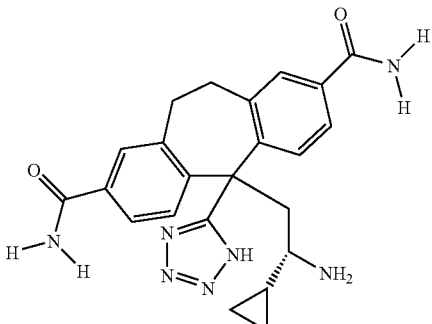
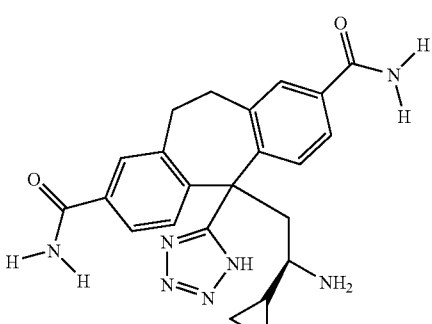
[0578] Preparative Examples 131-199 have been intentionally excluded.

Preparative Example 200-294

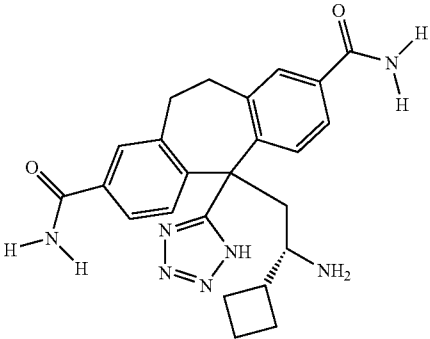
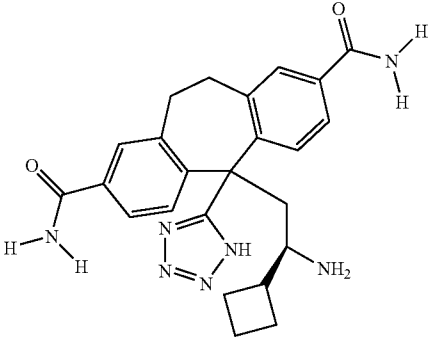
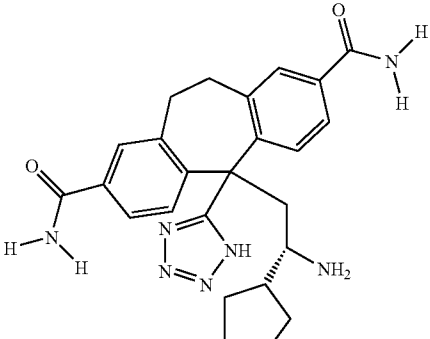
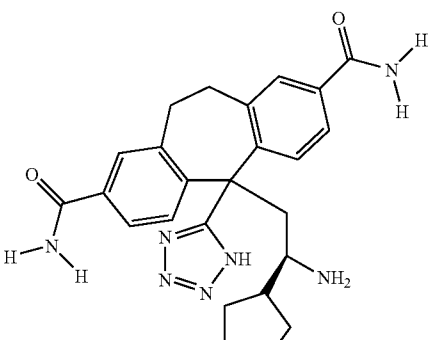
[0579] If one were to follow a similar procedure as that described in Preparative Example 61 and in Preparative Example 44, except using the sulfamides as indicated in the Table below in Step A of Preparative Example 61, one would obtain the title compounds, listed in the following Table in the "product" column.

Preparative Example	Preparative Example Sulfamidate	Product
200	24	
201	25	
202	26	
203	27	

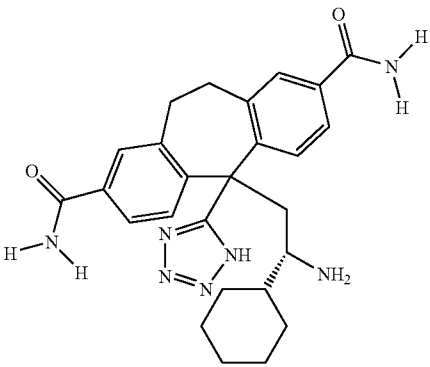
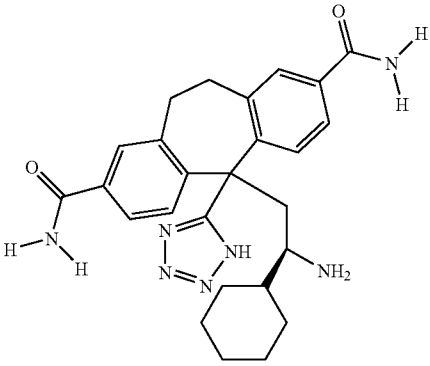
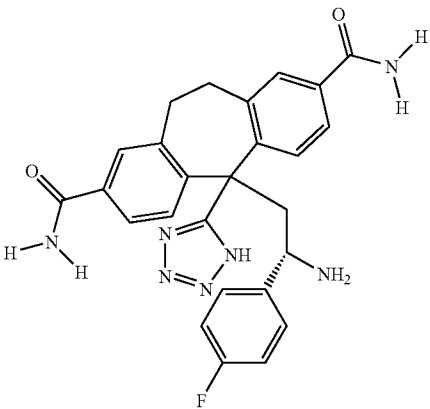
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Preparative Example	Preparative Example Sulfamidate	Product
204	28	
205	29	
206	30	
207	31	

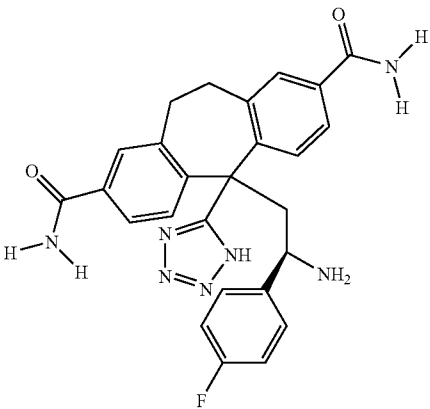
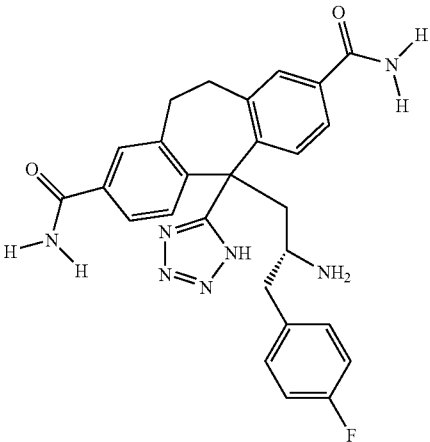
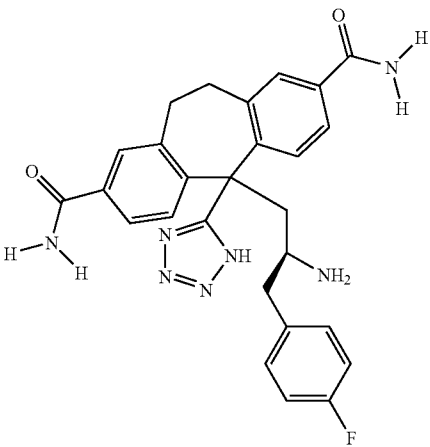
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Preparative Example	Preparative Example Sulfamidate	Product
208	32	
209	33	
210	34	
211	35	

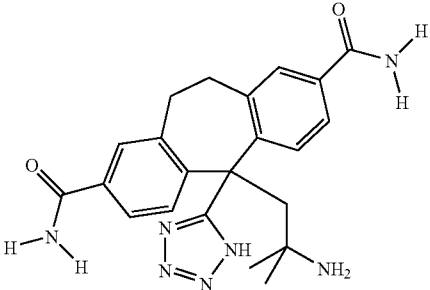
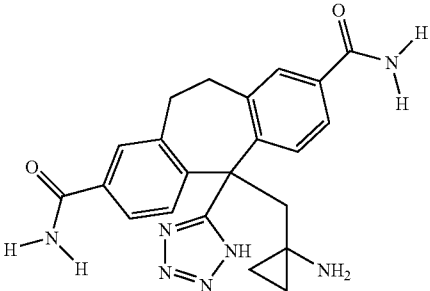
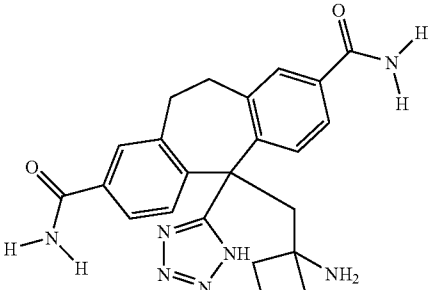
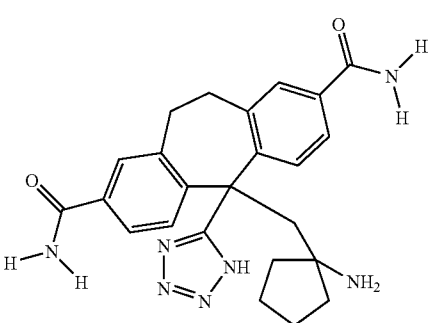
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Preparative Example	Preparative Example Sulfamidate	Product
212	36	
213	37	
214	38	

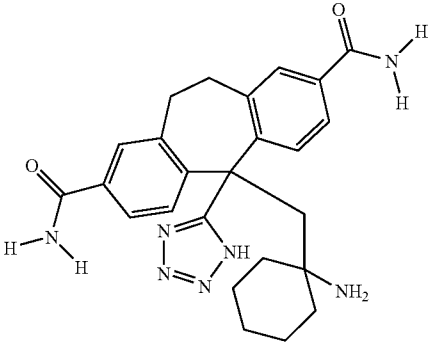
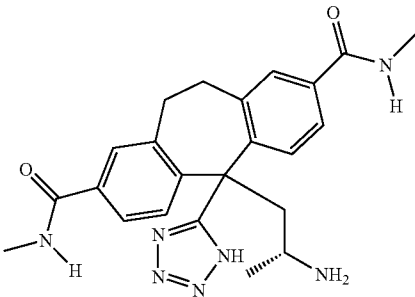
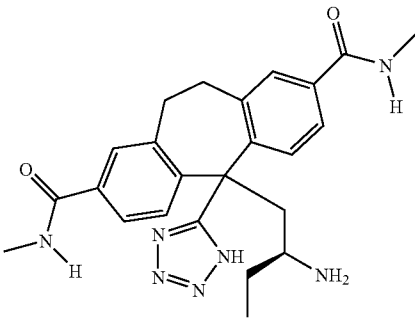
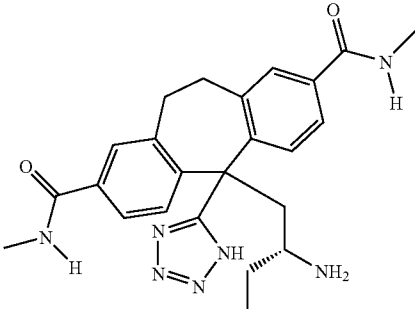
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Preparative Example	Preparative Example Sulfamidate	Product
215	39	
216	40	
217	41	

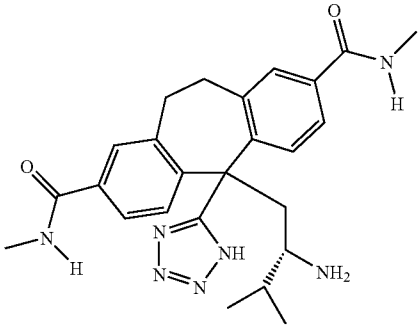
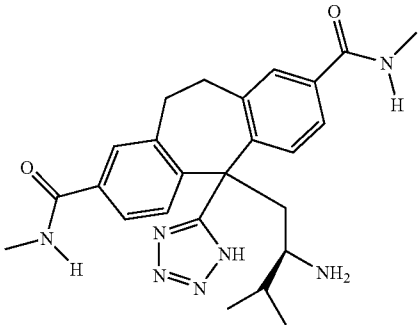
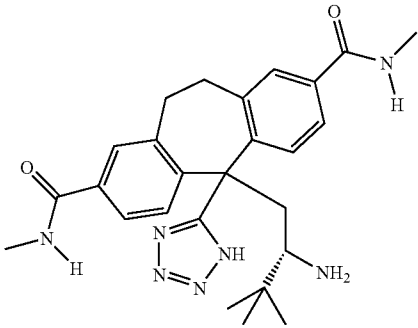
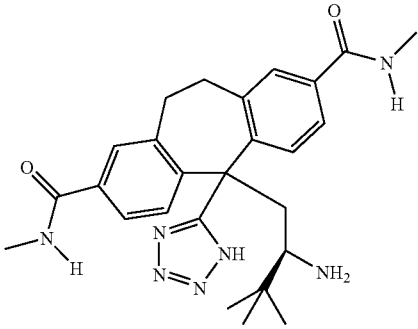
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Preparative Example	Preparative Example Sulfamidate	Product
218	42	
219	43	
220	44	
221	45	

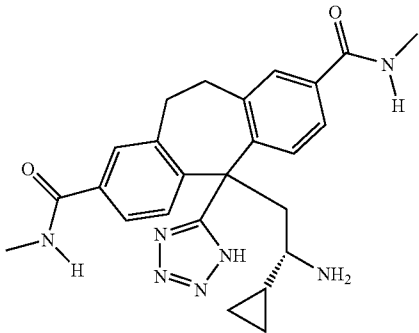
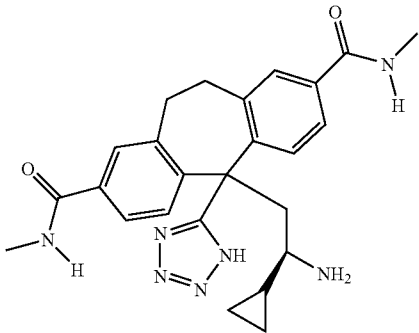
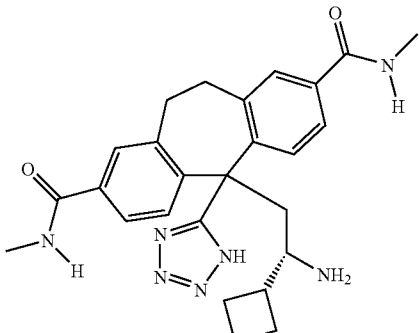
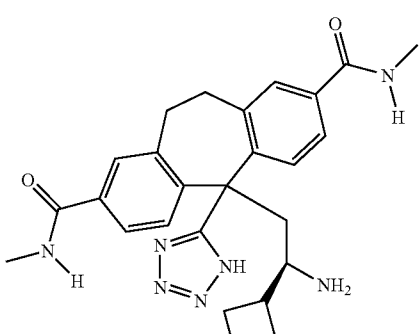
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Preparative Example	Preparative Example Sulfamidate	Product
222	46	
223	24	
224	23	
225	25	

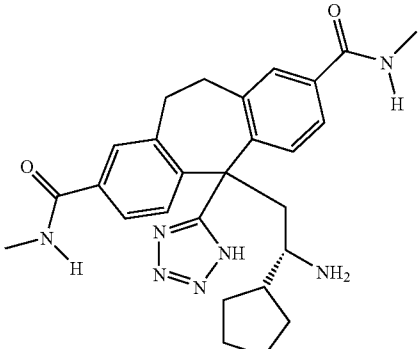
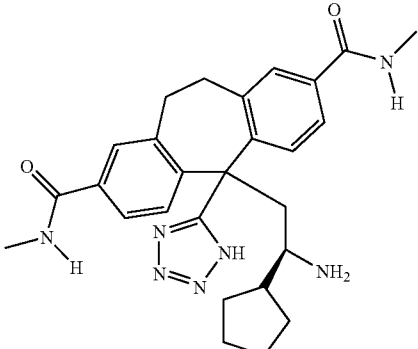
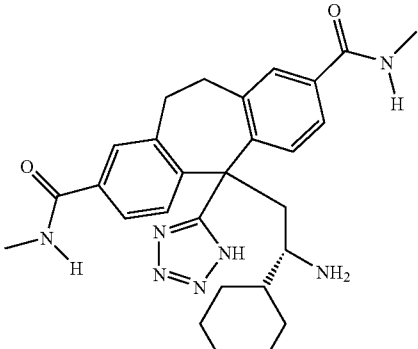
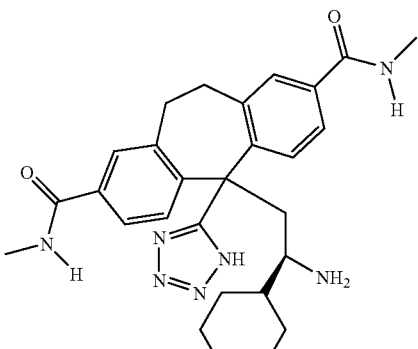
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Preparative Example	Preparative Example Sulfamidate	Product
226	26	
227	27	
228	28	
229	29	

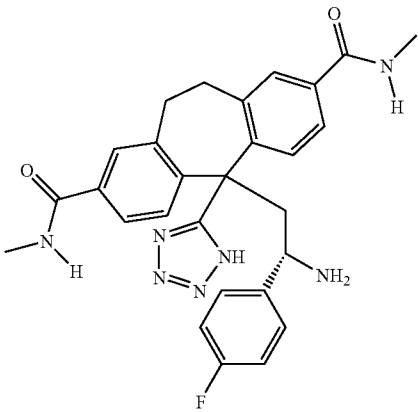
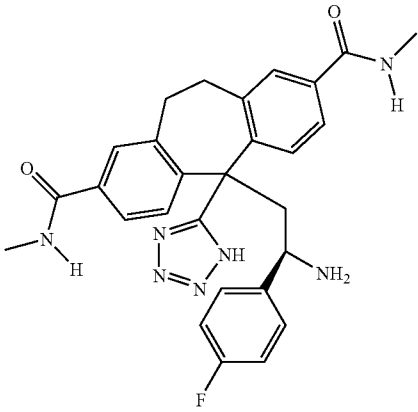
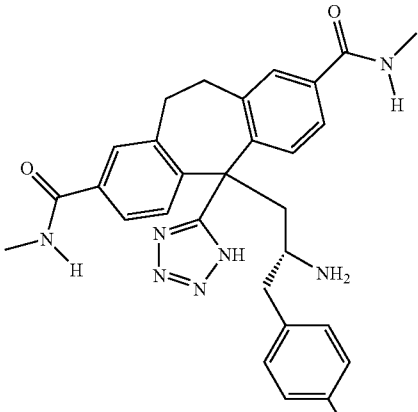
-continued

Preparative Example	Preparative Example Sulfamidate	Product
230	30	
231	31	
232	32	
233	33	

-continued

Preparative Example	Preparative Example Sulfamidate	Product
234	34	
235	35	
236	36	
237	37	

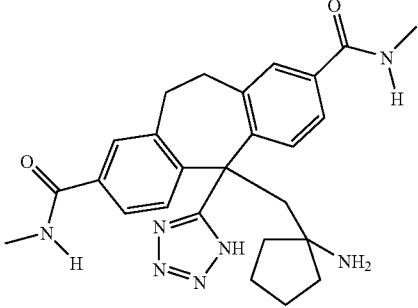
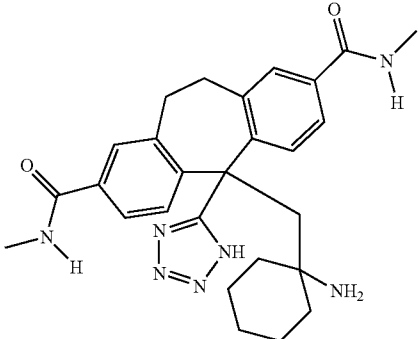
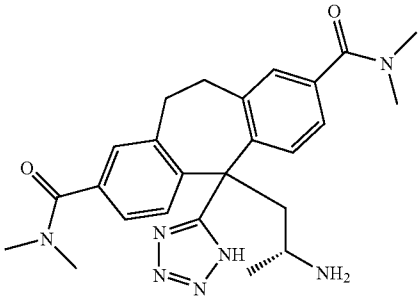
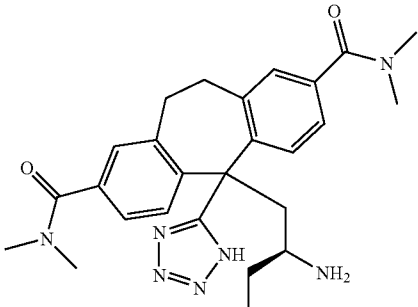
-continued

Preparative Example	Preparative Example Sulfamidate	Product
238	38	
239	39	
240	40	

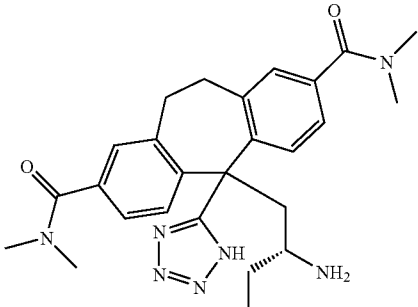
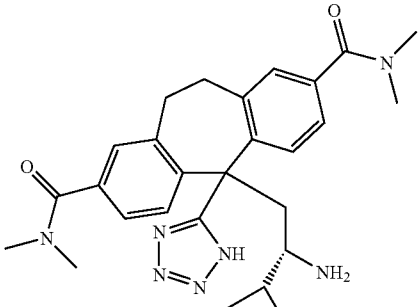
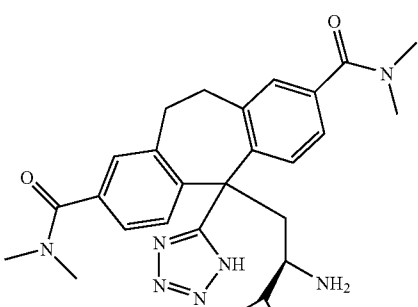
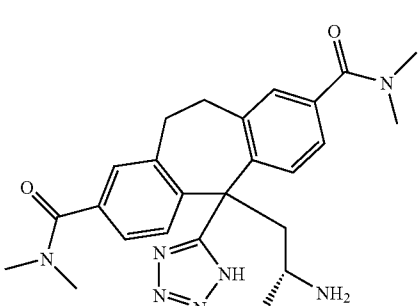
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Preparative Example	Preparative Example Sulfamidate	Product
241	41	
242	42	
243	43	
244	44	

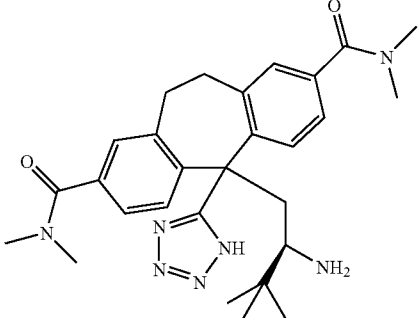
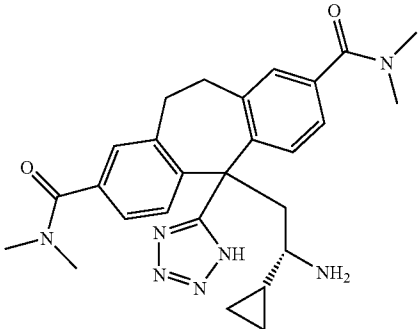
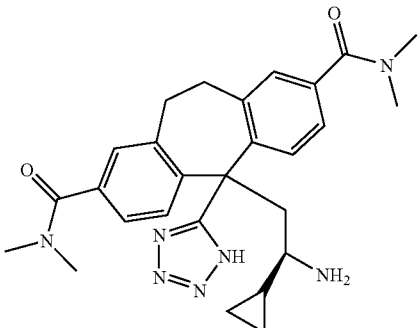
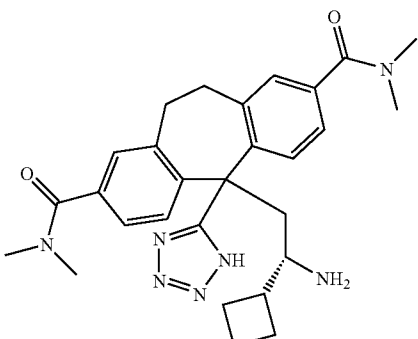
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Preparative Example	Preparative Example Sulfamidate	Product
245	45	
246	46	
247	24	
248	23	

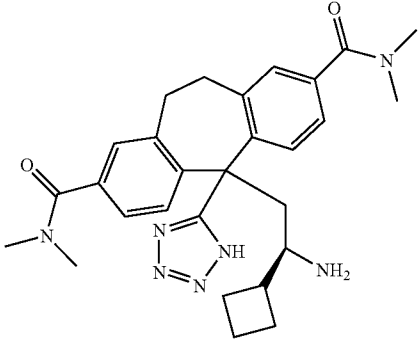
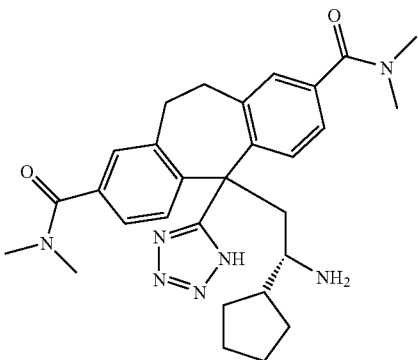
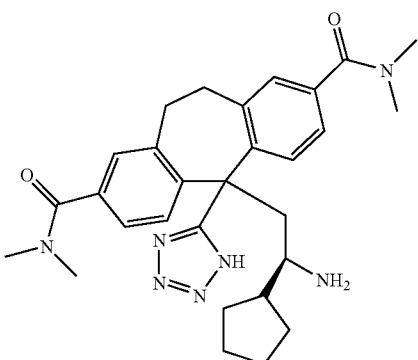
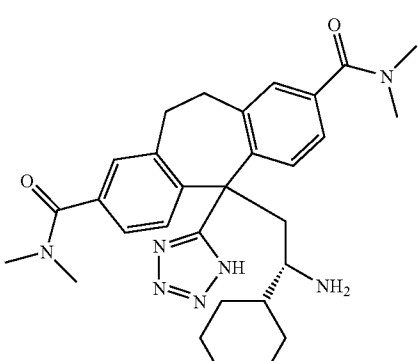
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Preparative Example	Preparative Example Sulfamidate	Product
249	25	
250	26	
251	27	
252	28	

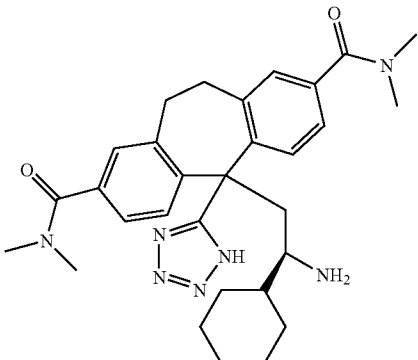
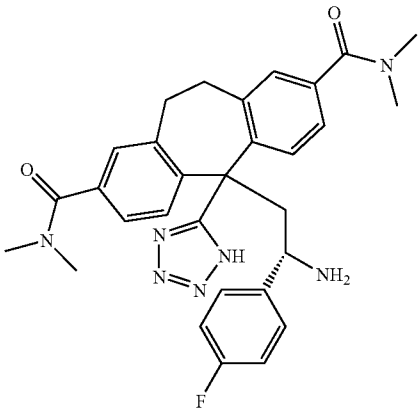
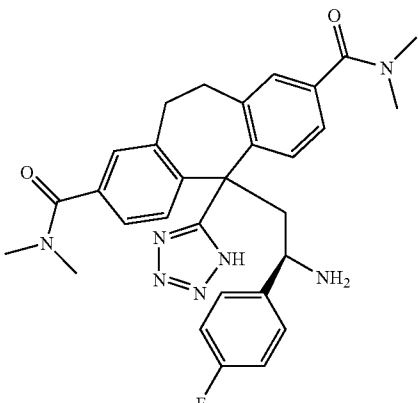
-continued

Preparative Example	Preparative Example Sulfamidate	Product
253	29	
254	30	
255	31	
256	32	

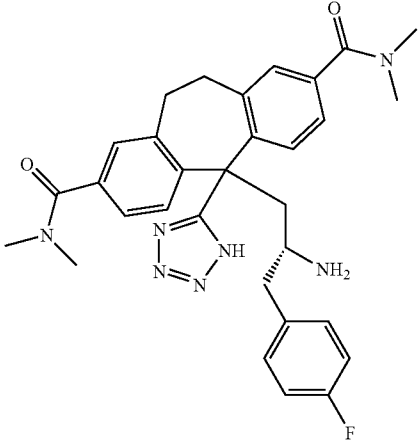
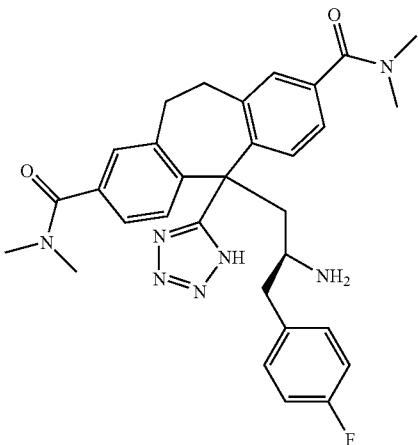
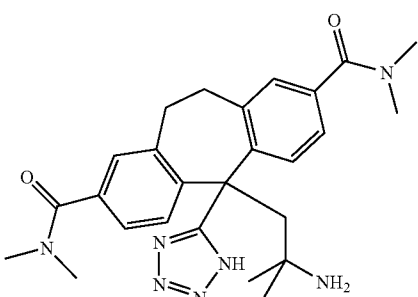
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Preparative Example	Preparative Example Sulfamidate	Product
257	33	
258	34	
259	35	
260	36	

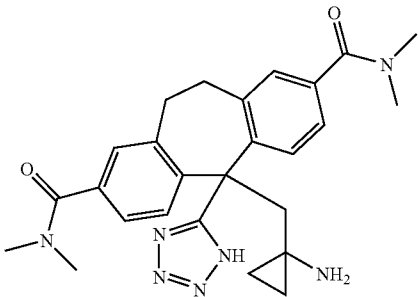
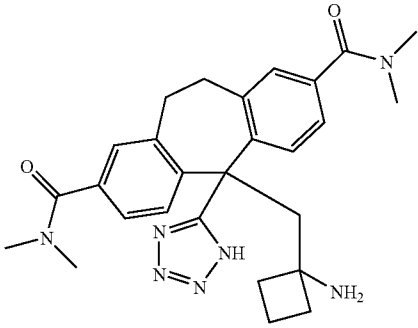
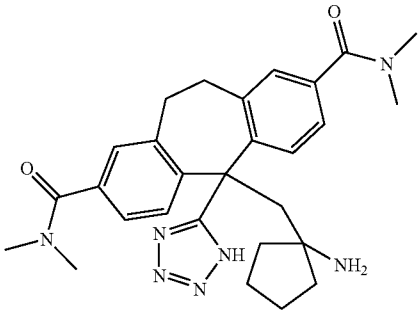
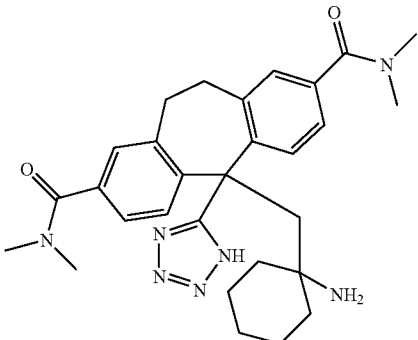
-continued

Preparative Example	Preparative Example Sulfamidate	Product
261	37	
262	38	
263	39	

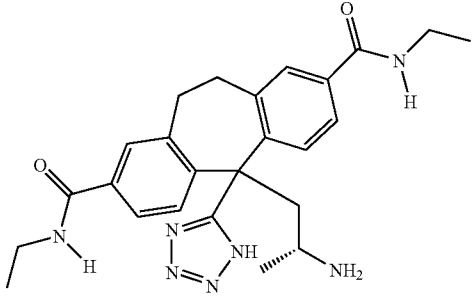
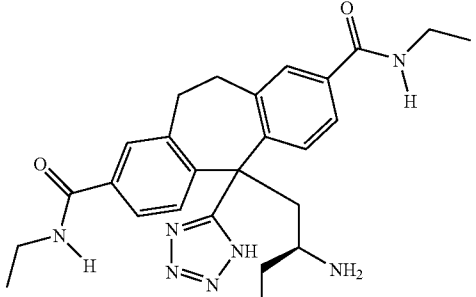
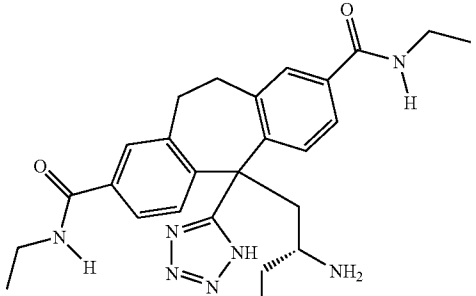
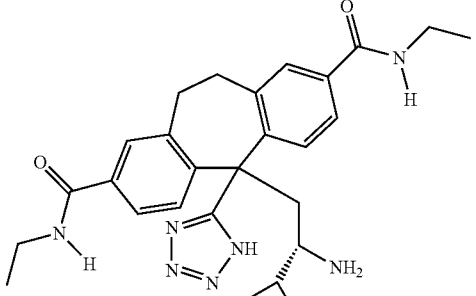
-continued

Preparative Example	Preparative Example Sulfamidate	Product
264	40	
265	41	
266	42	

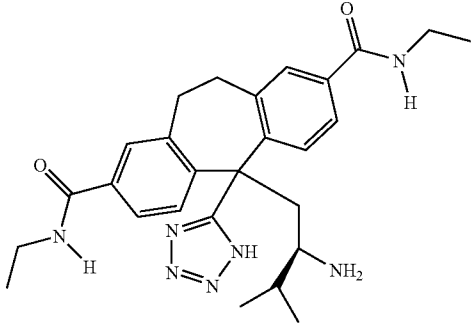
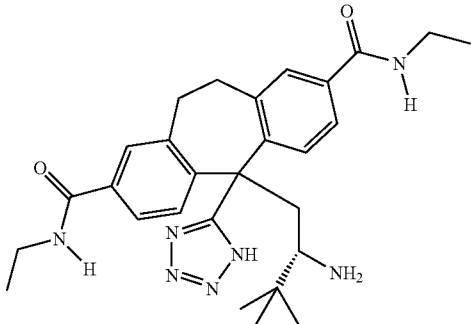
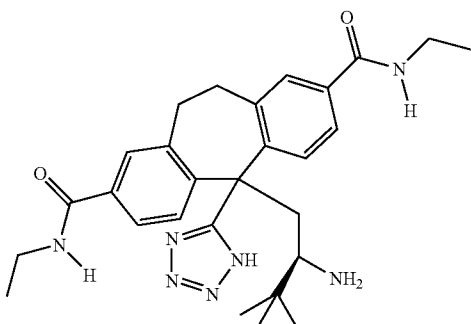
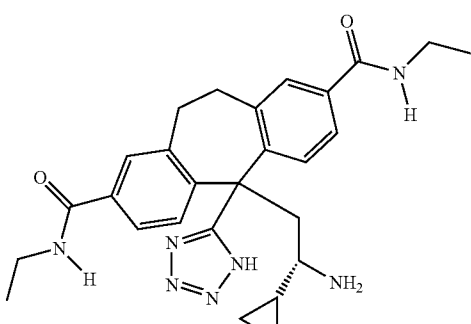
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Preparative Example	Preparative Example Sulfamidate	Product
267	43	
268	44	
269	45	
270	46	

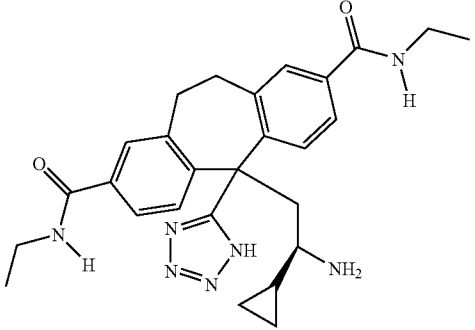
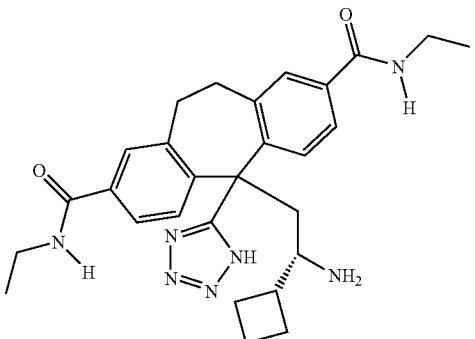
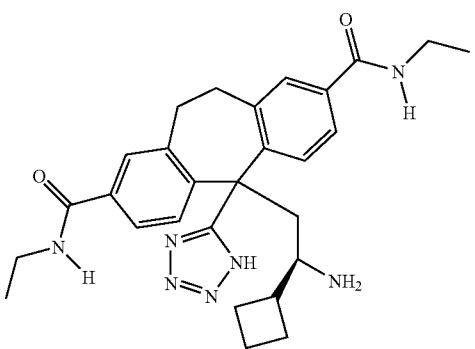
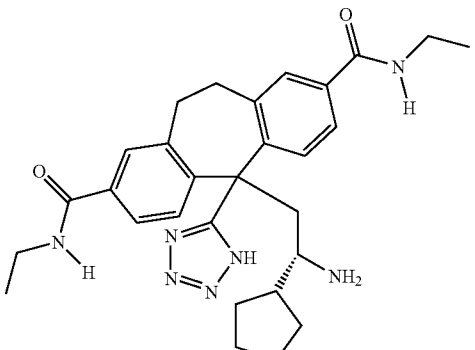
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Preparative Example	Preparative Example Sulfamidate	Product
271	24	
272	23	
273	25	
274	26	

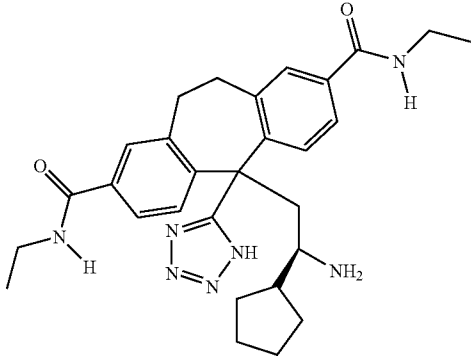
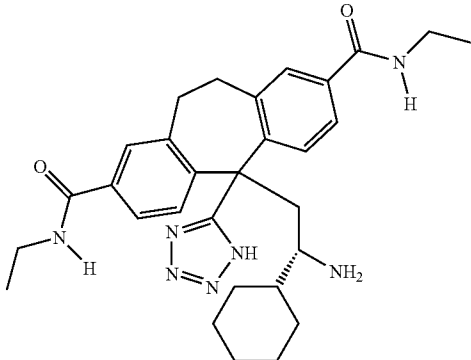
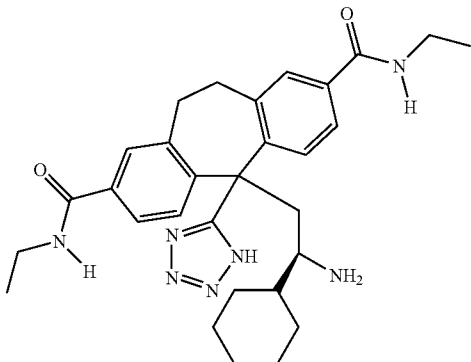
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Preparative Example	Preparative Example Sulfamidate	Product
275	27	
276	28	
277	29	
278	30	

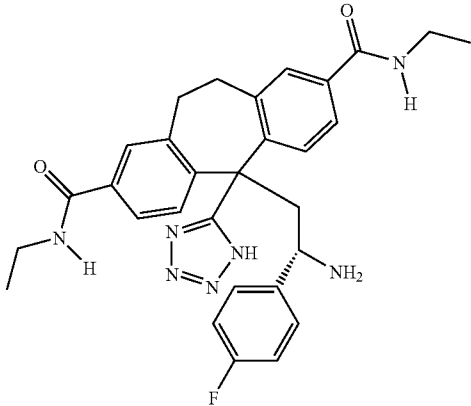
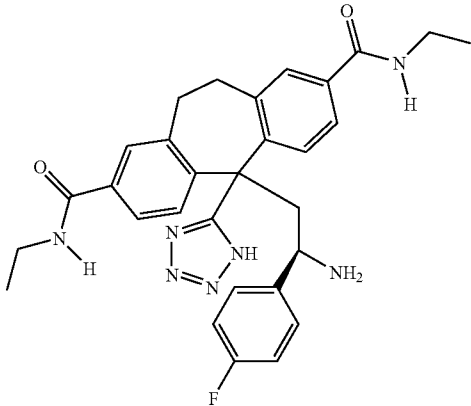
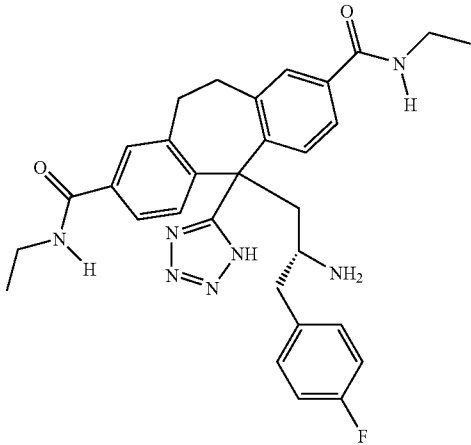
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Preparative Example	Preparative Example Sulfamidate	Product
279	31	
280	32	
281	33	
282	34	

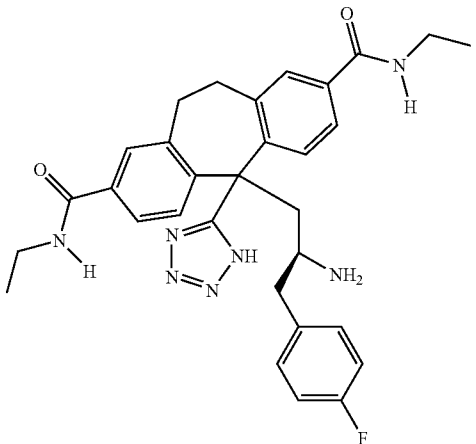
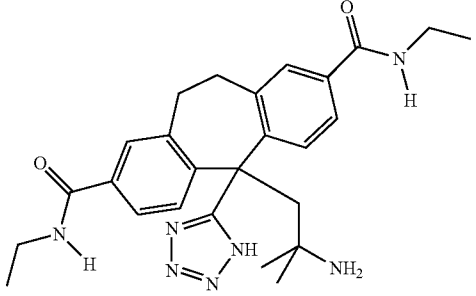
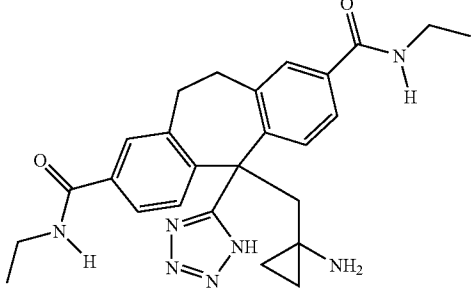
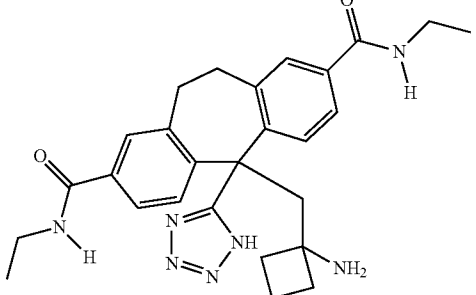
-continued

Preparative Example	Preparative Example Sulfamidate	Product
283	35	
284	36	
285	37	

-continued

Preparative Example	Preparative Example Sulfamidate	Product
286	38	
287	39	
288	40	

-continued

Preparative Example	Preparative Example Sulfamidate	Product
289	41	
290	42	
291	43	
292	44	

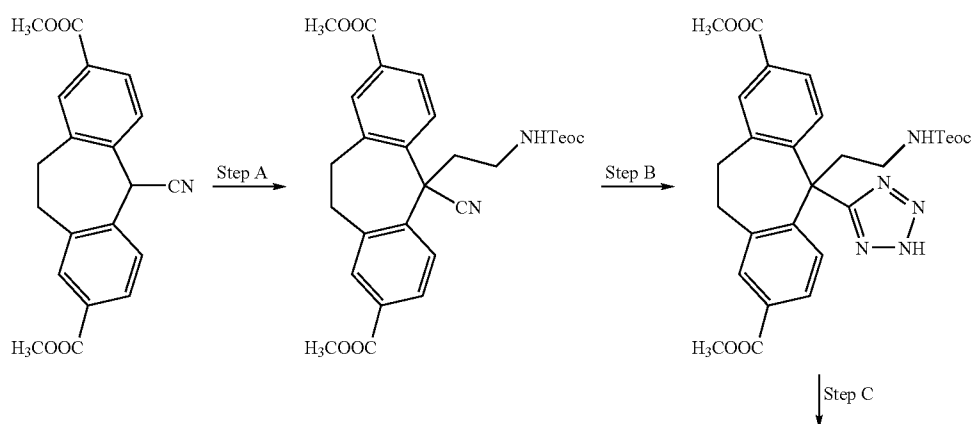
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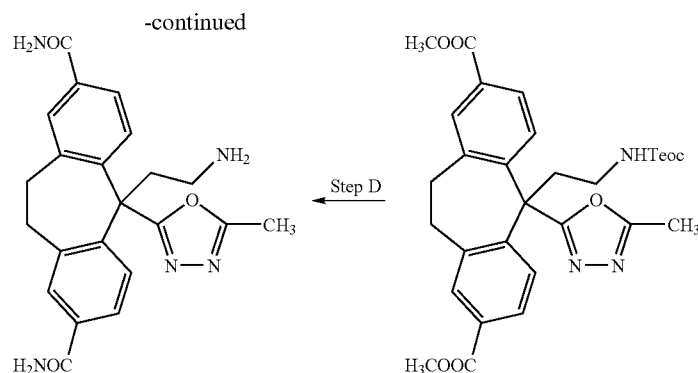
Preparative Example	Preparative Example Sulfamidate	Product
293	45	
294	46	

[0580] Examples 295-299 have been intentionally excluded.

Preparative Example 300

[0581]





Step A

[0582] If one were to treat the compound from Preparative Example 59 with the sulfimidate from Preparative Example 22 according to the procedure described in Preparative Example 61 Step A, one would obtain the title compound.

Step B

[0583] If one were to treat the title compound from Step A above with NaN_3 as described in Preparative Example 61 Step B, one would obtain the title compound.

Step C

[0584] If one were to treat the title compound from Step B above with acetic acid anhydride in pyridine at 100°C . for 2

h one would obtain, after the removal of the pyridine under reduced pressure and after column chromatography, the title compound.

Step D

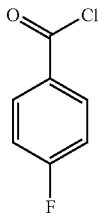
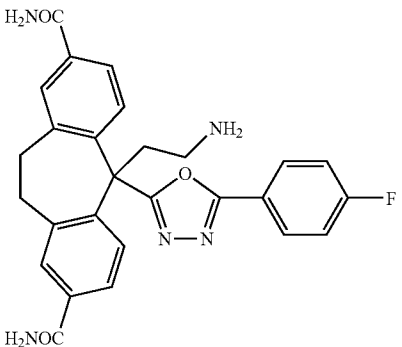
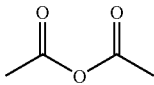
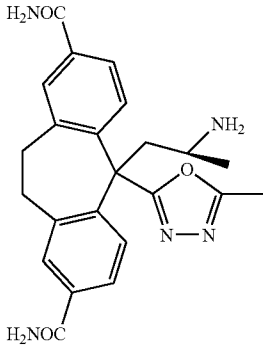
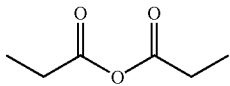
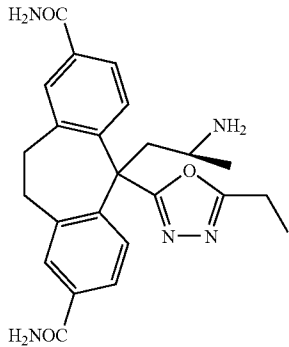
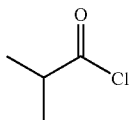
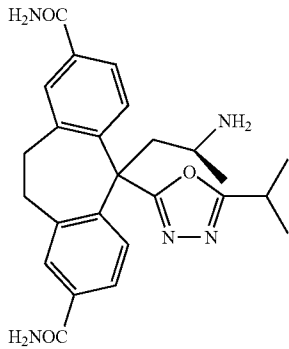
[0585] If one were to treat the title compound from Step A above according to the procedures described in Preparative Example 70 one would obtain the title compound.

Preparative Example 301-335

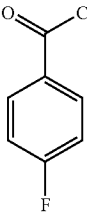
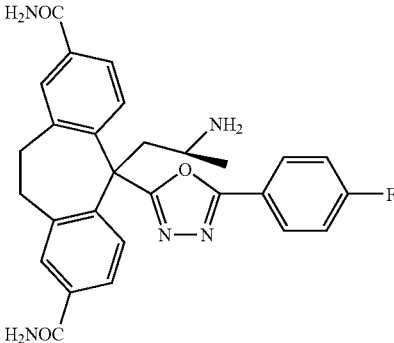
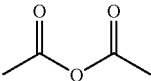
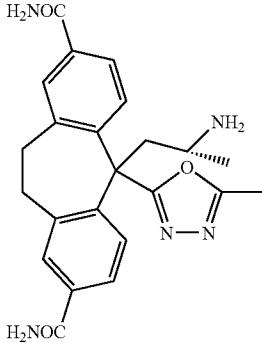
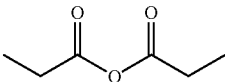
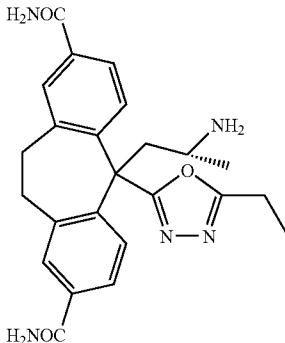
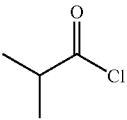
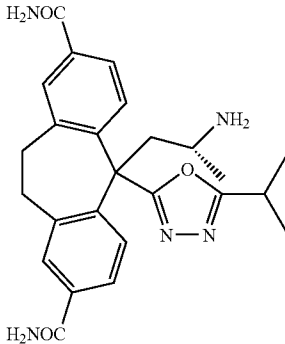
[0586] If one were to follow a similar procedure as that described in Preparative Example 300, except using the appropriate intermediate from the Preparative Examples and anhydrides or acid chlorides and amines as indicated in the Table below, one would obtain the desired amine product.

Preparative Example	Preparative Example	Acid Chloride/ Anhydride	Amine	Product
301	300		NH_3	
302	300		NH_3	

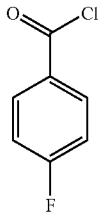
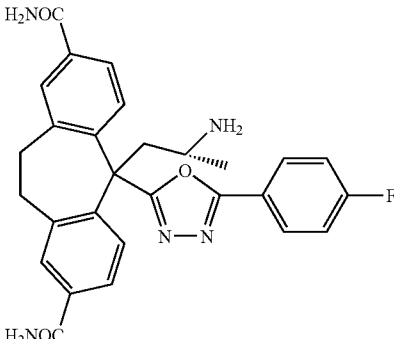
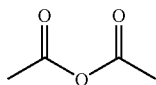
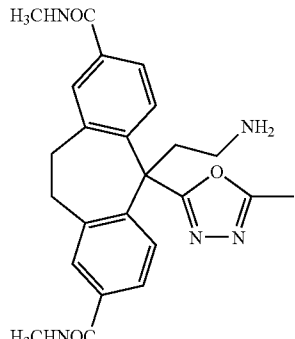
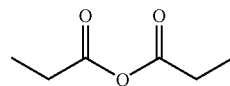
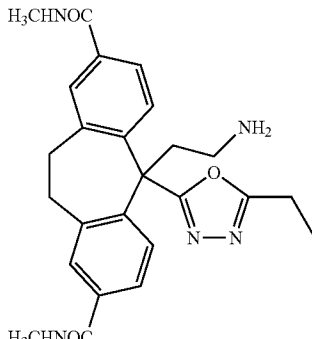
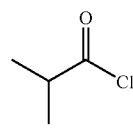
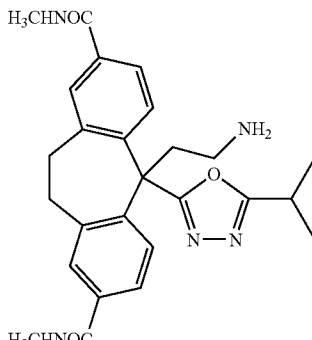
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Preparative Example	Preparative Example	Acid Chloride/ Anhydride	Amine	Product
303	300		NH ₃	
304	61		NH ₃	
305	61		NH ₃	
306	61		NH ₃	

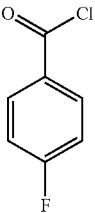
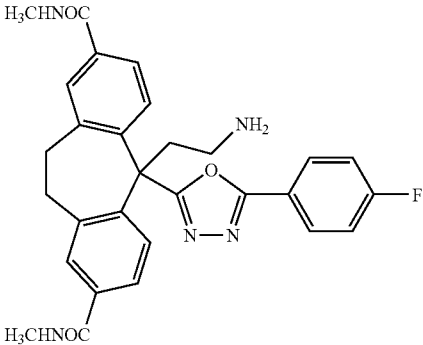
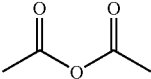
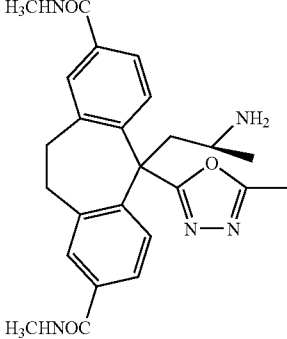
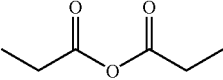
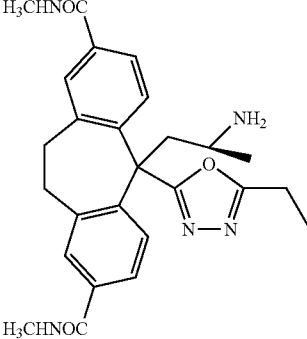
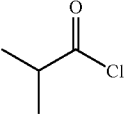
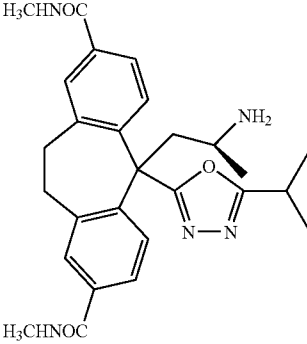
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Preparative Example	Preparative Example	Acid Chloride/ Anhydride	Amine	Product
307	61		NH ₃	
308	65		NH ₃	
309	65		NH ₃	
310	65		NH ₃	

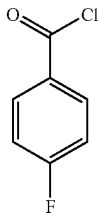
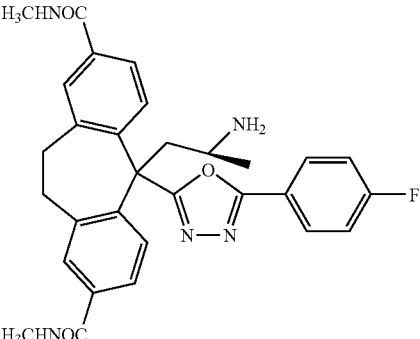
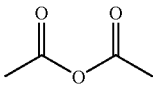
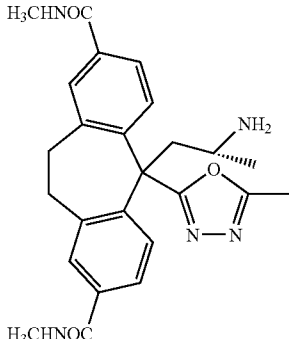
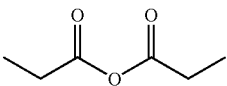
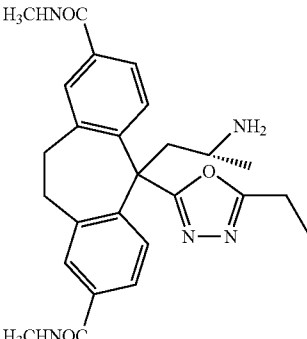
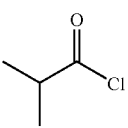
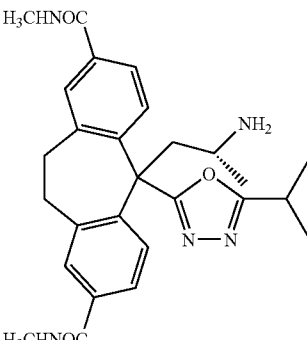
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Preparative Example	Preparative Example	Acid Chloride/ Anhydride	Amine	Product
311	65		NH ₃	
312	300		CH ₃ NH ₂	
313	300		CH ₃ NH ₂	
314	300		CH ₃ NH ₂	

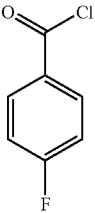
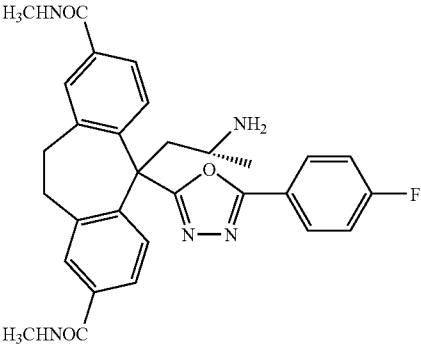
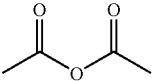
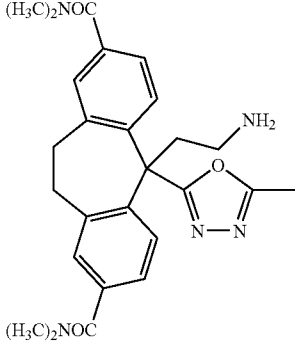
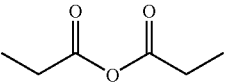
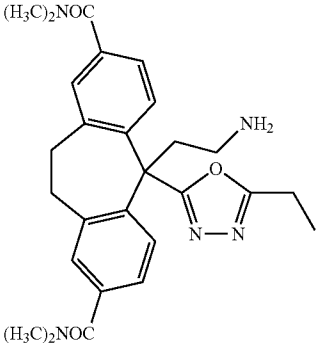
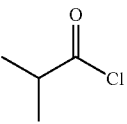
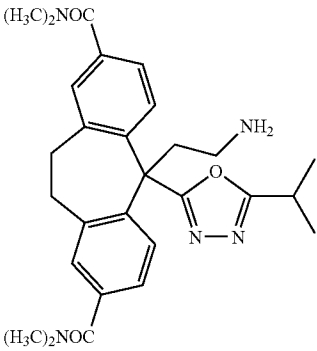
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Preparative Example	Preparative Example	Acid Chloride/ Anhydride	Amine	Product
315	300		CH_3NH_2	
316	61		CH_3NH_2	
317	61		CH_3NH_2	
318	61		CH_3NH_2	

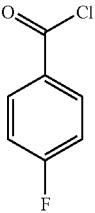
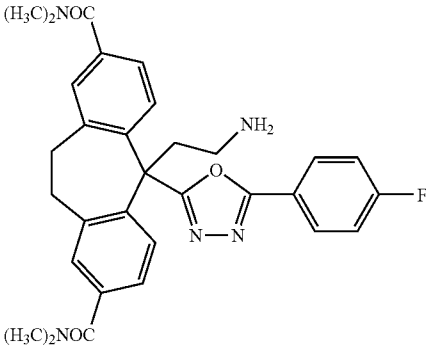
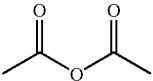
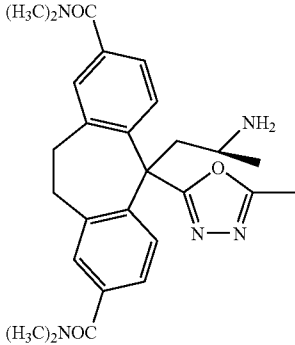
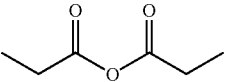
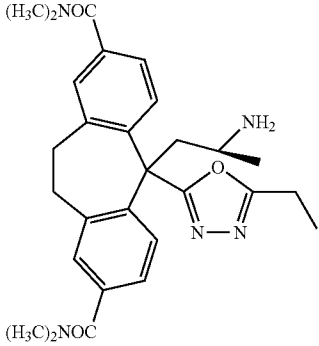
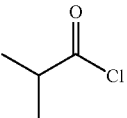
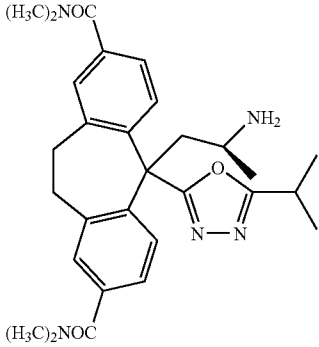
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Preparative Example	Preparative Example	Acid Chloride/ Anhydride	Amine	Product
319	61		CH_3NH_2	
320	65		CH_3NH_2	
321	65		CH_3NH_2	
322	65		CH_3NH_2	

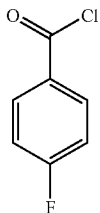
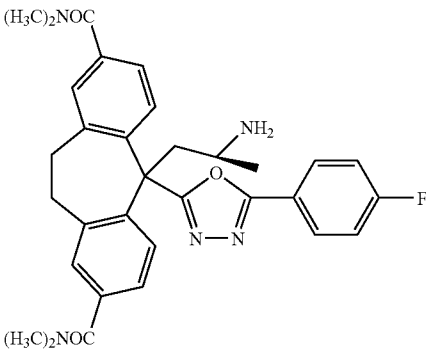
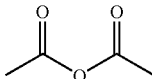
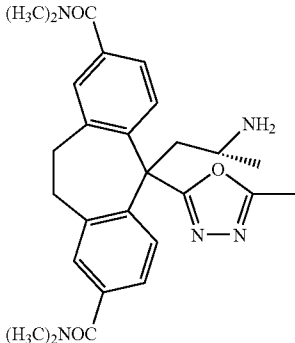
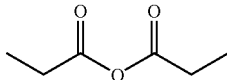
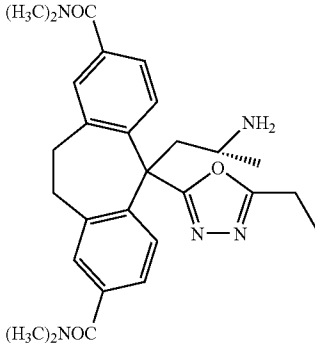
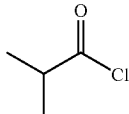
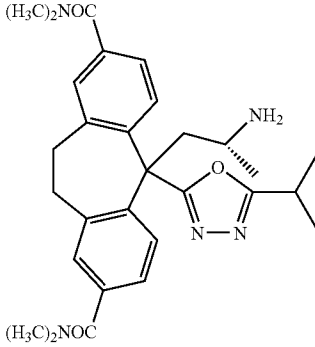
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Preparative Example	Preparative Example	Acid Chloride/ Anhydride	Amine	Product
323	65		CH_3NH_2	
324	300		$(\text{CH}_3)_2\text{NH}$	
325	300		$(\text{CH}_3)_2\text{NH}$	
326	300		$(\text{CH}_3)_2\text{NH}$	

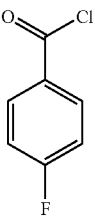
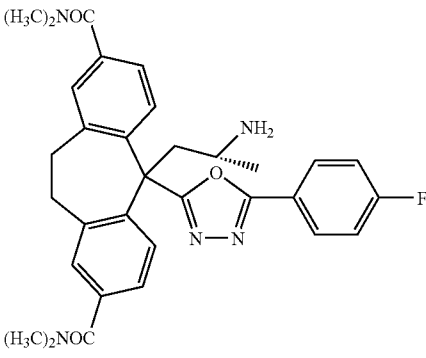
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Preparative Example	Preparative Example	Acid Chloride/ Anhydride	Amine	Product
327	300		$(\text{CH}_3)_2\text{NH}$ $(\text{H}_3\text{C})_2\text{NOC}$	
328	61		$(\text{CH}_3)_2\text{NH}$	
329	61		$(\text{CH}_3)_2\text{NH}$	
330	61		$(\text{CH}_3)_2\text{NH}$	

-continued

Preparative Example	Preparative Example	Acid Chloride/ Anhydride	Amine	Product
331	61		$(\text{CH}_3)_2\text{NH}$ $(\text{H}_3\text{C})_2\text{NOC}$	
332	65		$(\text{CH}_3)_2\text{NH}$ $(\text{H}_3\text{C})_2\text{NOC}$	
333	65		$(\text{CH}_3)_2\text{NH}$ $(\text{H}_3\text{C})_2\text{NOC}$	
334	65		$(\text{CH}_3)_2\text{NH}$ $(\text{H}_3\text{C})_2\text{NOC}$	

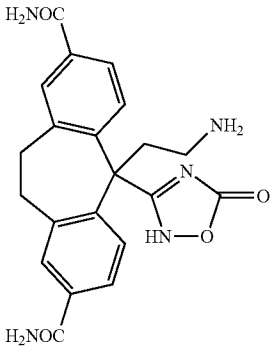
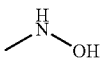
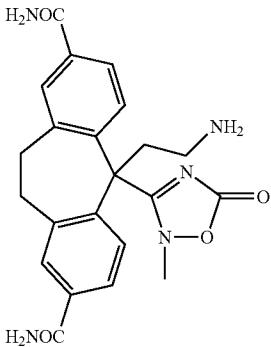
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Preparative Example	Preparative Example	Acid Chloride/ Anhydride	Amine	Product
335	65		$(\text{CH}_3)_2\text{NH}$ $(\text{H}_3\text{C})_2\text{NOC}$	

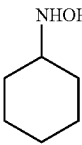
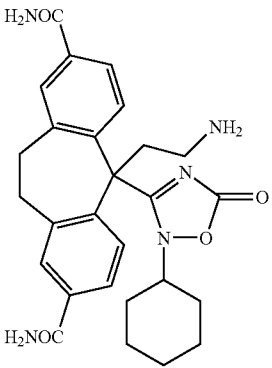
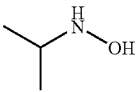
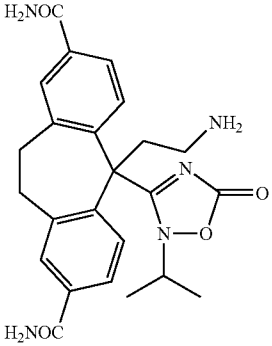

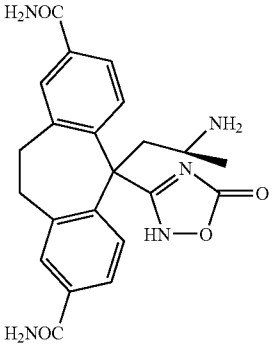
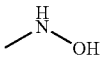
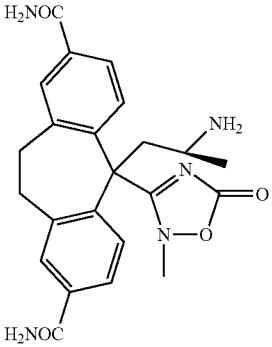
[0587] Example numbers 336-399 were intentionally excluded.

Preparative Example 400-434

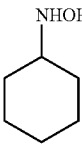
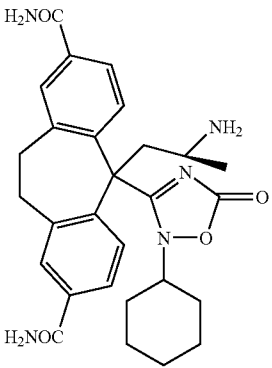
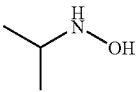
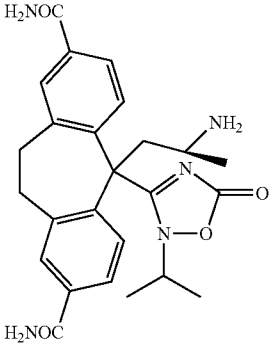

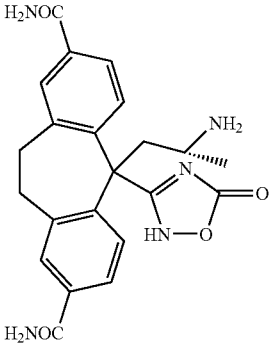
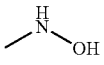
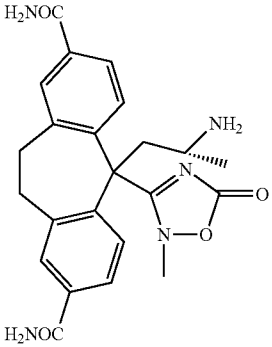
[0588] If one were to follow a similar procedure as that described in Preparative Example 66, except using the appropriate intermediate from the Preparative Examples and hydroxylamine hydrochlorides and amines as indicated in the Table below and treat the products according to Preparative Example 70, one would obtain the desired amine product.

Preparative Example	Preparative Example	Hydroxylamine hydrochloride	Amine	Product
400	300	$\text{H}_2\text{N}-\text{OH}$	NH_3	
401	300		NH_3	

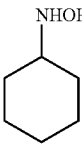
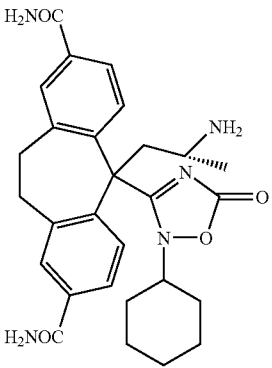
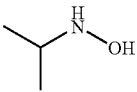
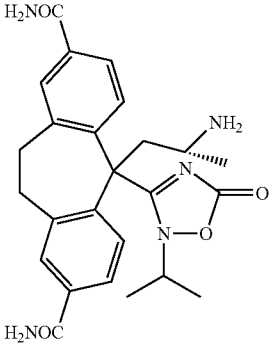

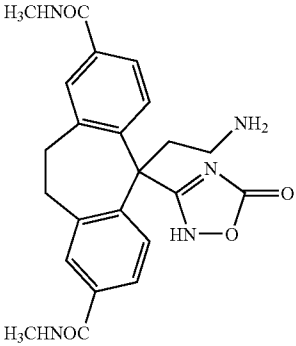
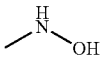
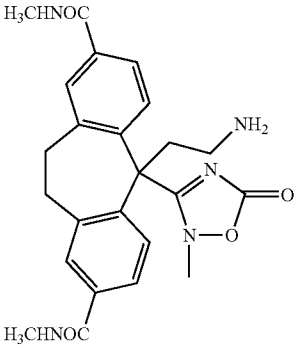
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Preparative Example	Preparative Example	Hydroxylamine hydrochloride	Amine	Product
402	300		NH ₃	
403	300		NH ₃	
404	61		NH ₃	
405	61		NH ₃	

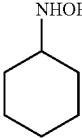
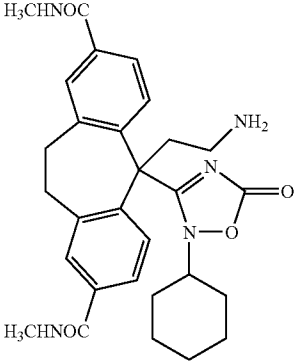
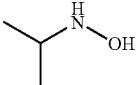
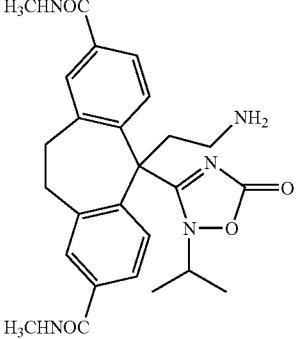
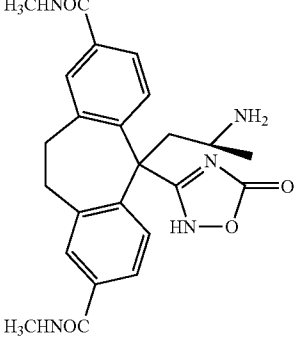
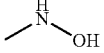
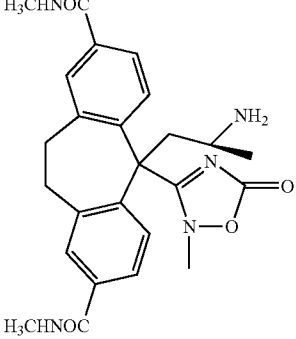
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Preparative Example	Preparative Example	Hydroxylamine hydrochloride	Amine	Product
406	61		NH ₃	
407	61		NH ₃	
408	65		NH ₃	
409	65		NH ₃	

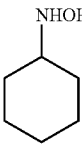
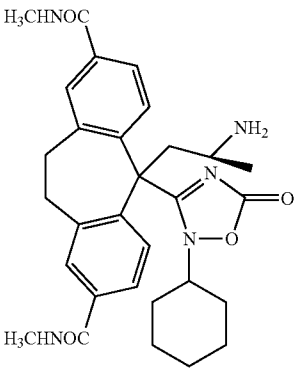
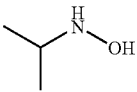
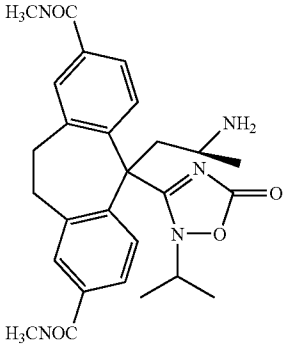

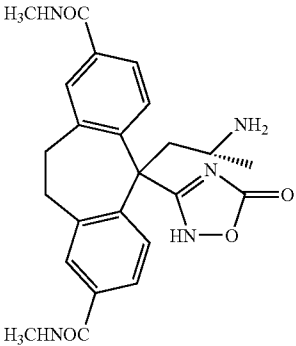
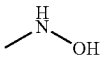
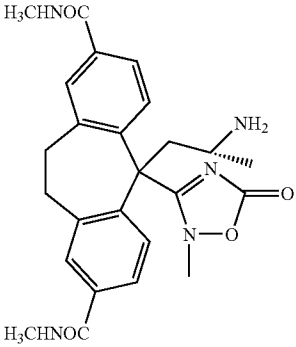
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Preparative Example	Preparative Example	Hydroxylamine hydrochloride	Amine	Product
410	65		NH ₃	
411	65		NH ₃	
412	300		CH ₃ NH ₂	
413	300		CH ₃ NH ₂	

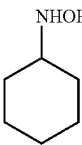
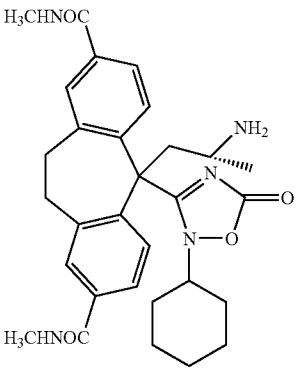
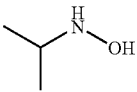
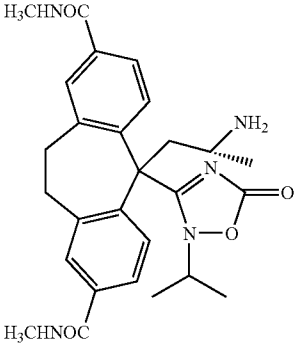

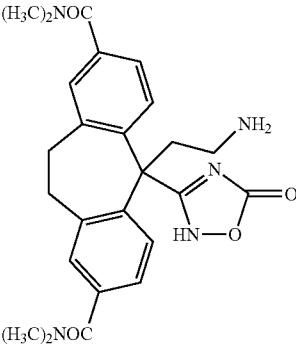
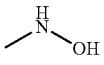
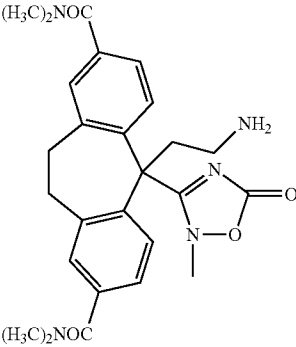
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Preparative Example	Preparative Example	Hydroxylamine hydrochloride	Amine	Product
414	300		CH_3NH_2	
415	300		CH_3NH_2	
416	61	$\text{H}_2\text{N}-\text{OH}$	CH_3NH_2	
417	61		CH_3NH_2	

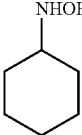
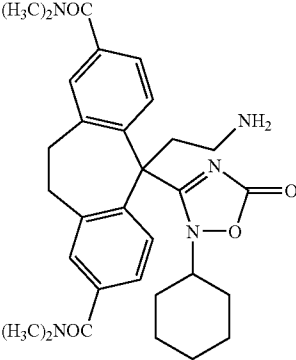
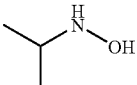
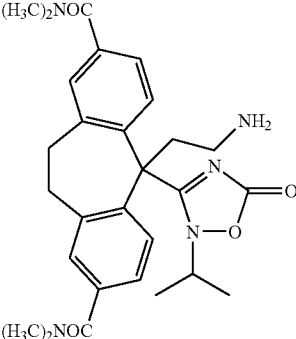
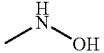
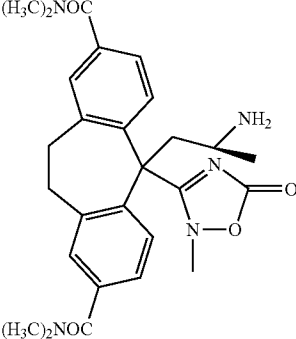
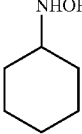
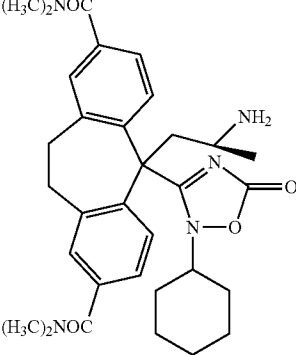
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Preparative Example	Preparative Example	Hydroxylamine hydrochloride	Amine	Product
418	61		CH ₃ NH ₂	
419	61		CH ₃ NH ₂	
420	65		CH ₃ NH ₂	
421	65		CH ₃ NH ₂	

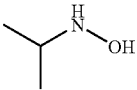
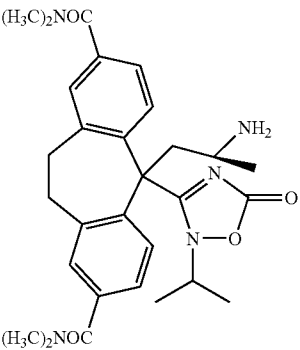

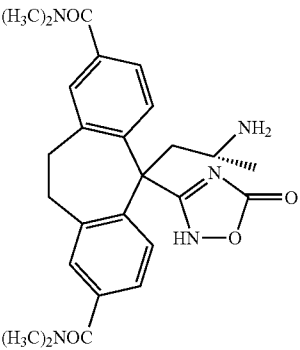
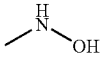
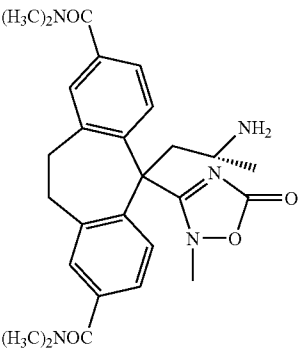
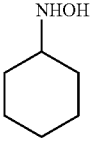
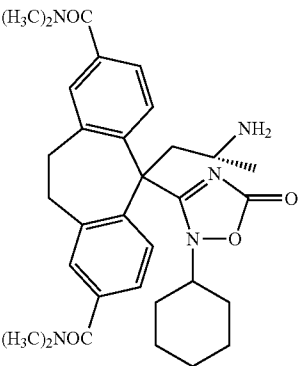
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Preparative Example	Preparative Example	Hydroxylamine hydrochloride	Amine	Product
422	65		CH_3NH_2	
423	65		CH_3NH_2	
424	300		$(\text{CH}_3)_2\text{NH}$	
425	300		$(\text{CH}_3)_2\text{NH}$	

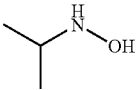
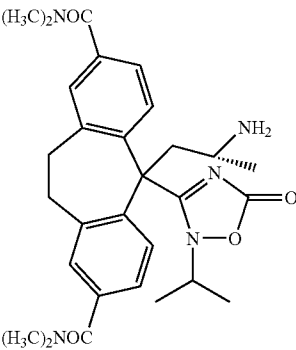
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Preparative Example	Preparative Example	Hydroxylamine hydrochloride	Amine	Product
426	300		$(\text{CH}_3)_2\text{NH}$	
427	300		$(\text{CH}_3)_2\text{NH}$	
428	61		$(\text{CH}_3)_2\text{NH}$	
429	61		$(\text{CH}_3)_2\text{NH}$	

-continued

Preparative Example	Preparative Example	Hydroxylamine hydrochloride	Amine	Product
430	61		(CH ₃) ₂ NH	
431	65		(CH ₃) ₂ NH	
432	65		(CH ₃) ₂ NH	
433	65		(CH ₃) ₂ NH	

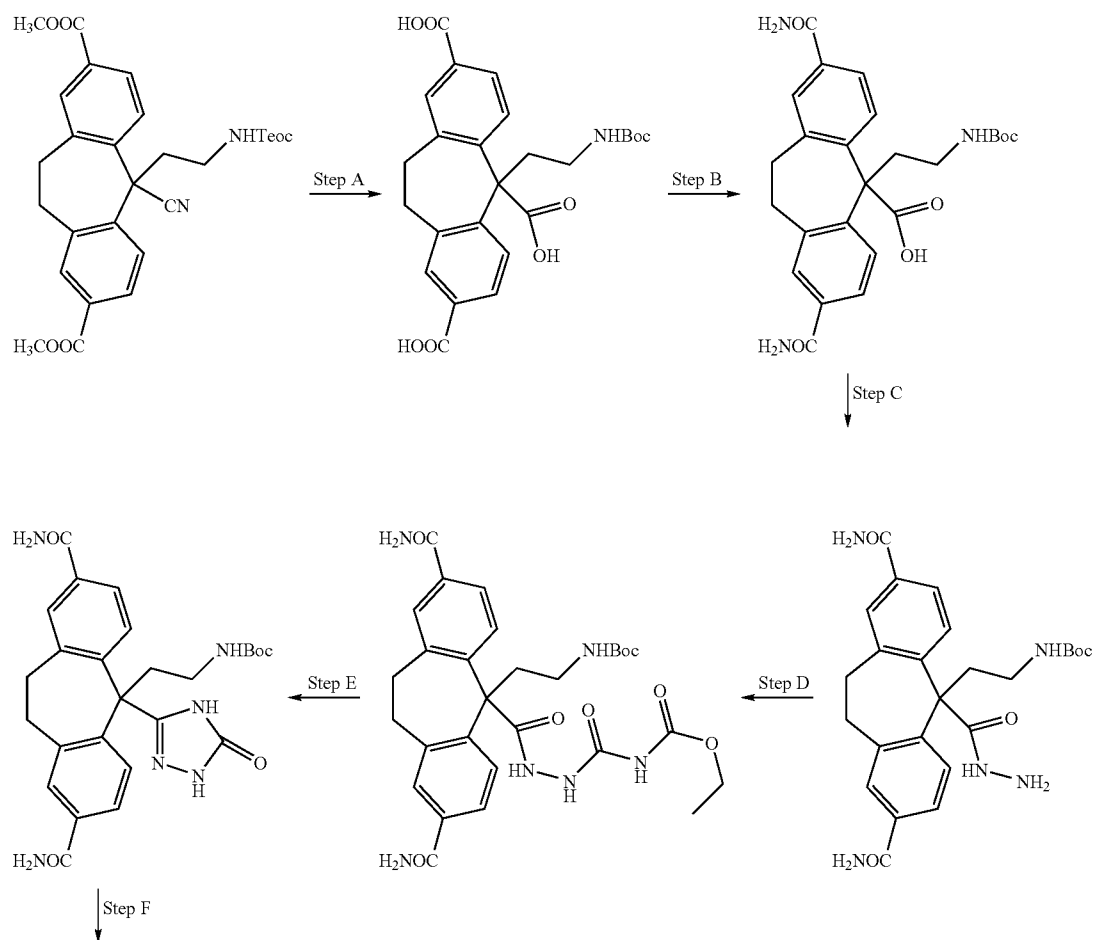
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Preparative Example	Preparative Example	Hydroxylamine hydrochloride	Amine	Product
434	65		$(\text{CH}_3)_2\text{NH}$	

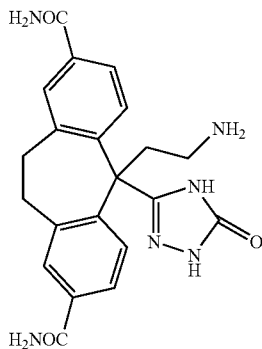
[0589] Example numbers 435-499 were intentionally excluded.

Preparative Example 500

[0590]



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Step A

[0591] If one were to treat the compound from Preparative Example 300 Step A with conc. HCl in acetic acid according to the procedure described in Preparative Example 49 Step J, one would obtain the title compound.

Step B

[0592] If one were to treat the title compound from Step A above according to the procedure described in Preparative Example 70 Step A, one would obtain the title compound.

Step C

[0593] If one were to treat the title compound from Step B above according to the procedure described in Preparative Example 70 Step A but using hydrazine instead of an amine, one would obtain the title compound.

Step D

[0594] If one were to stir the title compound from Step C above with 1 eq. ethyl isocyanate in DMA one would obtain after removing of DMA and the title compound.

Step E

[0595] If one were to treat the title compound from Step D above with a 2% aqueous NaOH at 100° C. for several hours one would obtain after neutralisation, precipitation and recrystallisation from ethanol the title compound.

Step F

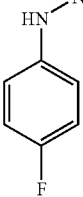
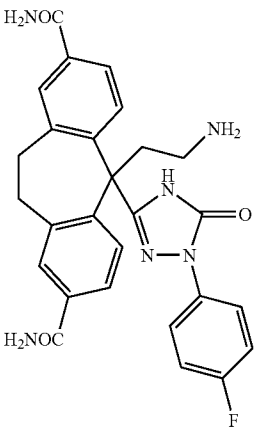
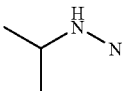
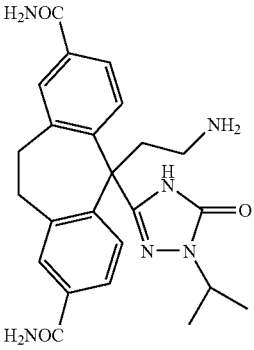
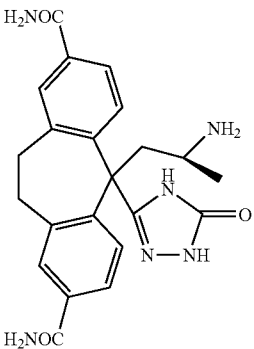
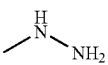
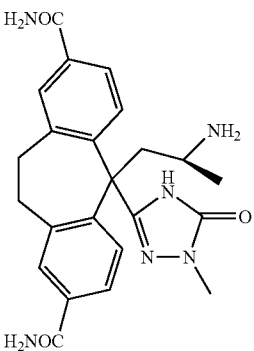
[0596] If one were to treat the title compound from Step E above according to the procedure described in Preparative Example 70 Step B, one would obtain the title compound.

Preparative Example 501-535

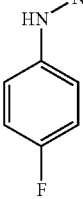
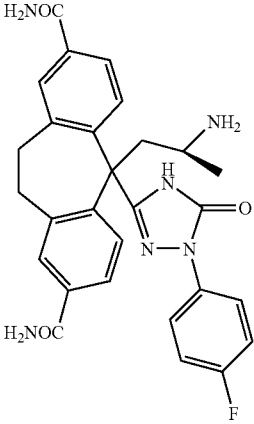
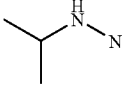
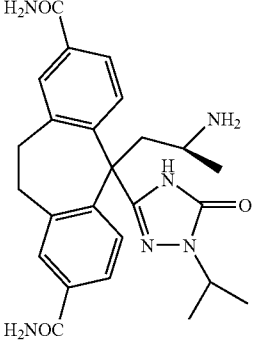
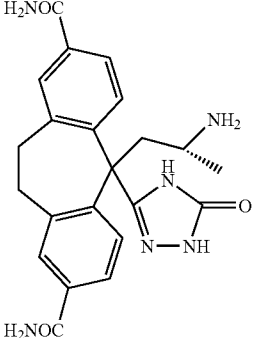
[0597] If one were to follow a similar procedure as that described in Preparative Example 500, except using the appropriate intermediate from the Preparative Examples and hydrazines and amines as indicated in the Table below, one would obtain the desired amine product.

Preparative Example	Preparative Example	Hydrazine	Amine	Product
501	300		NH ₃	

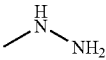
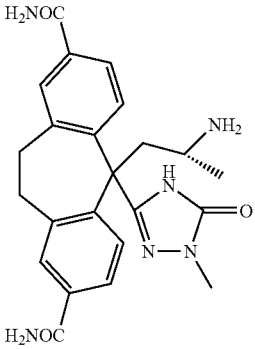
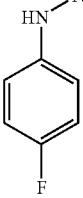
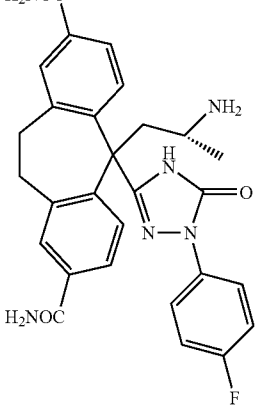
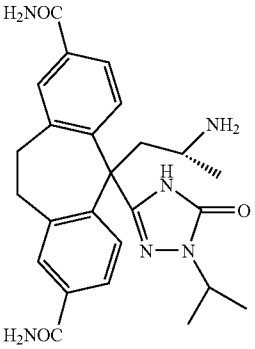
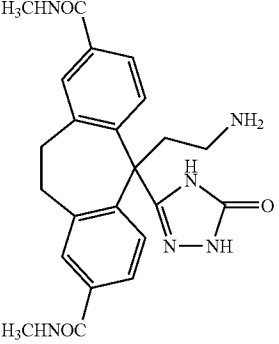
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Preparative Example	Preparative Example	Hydrazine	Amine	Product
502	300		NH ₃	
503	300		NH ₃	
504	61	N ₂ H ₄	NH ₃	
505	61		NH ₃	

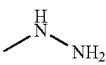
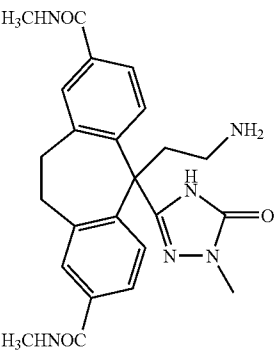
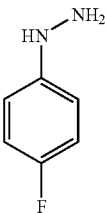
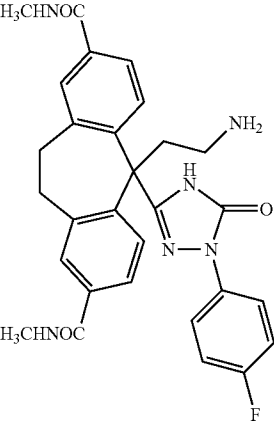
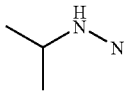
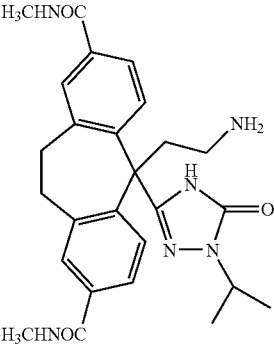
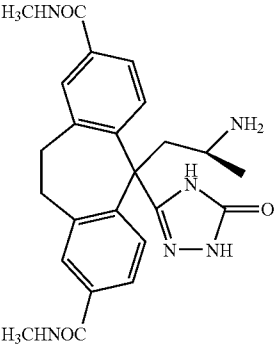
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Preparative Example	Preparative Example	Hydrazine	Amine	Product
506	61		NH ₃	
507	61		NH ₃	
508	65	N ₂ H ₄	NH ₃	

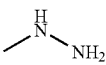
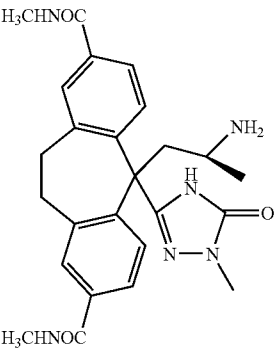
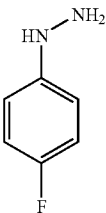
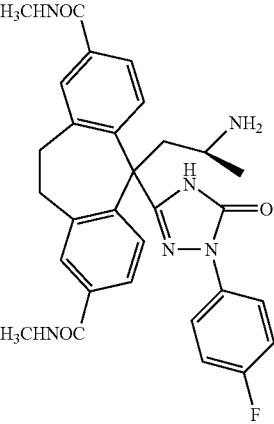
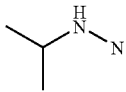
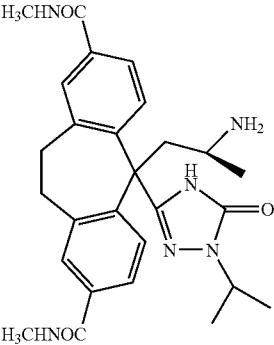
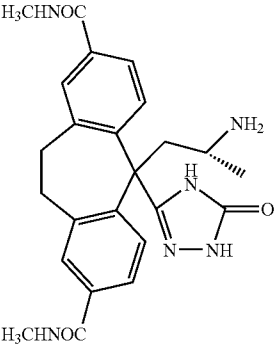
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Preparative Example	Preparative Example	Hydrazine	Amine	Product
509	65		NH ₃	
510	65		NH ₃	
511	65	NH ₃	H ₂ NOC	
512	300	N ₂ H ₄	CH ₃ NH ₂	

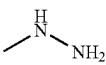
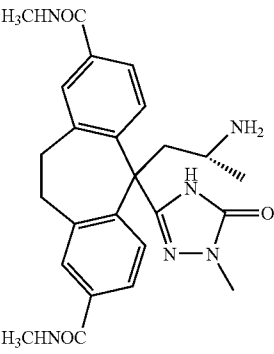
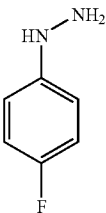
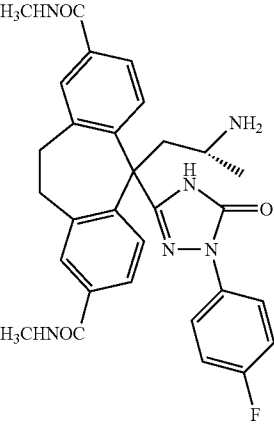
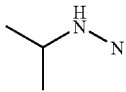
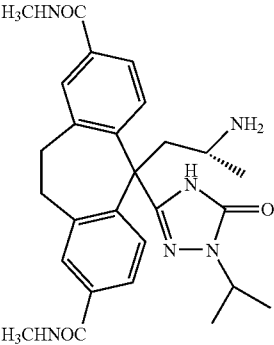
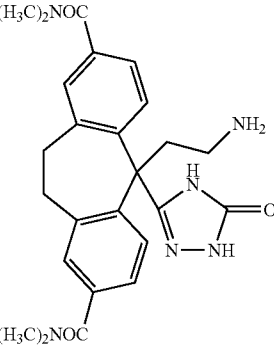
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Preparative Example	Preparative Example	Hydrazine	Amine	Product
513	300		CH ₃ NH ₂	
514	300		CH ₃ NH ₂	
515	300		CH ₃ NH ₂	
516	61	N ₂ H ₄	CH ₃ NH ₂	

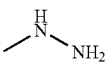
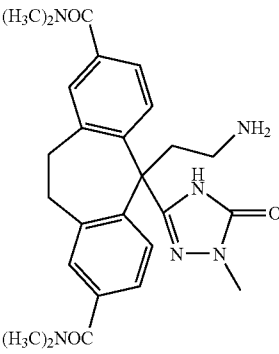
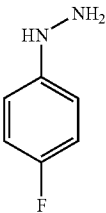
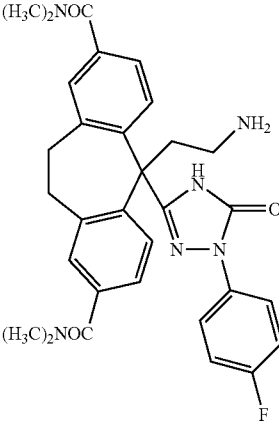
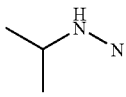
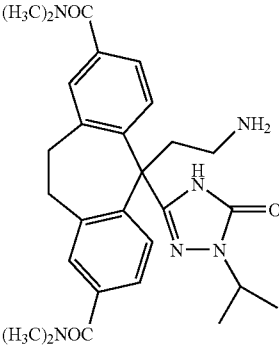
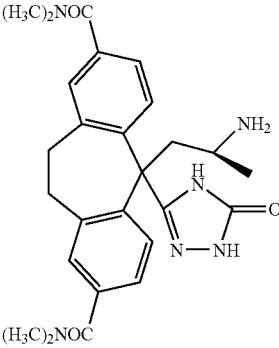
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Preparative Example	Preparative Example	Hydrazine	Amine	Product
517	61		CH ₃ NH ₂	
518	61		CH ₃ NH ₂	
519	61		CH ₃ NH ₂	
520	65	N ₂ H ₄	CH ₃ NH ₂	

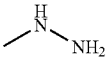
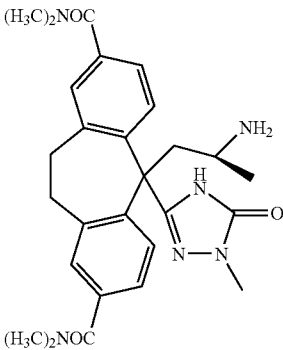
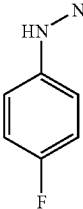
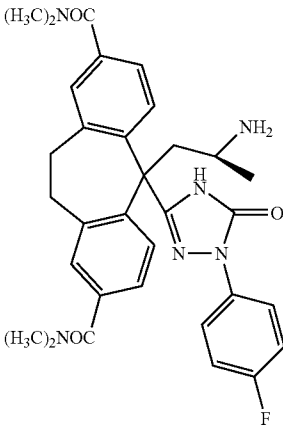
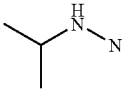
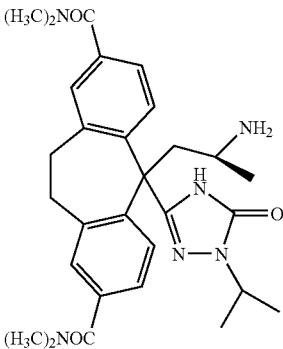
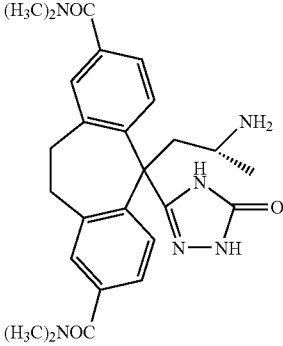
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Preparative Example	Preparative Example	Hydrazine	Amine	Product
521	65		CH ₃ NH ₂	
522	65		CH ₃ NH ₂	
523	65		CH ₃ NH ₂	
524	300	N ₂ H ₄	(CH ₃) ₂ NH	

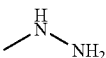
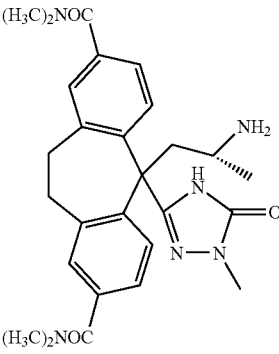
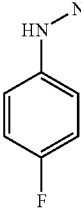
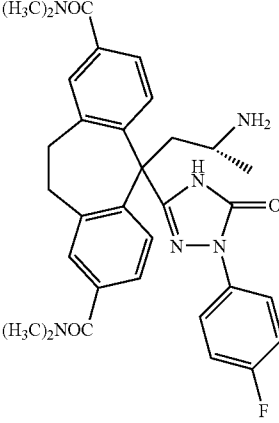
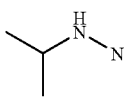
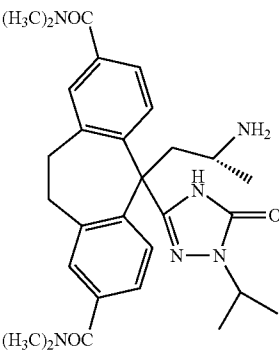
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Preparative Example	Preparative Example	Hydrazine	Amine	Product
525	300		$(\text{CH}_3)_2\text{NH}$	
526	300		$(\text{CH}_3)_2\text{NH}$	
527	300		$(\text{CH}_3)_2\text{NH}$	
528	61	N_2H_4	$(\text{CH}_3)_2\text{NH}$	

-continued

Preparative Example	Preparative Example	Hydrazine	Amine	Product
529	61		(CH ₃) ₂ NH	
530	61		(CH ₃) ₂ NH	
531	61		(CH ₃) ₂ NH	
532	65	N ₂ H ₄	(CH ₃) ₂ NH	

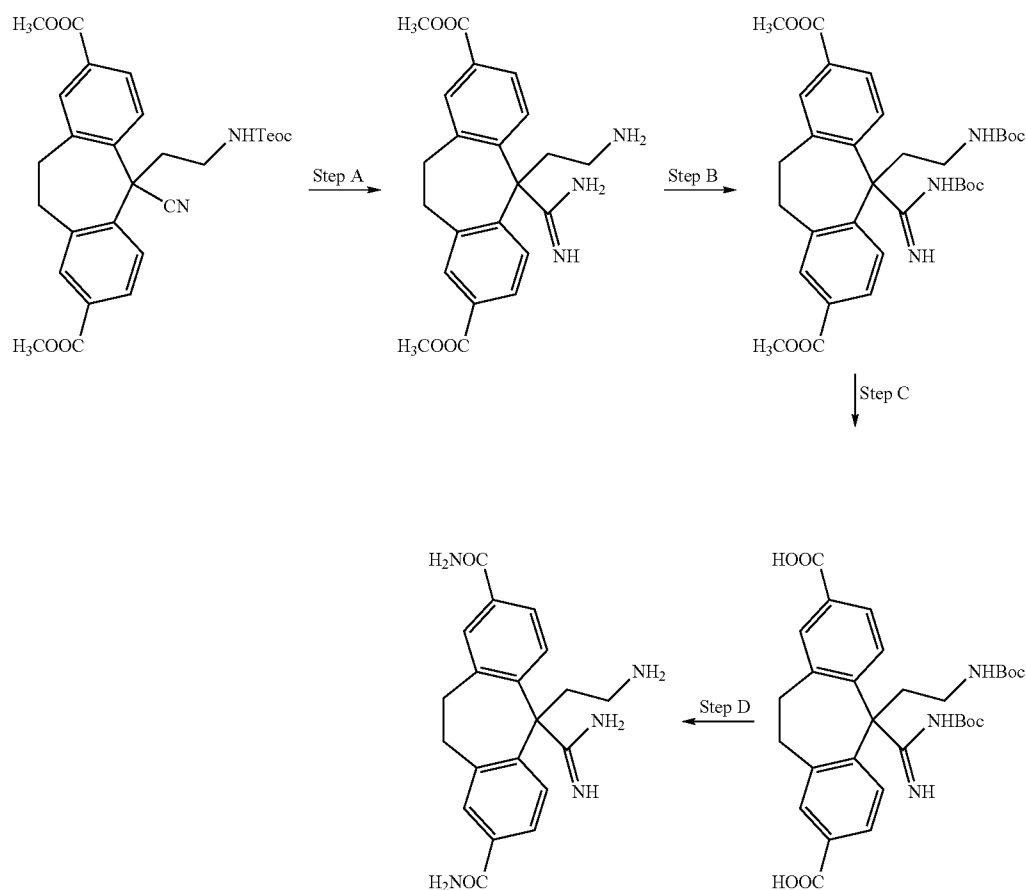
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Preparative Example	Preparative Example	Hydrazine	Amine	Product
533	65		$(\text{CH}_3)_2\text{NH}$	
534	65		$(\text{CH}_3)_2\text{NH}$	
535	65		$(\text{CH}_3)_2\text{NH}$	

[0598] Example numbers 536-599 were intentionally excluded.

Preparative Example 600

[0599]



Step A

[0600] If one were to treat the intermediate from Preparative Example 300 Step A with dry HCl gas in EtOH/CHCl₃ at 0° C. and set aside for 10 days, one would obtain after removal of the solvents the imidate hydrochloride. If one were to treat the imidate hydrochloride with NH₃ in dry EtOH and heat it to reflux for 7 h, one would obtain, after filtration and evaporation of the filtrate followed by recrystallization, the title compound.

Step B

[0601] If one were to treat the title compound from Step A above with Boc₂O according to the procedure described in Preparative Example 49 Step J but without the acid treatment, one would obtain the title compound.

Step C

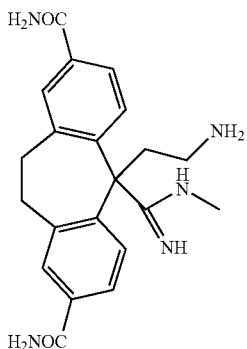

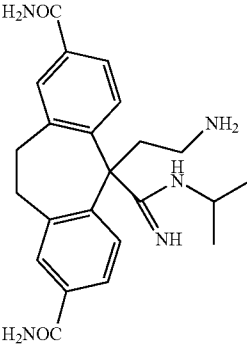
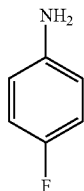
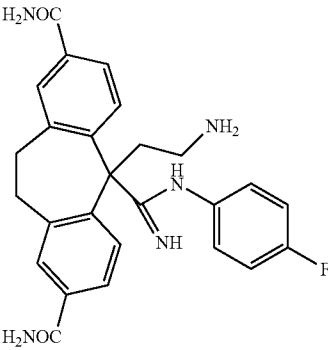
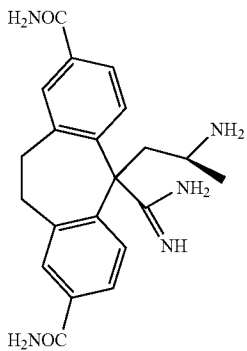
[0602] If one were to treat the title compound from Step B above according to Preparative Example 61 Step C, one would obtain the title compound.

Step D

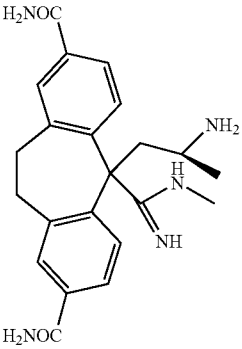

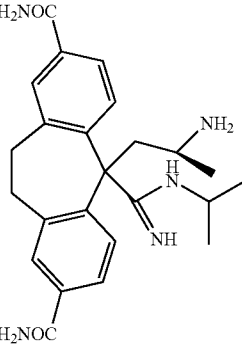
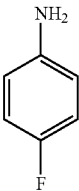
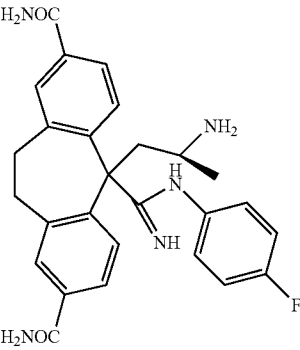
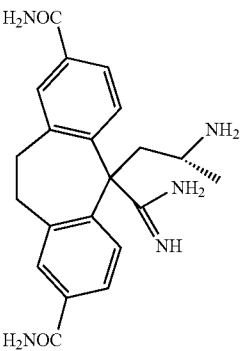
[0603] If one were to treat the title compound from Step C above according to the procedures described in Preparative Example 70, one would obtain the title compound.

Preparative Example 601-635

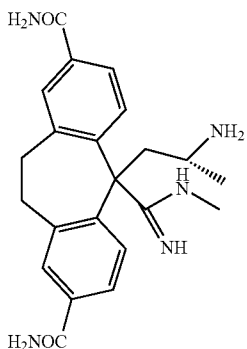

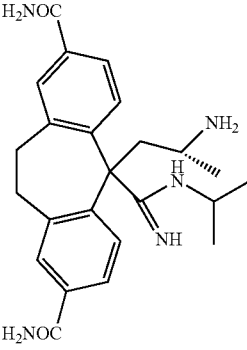
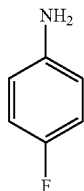
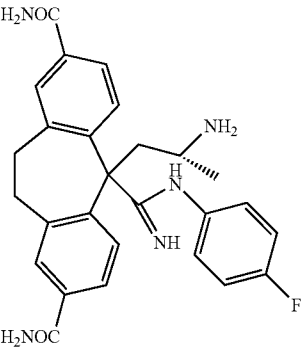
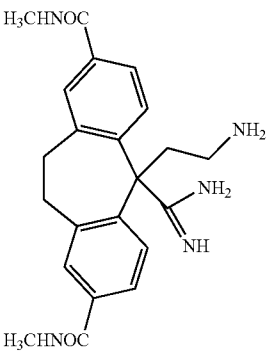
[0604] If one were to follow a similar procedure as that described in Preparative Example 600 except using the amines and appropriate intermediate from the Preparative Examples as indicated in the Table below, one would obtain the desired amine product.

Preparative Example	Preparative Example	Amine Step A	Amine Step B	Product
601	300	CH_3NH_2	NH_3	
602	300		NH_3	
603	300		NH_3	
604	61	NH_3	NH_3	

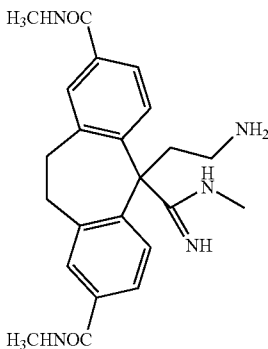

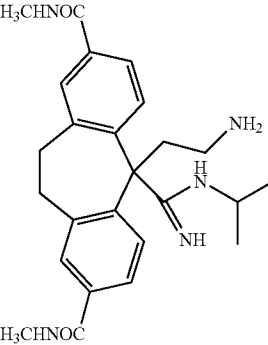
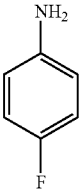
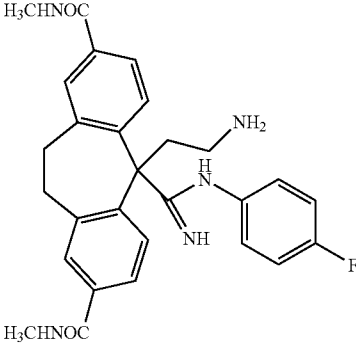
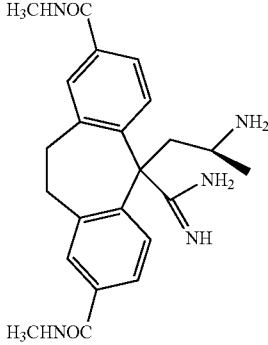
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Preparative Example	Preparative Example	Amine Step A	Amine Step B	Product
605	61	CH_3NH_2	NH_3	
606	61		NH_3	
607	61		NH_3	
608	65	NH_3	NH_3	

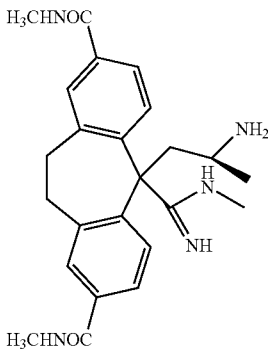

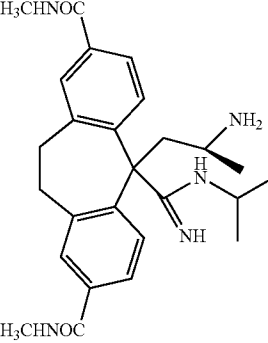
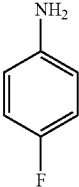
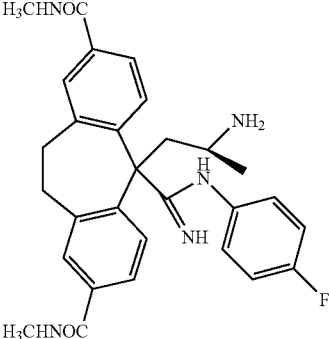
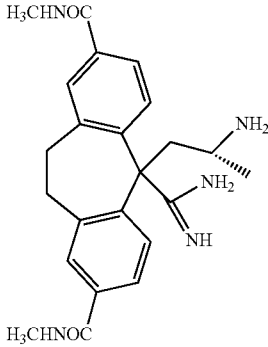
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Preparative Example	Preparative Example	Amine Step A	Amine Step B	Product
609	65	CH_3NH_2	NH_3	
610	65		NH_3	
611	65		NH_3	
612	300	NH_3	CH_3NH_2	

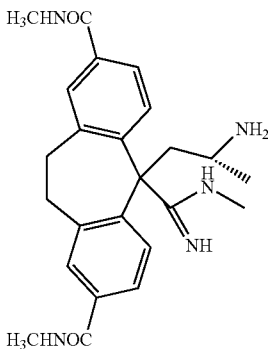

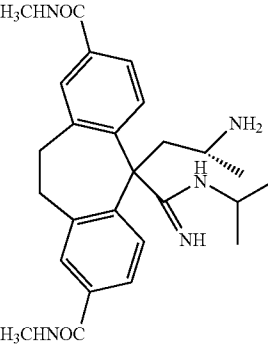
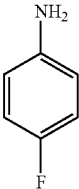
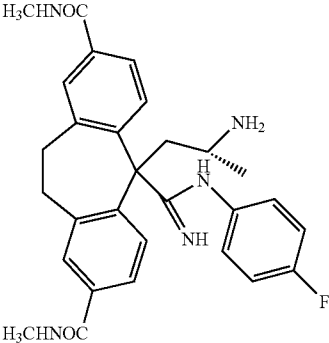
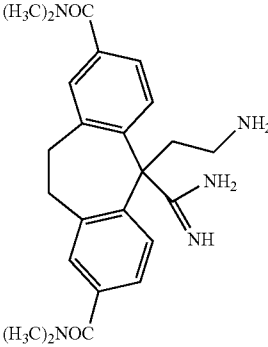
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Preparative Example	Preparative Example	Amine Step A	Amine Step B	Product
613	300	CH_3NH_2	CH_3NH_2	
614	300		CH_3NH_2	
615	300		CH_3NH_2	
616	61	NH_3	CH_3NH_2	

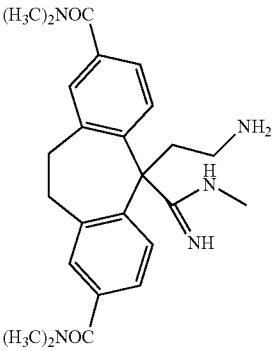

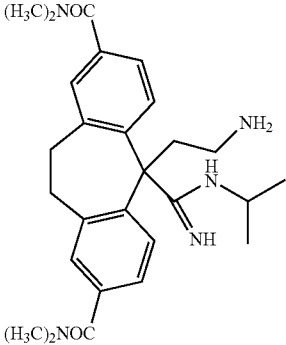
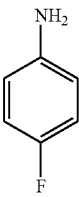
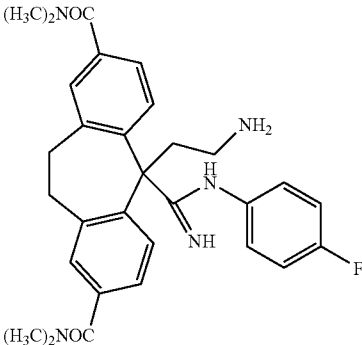
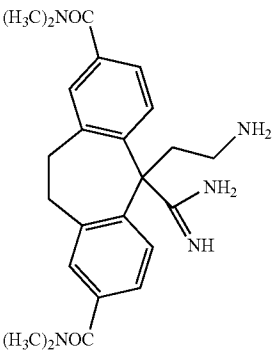
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Preparative Example	Preparative Example	Amine Step A	Amine Step B	Product
617	61	CH_3NH_2	CH_3NH_2	
618	61		CH_3NH_2	
619	61		CH_3NH_2	
620	65	NH_3	CH_3NH_2	

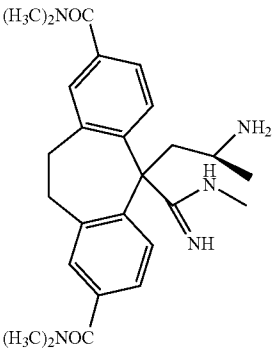

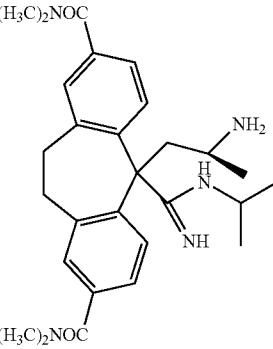
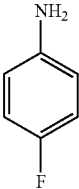
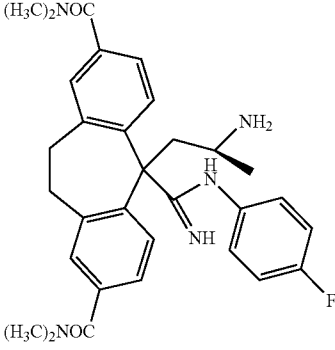
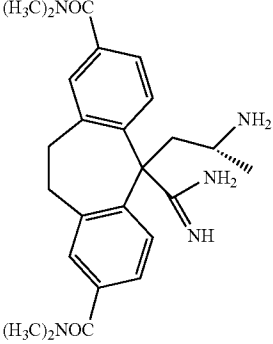
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Preparative Example	Preparative Example	Amine Step A	Amine Step B	Product
621	65	CH_3NH_2	CH_3NH_2	
622	65		CH_3NH_2	
623	65		CH_3NH_2	
624	300	NH_3	$(\text{CH}_3)_2\text{NH}$	

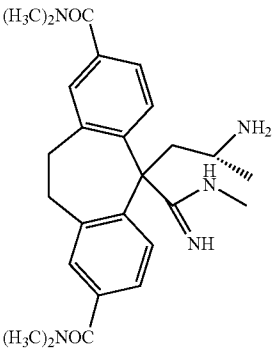

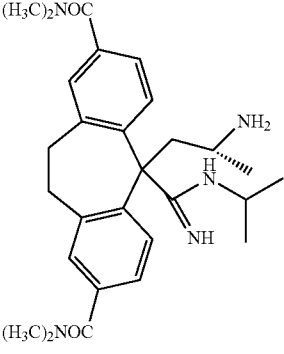
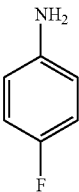
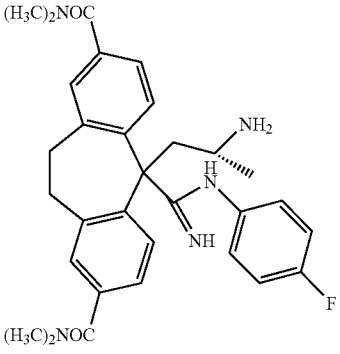
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Preparative Example	Preparative Example	Amine Step A	Amine Step B	Product
625	300	CH_3NH_2	$(\text{CH}_3)_2\text{NH}$	
626	300		$(\text{CH}_3)_2\text{NH}$	
627	300		$(\text{CH}_3)_2\text{NH}$	
628	61	NH_3	$(\text{CH}_3)_2\text{NH}$	

-continued

Preparative Example	Preparative Example	Amine Step A	Amine Step B	Product
629	61	CH_3NH_2	$(\text{CH}_3)_2\text{NH}$	
630	61		$(\text{CH}_3)_2\text{NH}$	
631	61		$(\text{CH}_3)_2\text{NH}$	
632	65	NH_3	$(\text{CH}_3)_2\text{NH}$	

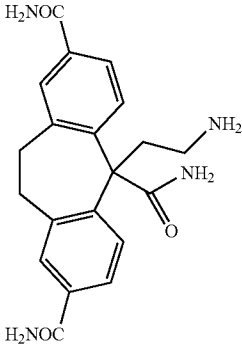
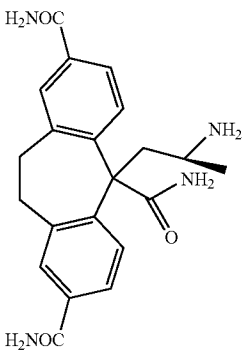
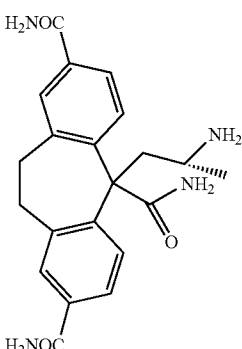
-continued

Preparative Example	Preparative Example	Amine Step A	Amine Step B	Product
633	65	CH_3NH_2	$(\text{CH}_3)_2\text{NH}$	
634	65		$(\text{CH}_3)_2\text{NH}$	
635	65		$(\text{CH}_3)_2\text{NH}$	

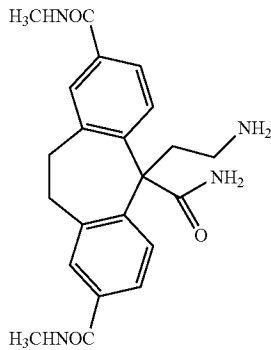
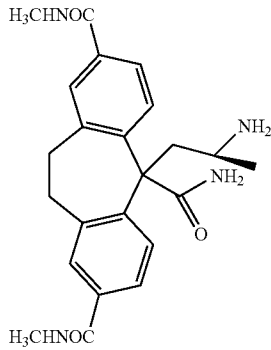
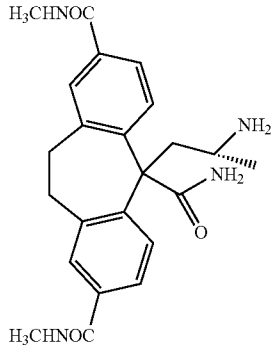
[0605] Example numbers 636-679 were intentionally excluded.

Preparative Example 680-687

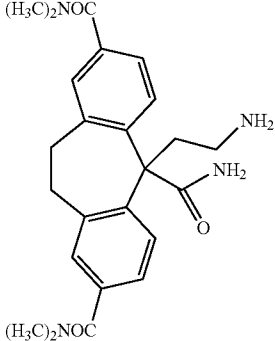
[0606] If one were to follow a similar procedure as that described in Preparative Example 67 and 70, except using the appropriate intermediate from the Preparative Examples and amines as indicated in the Table below, one would obtain the desired amine product.

Prepa- rative Example	Preparative Example	Amine	Product
680	300	NH ₃	
681	61	NH ₃	
682	65	NH ₃	

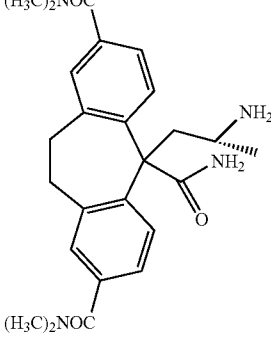
-continued

Prepa- rative Example	Preparative Example	Amine	Product
683	300	CH ₃ NH ₂	
684	61	CH ₃ NH ₂	
685	65	CH ₃ NH ₂	

-continued

Prepa- rative Example	Preparative Example	Amine	Product
686	300	$(\text{CH}_3)_2\text{NH}$	

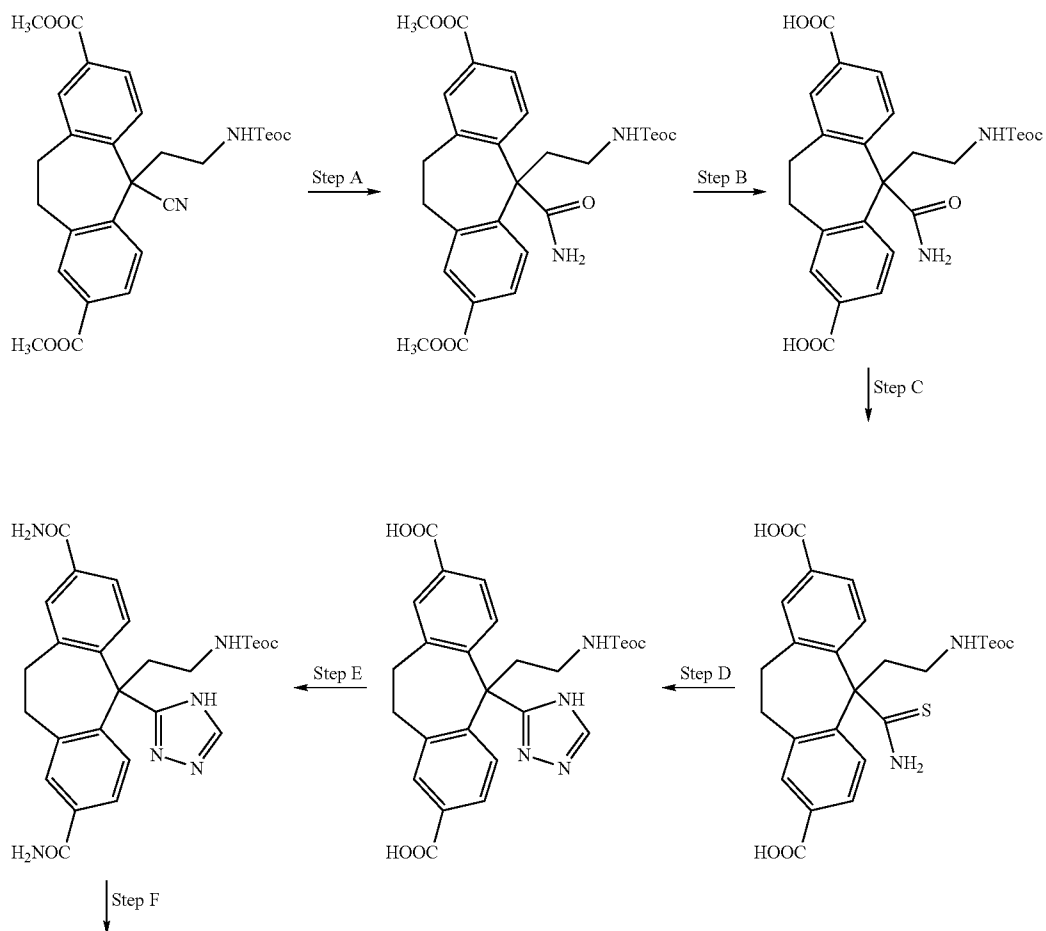
-continued

Prepa- rative Example	Preparative Example	Amine	Product
687	65	$(\text{CH}_3)_2\text{NH}$	

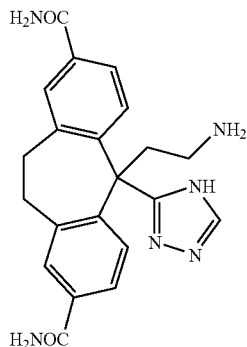
[0607] Example numbers 688-699 were intentionally excluded.

Preparative Example 700

[0608]



-continued



Step A

[0609] If one were to treat the compound from Preparative Example 300 Step A with hydroxylamine hydrochloride and base according to Preparative Example 67 Step A, one would obtain the title compound.

Step B

[0610] If one were to treat the title compound from Step A above according to Preparative Example 67 Step B, one would obtain the title compound.

Step C

[0611] If one were to treat the title compound from step B above with Lawesson's Reagent in toluene and heat the mixture to reflux for 4 h, one would obtain after column chromatography the title compound.

Step D

[0612] If one were to treat the title compound from Step C above with formic acid hydrazide (Pellizzari-Synthesis), one would obtain the title compound.

Step E

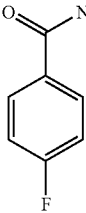
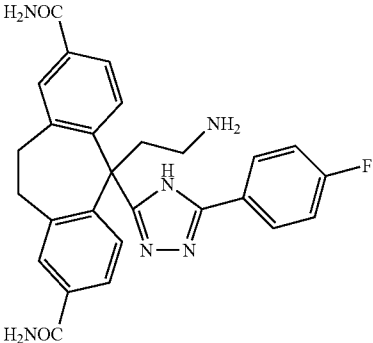

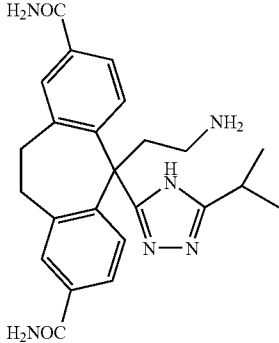
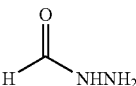
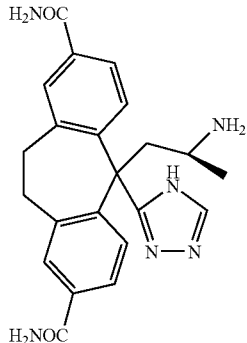
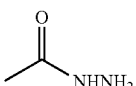
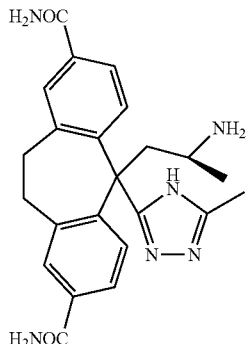
[0613] If one were to treat the title compound from Step D above according to the procedures described in Preparative Example 70, one would obtain the title compound.

Preparative Example 701-735

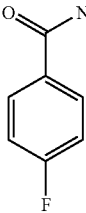
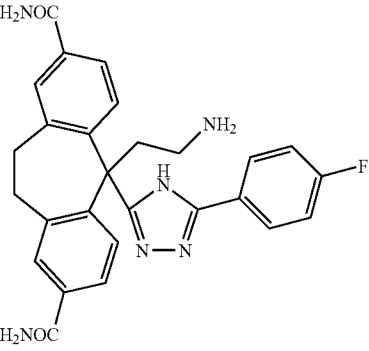
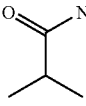
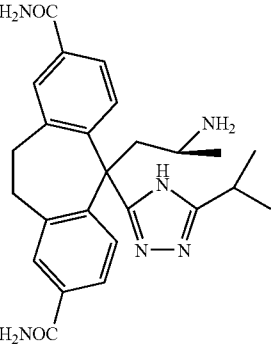
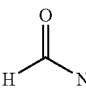
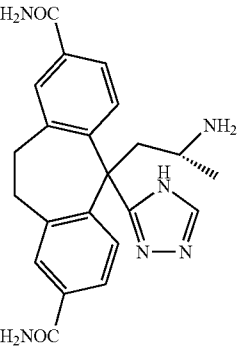
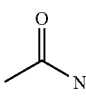
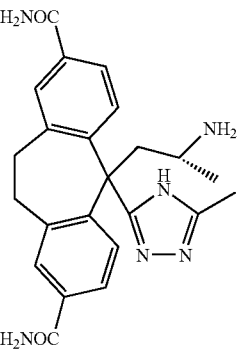
[0614] If one were to follow a similar procedure as that described in Preparative Example 700, except using the appropriate intermediate from the Preparative Examples, acid hydrazides and amines as indicated in the Table below, one would obtain the desired amine product.

Preparative Example	Preparative Example	Acid hydrazide	Amine	Product
701	300		NH ₃	

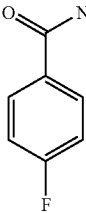
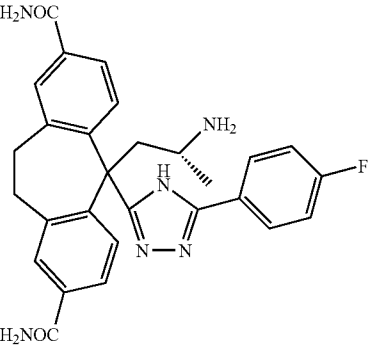
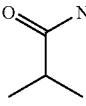
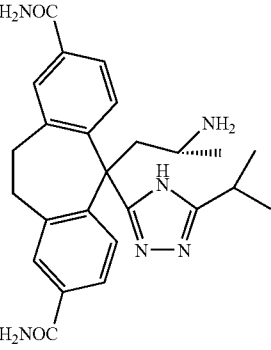
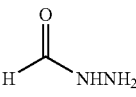
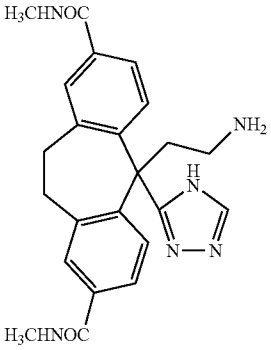
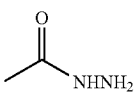
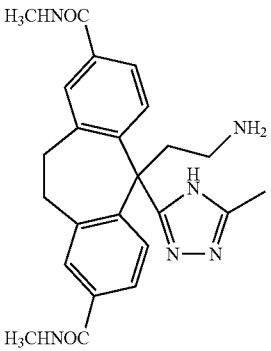
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Preparative Example	Preparative Example	Acid hydrazide	Amine	Product
702	300		NH_3	
703	300		NH_3	
704	61		NH_3	
705	61		NH_3	

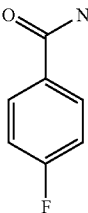
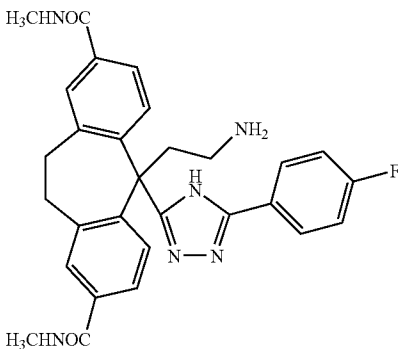
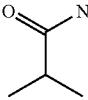
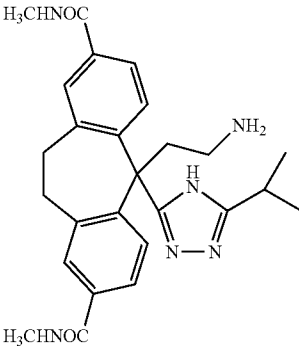
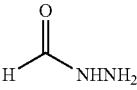
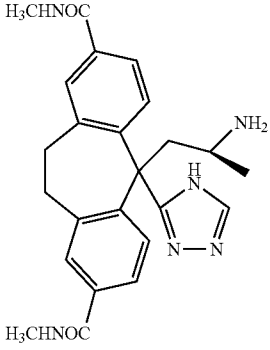
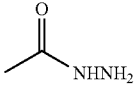
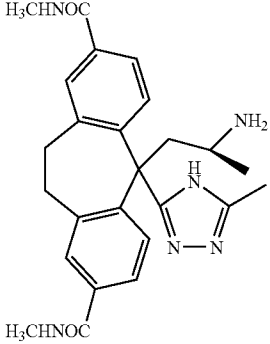
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Preparative Example	Preparative Example	Acid hydrazide	Amine	Product
706	61		NH_3	
707	61		NH_3	
708	65		NH_3	
709	65		NH_3	

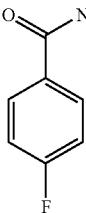
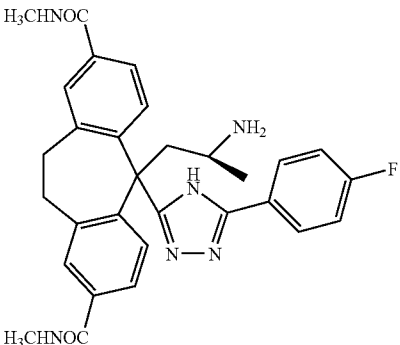

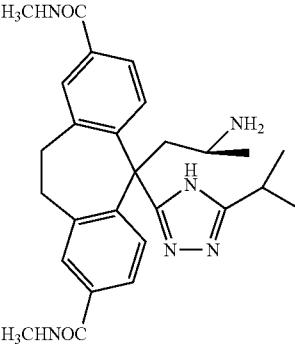
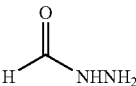
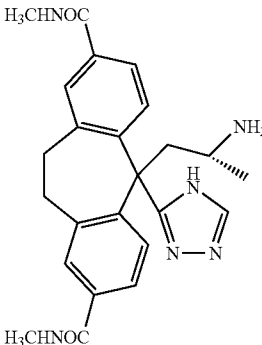
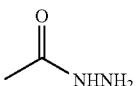
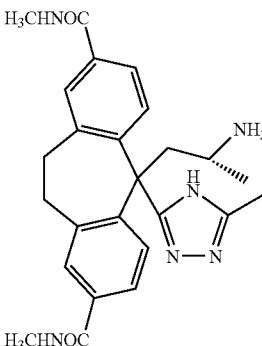
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Preparative Example	Preparative Example	Acid hydrazide	Amine	Product
710	65		NH_3	
711	65		NH_3	
712	300		CH_3NH_2	
713	300		CH_3NH_2	

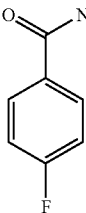
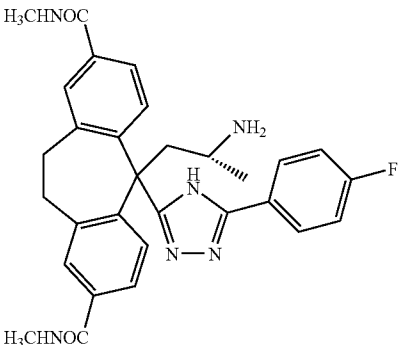

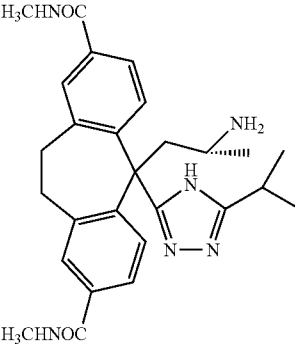
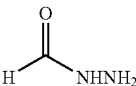
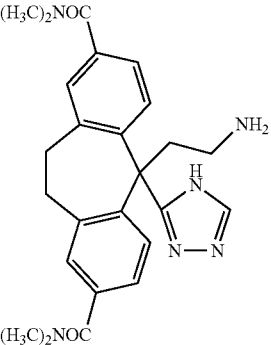
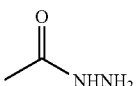
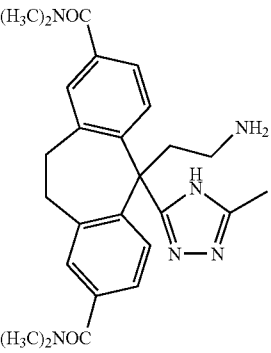
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Preparative Example	Preparative Example	Acid hydrazide	Amine	Product
714	300		CH_3NH_2	
715	300		CH_3NH_2	
716	61		CH_3NH_2	
717	61		CH_3NH_2	

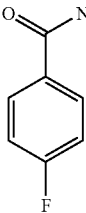
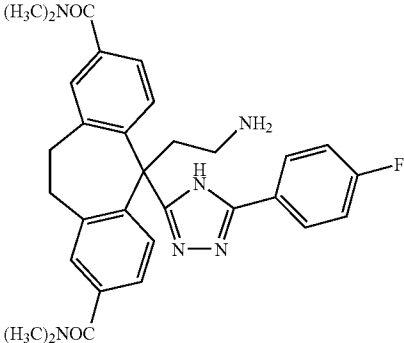

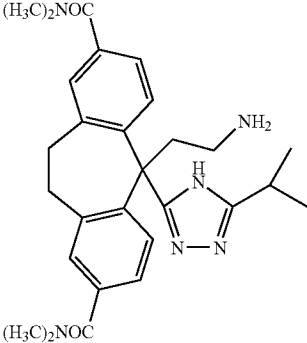
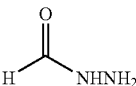
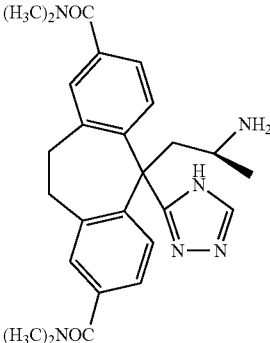
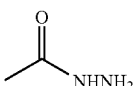
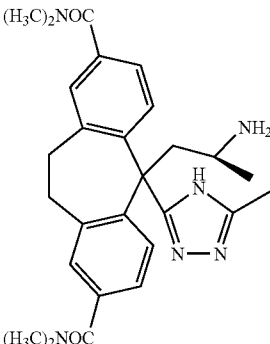
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Preparative Example	Preparative Example	Acid hydrazide	Amine	Product
718	61		CH ₃ NH ₂	
719	61		CH ₃ NH ₂	
720	65		CH ₃ NH ₂	
721	65		CH ₃ NH ₂	

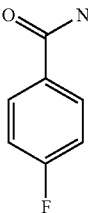
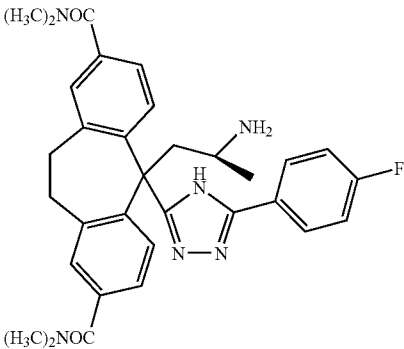
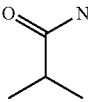
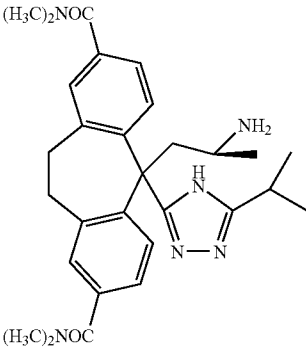
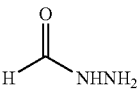
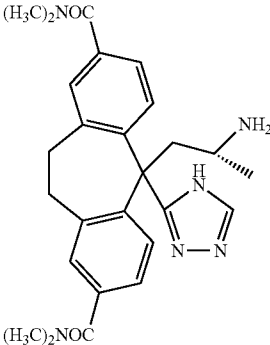
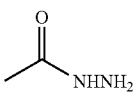
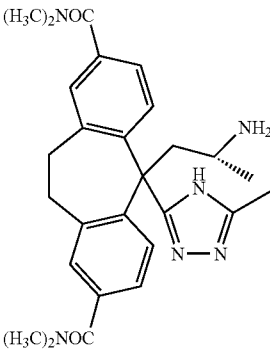
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Preparative Example	Preparative Example	Acid hydrazide	Amine	Product
722	65		CH_3NH_2	
723	65		CH_3NH_2	
724	300		$(\text{CH}_3)_2\text{NH}$	
725	300		$(\text{CH}_3)_2\text{NH}$	

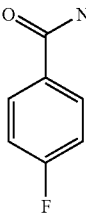
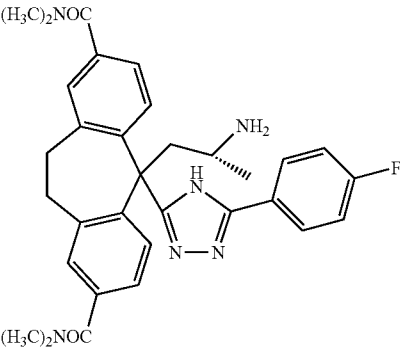

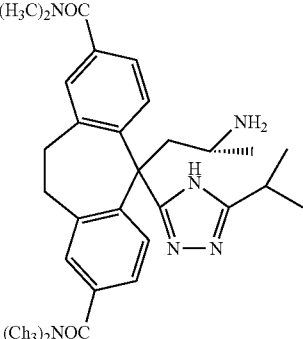
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Preparative Example	Preparative Example	Acid hydrazide	Amine	Product
726	300		$(\text{CH}_3)_2\text{NH}$	
727	300		$(\text{CH}_3)_2\text{NH}$	
728	61		$(\text{CH}_3)_2\text{NH}$	
729	61		$(\text{CH}_3)_2\text{NH}$	

-continued

Preparative Example	Preparative Example	Acid hydrazide	Amine	Product
730	61		(CH ₃) ₂ NH	
731	61		(CH ₃) ₂ NH	
732	65		(CH ₃) ₂ NH	
733	65		(CH ₃) ₂ NH	

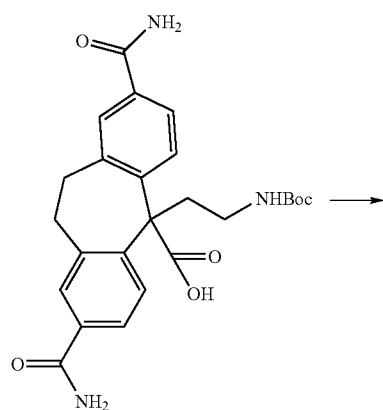
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Preparative Example	Preparative Example	Acid hydrazide	Amine	Product
734	65		$(\text{CH}_3)_2\text{NH}$	
735	65		$(\text{CH}_3)_2\text{NH}$	

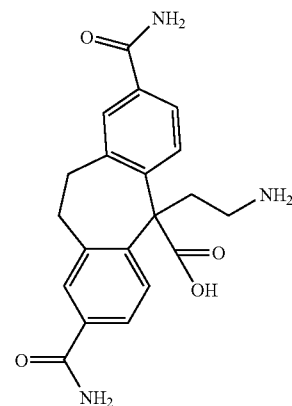
[0615] Example numbers 736-779 were intentionally excluded.

Preparative Example 780

[0616]



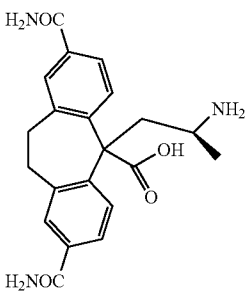
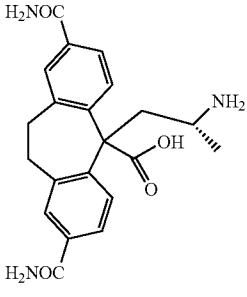
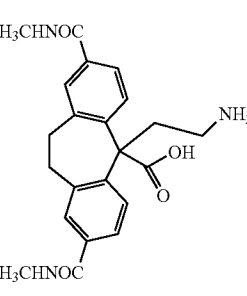
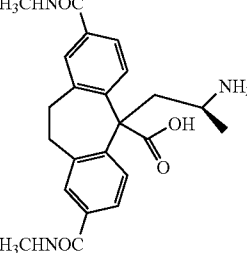
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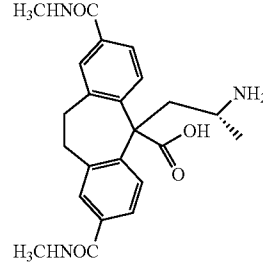
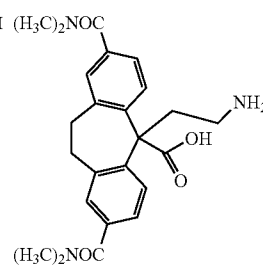
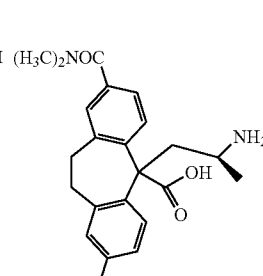
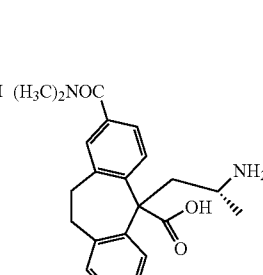
[0617] If one were to treat the starting material, which was obtained by treating the title compound from Preparative Example 300 Step A according to the procedures described in Preparative Example 500 Step A-C, according to the procedure described in Preparative Example 70 Step B, one would obtain the title compound.

Preparative Example 781-788

[0618] If one were to follow a similar procedure as that described in Preparative Example 780, except using the appropriate intermediate from the Preparative Examples and amines as indicated in the Table below, one would obtain the desired amine product.

Preparative Example	Preparative Example	Amine	Product
781	61	NH ₃	
782	65	NH ₃	
783	300	CH ₃ NH ₂	
784	61	CH ₃ NH ₂	

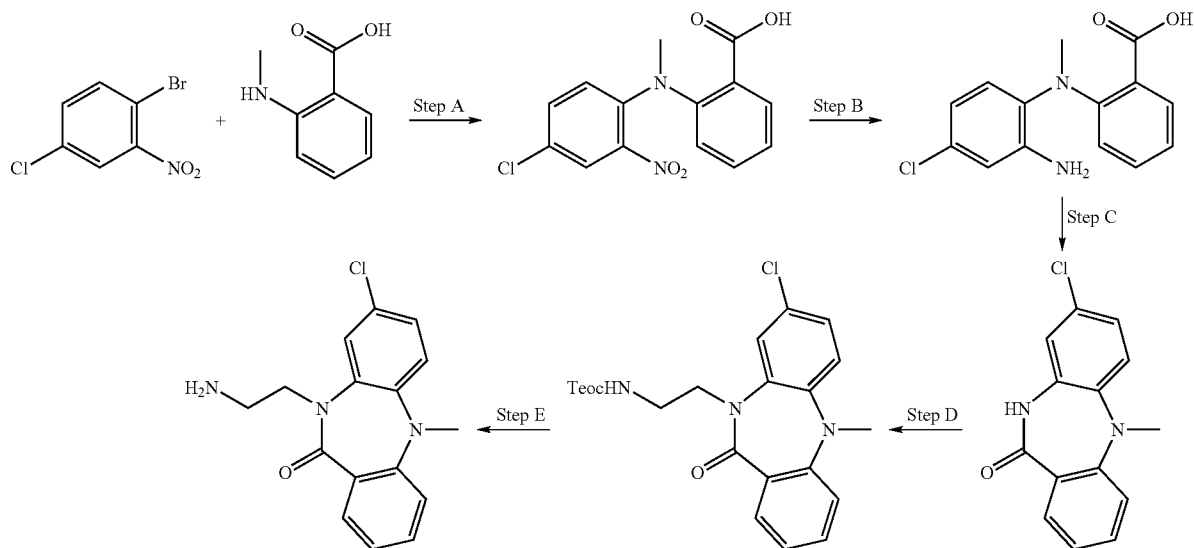
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Preparative Example	Preparative Example	Amine	Product
785	65	CH ₃ NH ₂	
786	300	(CH ₃) ₂ NH	
787	61	(CH ₃) ₂ NH	
788	65	(CH ₃) ₂ NH	

[0619] Example numbers 789-799 were intentionally excluded.

Preparative Example 800

[0620]



Step A

[0621] If one were to treat commercial available N methyl anthranilic acid with 2 eq. of 2-bromo-5-chloronitrobenzene, 10 eq. of potassium carbonate and a catalytic amount of copper powder in 3-methylbutan-1-ol under reflux for several hours one would obtain, after removing of the volatile compound by steam distillation, acidification of the residue with 2 M HCl, precipitation and recrystallisation of the precipitate from ethanol, the title compound.

Step B

[0622] If one were to treat the title compound from Step A above with 7 eq. of sodium dithionite in 2 M aqueous ammonia at 80° C. one would obtain, after filtration, acidification of the filtrate with glacial acetic acid to pH 4, precipitation and recrystallisation from methanol, the title compound.

Step C

[0623] If one were to reflux the title compound from Step B above in xylene under Dean Stark conditions one would

obtain, after evaporation of the solvent, washing of the residue with 2 M aqueous ammonia and recrystallisation from acetone, the title compound.

Step D

[0624] If one were to treat the title compound from Step C above with the sulfamidate from Preparative Example 22 according to Preparative Example 61 Step A one would obtain the title compound.

Step E

[0625] If one were to treat the title compound from Step A above with TFA as described in Preparative Example 70 Step B, one would obtain the title compound.

Preparative Example 801-805

[0626] If one were to follow a similar procedure as that described in Preparative Example 800, except using the diazepines and sulfamidates as indicated in the Table below, one would obtain the desired amine product.

Preparative Example	Diazepine	Sulfamidate	Product
801		22	

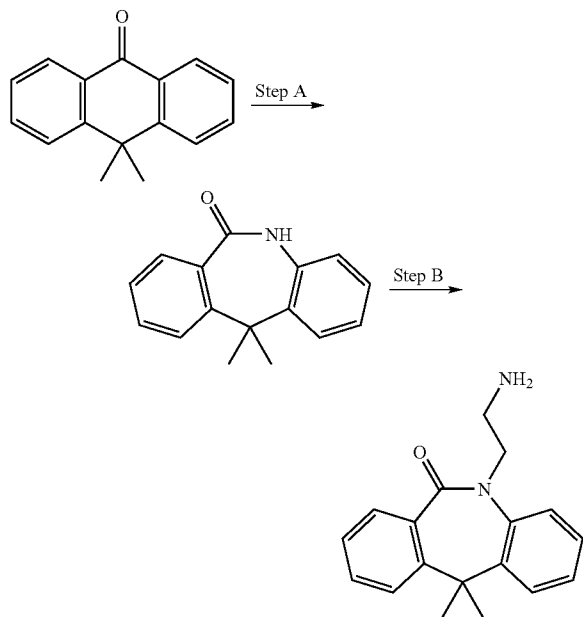
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Preparative Example	Diazepine	Sulfamidate	Product
802		21	
803		24	
804		21	
805		24	

[0627] Examples 806-809 have been intentionally excluded.

Preparative Example 810

[0628]



Step A

[0629] If one were to treat commercially available 10,10-dimethyl-10H-anthracen-9-one and concentrated sulphuric acid in chloroform in a flask equipped with reflux condenser with sodium azide at room temperature, followed by heating this mixture at 50° C. and subsequently pouring it on crushed ice followed by neutralization with conc. aqueous ammonia, separation and evaporation of the organic phase, one would obtain the title compound.

Step B

[0630] If one were to treat the title compound from Step A above with the sulfamate from Preparative Example 22 as described in Preparative Example 800, one would obtain the title compound.

Preparative Example 811-812

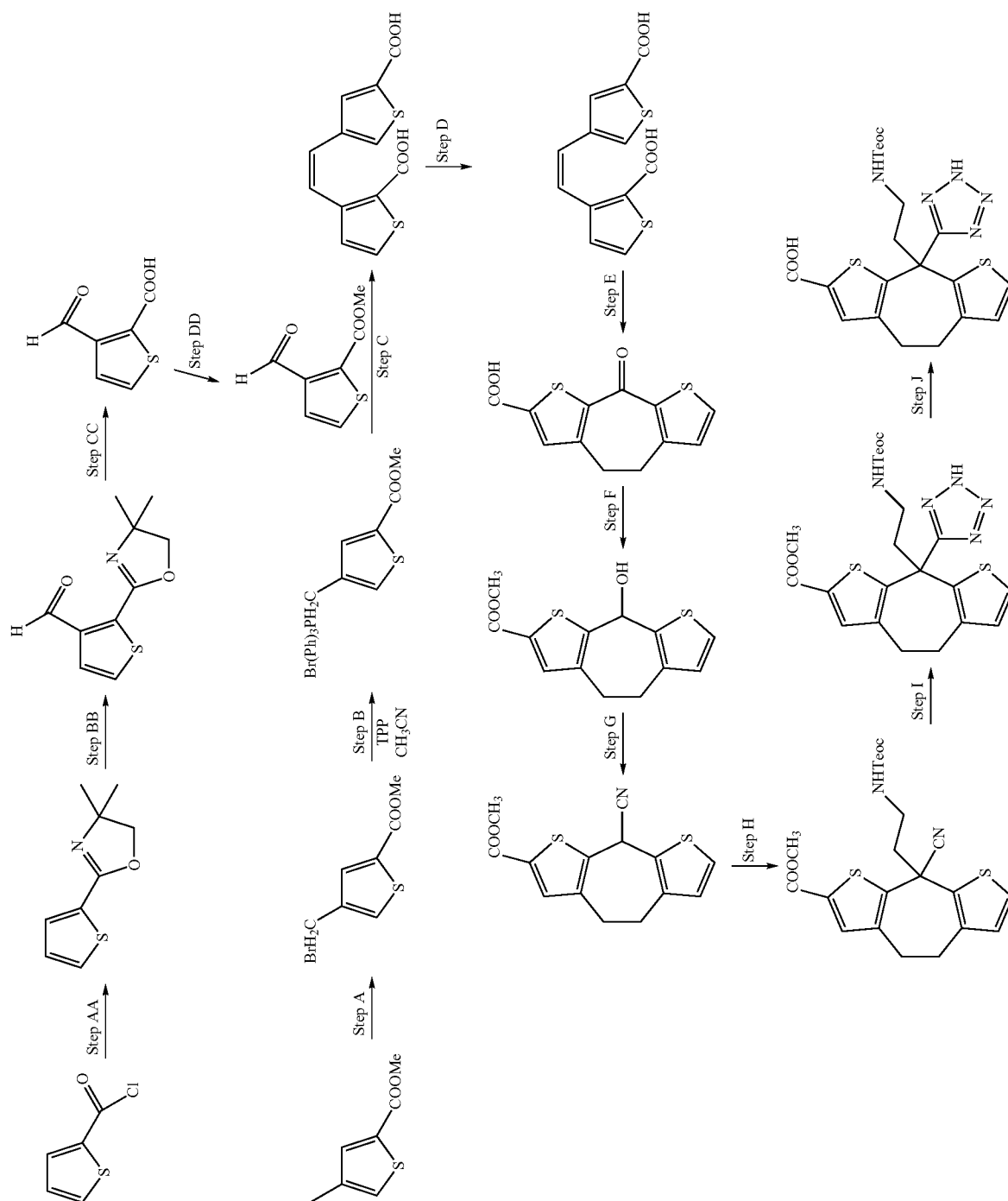
[0631] If one were to follow a similar procedure as described in Preparative Example 810, except using the azepines and sulfamides as indicated in the table below, one would obtain the desired amine product.

Preparative Example	Azepine	Sulfamate	Product
811		24	
812		21	

[0632] Examples 813-829 have been intentionally excluded.

Preparative Example 830

[0633]



Step AA

[0634] If one were to add a solution of commercially available 2-amino-2-methyl-1-propanol in methylene chloride to a solution of commercially available 2-thiophenecarbonyl chloride in methylene chloride dropwise while maintaining the temperature below 20° C., subsequently stir the mixture at room temperature for 2 h and wash with water, dry the organic layer (MgSO₄) and evaporate, suspend the residue in toluene and add thionyl chloride dropwise with stirring while maintaining the temperature below 30° C., subsequently continue the stirring overnight, evaporate the toluene, dissolve the residue in water, basify with 1 N aqueous NaOH and extract with ether, then, after drying (MgSO₄) and evaporation of the solvent, followed by distillation, one would obtain the title compound.

Step BB

[0635] If one were to add commercial -nBuLi in hexane to the title compound from Step AA above in ether at -78° C., stir the mixture under argon for 0.25 h, add DMF, allow the mixture to slowly warm to room temperature and leave the mixture at this temperature for 18 h, subsequently add water and ether, separate the organic solution, wash with water, brine and dry the solution (MgSO₄), then, after evaporation of the solvent, followed by chromatographic purification, one would obtain the title compound.

Step CC

[0636] If one were to boil the title compound from Step BB above under reflux with 4M aqueous hydrochloric acid under argon atmosphere for 14 h, saturate the cooled solution with NaCl, extract repeatedly with ethyl acetate, dry the combined organic extracts (MgSO₄), then, after evaporation of the solvent, followed by recrystallization from ethyl acetate/hexane, one would obtain the title compound.

Step DD

[0637] If one were to treat the title compound from Step CC above in methanol dropwise with an ethereal solution of diazomethane at -15° C., followed by careful removal of all volatiles, then one would obtain the title compound.

Step A

[0638] If one were to add commercially available methyl 4-methylthiophene-2-carboxylate to N-bromosuccinimide, benzoyl peroxide and tetrachloromethane and would heat the mixture under reflux for 4 h followed by filtration and evaporation of the solvent, one would obtain the title compound.

Step B

[0639] If one were to treat the title compound from Step A above with triphenylphosphine according to Preparative Example 51 Step C, one would obtain the title compound.

Step C

[0640] If one were to treat the title compound from Step B above with the thiophene aldehyde from Step DD as described in Preparative Example 54 Step A, one would obtain the title compound.

Step D

[0641] If one were to treat a suspension of the title compound from Step C above, hydroiodic acid and red phospho-

rus at 140° C. for 18 h, followed by cooling and pouring the reaction mixture into an ice/water mixture, subsequent filtration, washing of the precipitate with water, dissolving the precipitate in refluxing conc. ammonia and subsequent filtration, acidification of the filtrate with conc. aqueous hydrochloric acid and extraction of the aqueous phase with dichloromethane, washing of the organic phase with water and drying (MgSO₄) followed by evaporation of the solvent, one would obtain the title compound.

Step E

[0642] If one were to treat a suspension of the title compound from Step D above with polyphosphoric acid at 170° C., followed by cooling to 30° C., pouring into water, extraction with diethyl ether, washing with 1N aqueous sodium hydroxide solution and drying (MgSO₄) followed by evaporation of the solvent, one would obtain the title compound.

Step F

[0643] If one were to treat the title compound from Step E above as described in Preparative Example 59 Step G, one would obtain the title compound.

Step G

[0644] If one were to treat the title compound from Step F above as described in Preparative Example 59 Step H and Step I, one would obtain the title compound.

Step H

[0645] If one were to treat the title compound from Step G above with the compound from Preparative Example 22 as described in Preparative Example 61 Step A, one would obtain the title compound.

Step I

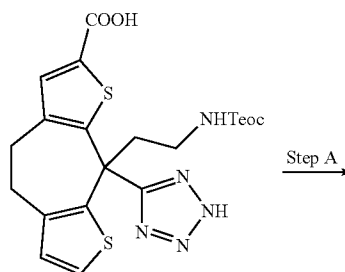
[0646] If one were to treat the title compound from Step H above as described in Preparative Example 61 Step B, one would obtain the title compound.

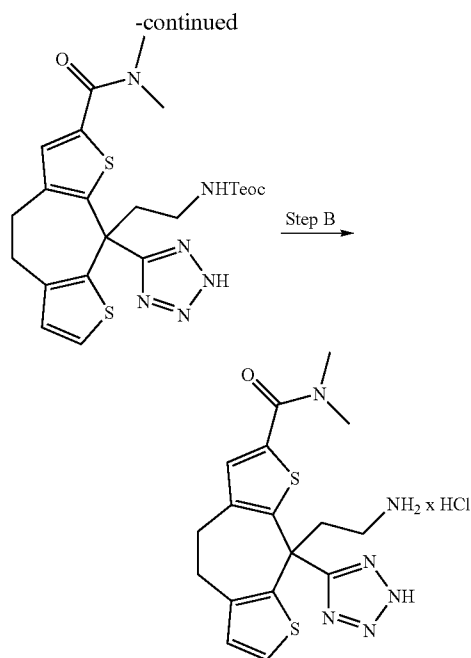
Step J

[0647] If one were to treat the title compound from Step I above as described in Preparative Example 61 Step C, one would obtain the title compound.

Preparative Example 831

[0648]





Step A

[0649] If one were to treat the title compound from Preparative Example 830 as described in Preparative Example 71 Step A, one would obtain the title compound.

Step B

[0650] If one were to treat the title compound from Step A above as described in Preparative Example 71 Step B, one would obtain the title compound.

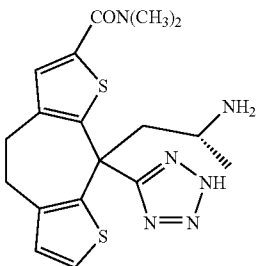
Preparative Example 832-839

[0651] If one were to follow a similar procedure as that described in Preparative Example 830, except using the sulfamides in Step H, and treat the product obtained according to Preparative Example 831 with the amine as indicated in the table below, one would obtain the desired title compound as HCl salts.

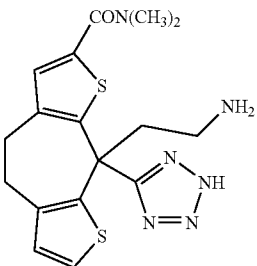
Preparative Example	Sulfamide	Amine	Title compound
831	21	NH ₃	

-continued			
Preparative Example	Sulfamide	Amine	Title compound
832	24	NH ₃	
833	22	NH ₃	
834	21	CH ₃ NH ₂	
835	24	CH ₃ NH ₂	
836	22	CH ₃ NH ₂	

-continued

Preparative Example	Sulfamidate	Amine	Title compound
837	24	$(\text{CH}_3)_2\text{NH}$	

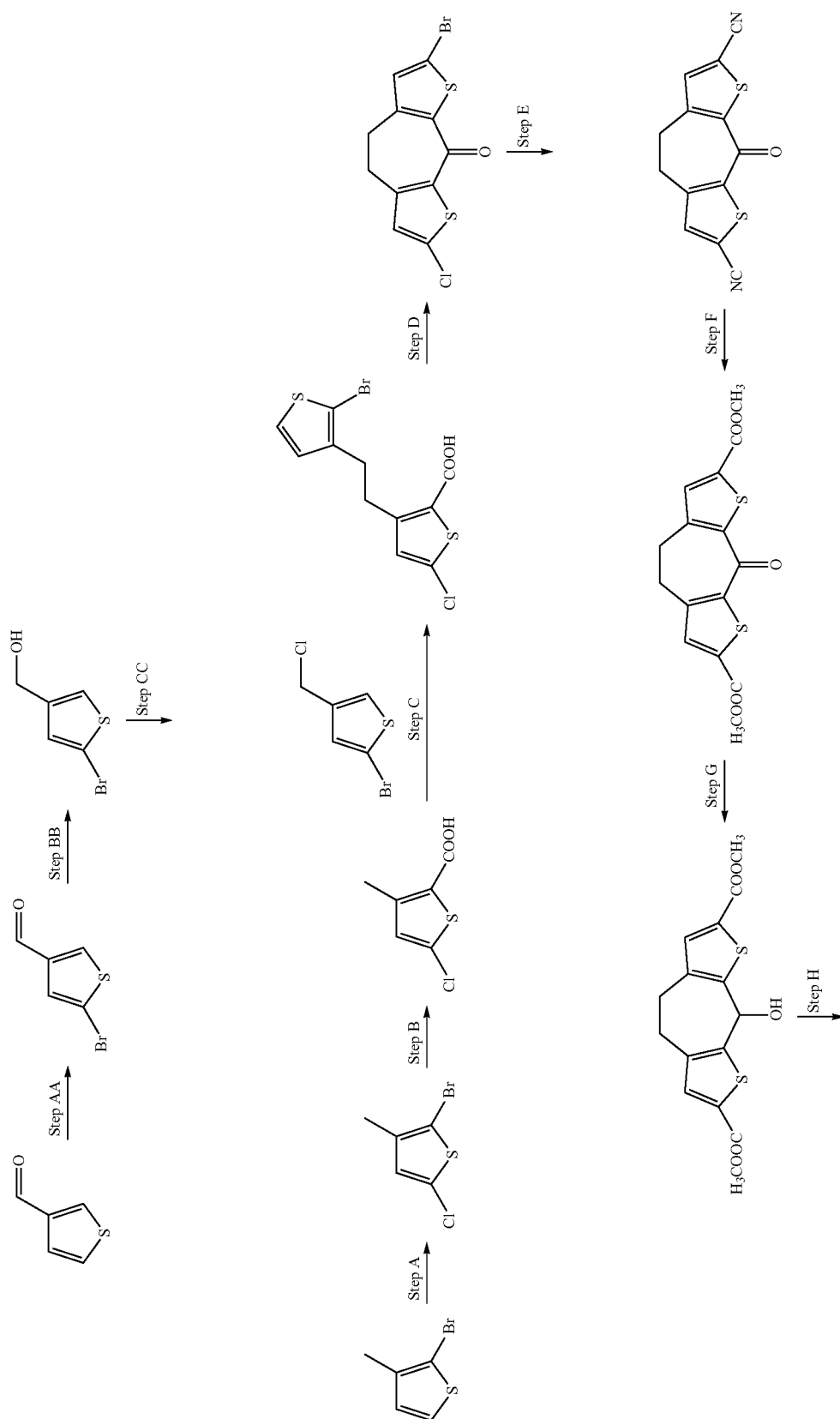
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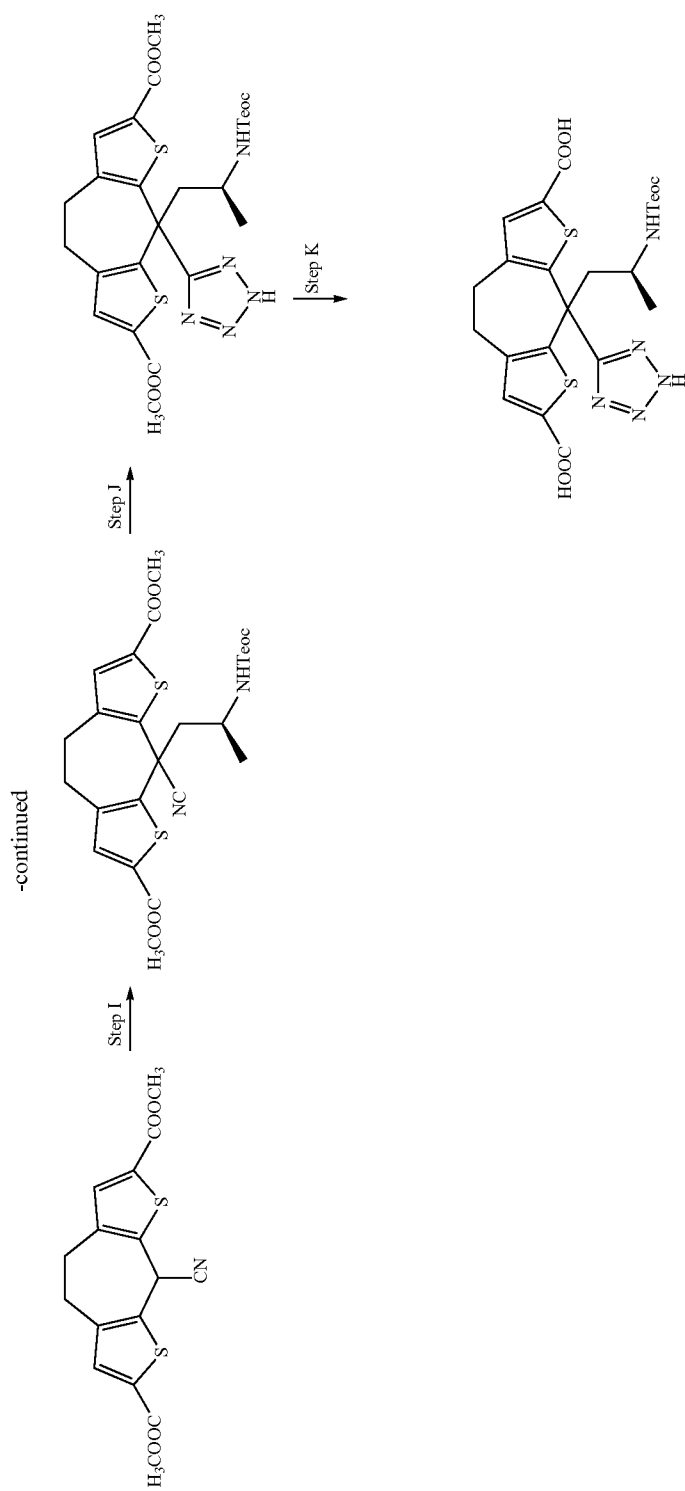
Preparative Example	Sulfamidate	Amine	Title compound
838	22	$(\text{CH}_3)_2\text{NH}$	

[0652] Examples 839 to 849 have been intentionally excluded.

Preparative Example 850

[0653]





Step AA

[0654] If one were to treat commercially available thiophene-3-carbaldehyde with bromine and aluminium trichloride in dichloromethane and heat the reaction mixture for 2 h, subsequently pouring it into water, followed by extraction with ether, washing of the organic phase successively with aqueous 1N NaOH solution and water until neutral, then, after drying (MgSO_4) and evaporation of the solvent, followed by distillation, one would obtain the title compound.

Step BB

[0655] If one were to treat a solution of the title compound from Step AA above in tetrahydrofuran with NaBH_4 for 1 h and quench the reaction by the addition of saturated aqueous ammonium chloride solution followed by dilution with ethyl acetate, separation of the organic layer, washing with H_2O and brine, then, after drying (MgSO_4) and evaporation of the solvent, one would obtain the title compound.

Step CC

[0656] If one were to treat a solution of the title compound from Step BB above in chloroform with thionyl chloride at room temperature for 4 h, subsequently pouring it into water, followed by extraction with chloroform, washing of the organic phase with water, then, after drying (MgSO_4) and evaporation of the solvent, one would obtain the title compound.

Step A

[0657] If one were to treat commercially available 2-bromo-3-methylthiophene in acetic acid with N-chlorosuccinimide and stir the reaction mixture for about 2 h, then refluxing it for 1 h, subsequently pouring it into water, followed by extraction with ether, washing of the organic phase successively with aqueous 1N NaOH solution and water until neutral, then, after drying (MgSO_4) and evaporation of the solvent, followed by distillation, one would obtain the title compound.

Step B

[0658] If one were to treat the title compound from Step A above as described in Preparative Example 59 Step A, one would obtain the title compound.

Step C

[0659] If one were to treat the title compound from Step B above with the title compound from Step CC above, as described in Preparative Example 59 Step B, one would obtain the title compound.

Step D

[0660] If one were to treat the title compound from Step C above as described in Preparative Example 59 Step C, one would obtain the title compound.

Step E

[0661] If one were to treat the title compound from Step D above as described in Preparative Example 59 Step D, one would obtain the title compound.

Step F

[0662] If one were to treat the title compound from Step E above as described in Preparative Example 59 Step E and Step F, one would obtain the title compound.

Step G

[0663] If one were to treat the title compound from Step F above as described in Preparative Example 59 Step G, one would obtain the title compound.

Step H

[0664] If one were to treat the title compound from Step G above as described in Preparative Example 59 Step H and Step I, one would obtain the title compound.

Step I

[0665] If one were to treat the title compound from Step H above as described in Preparative Example 61 Step A, one would obtain the title compound.

Step J

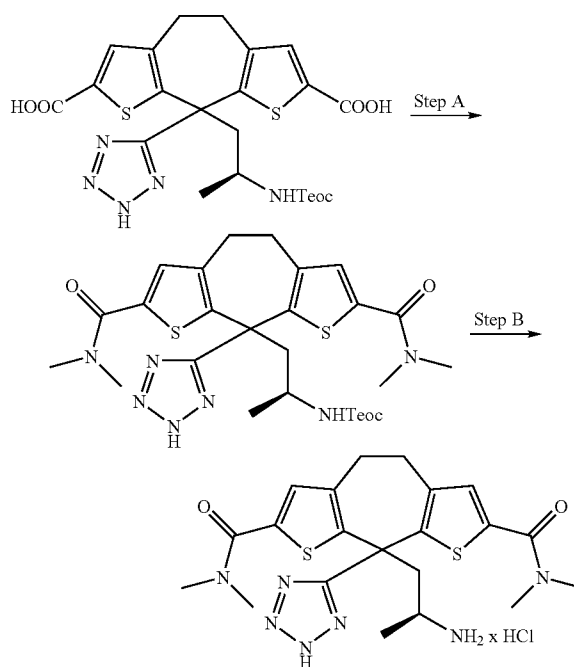
[0666] If one were to treat the title compound from Step I above as described in Preparative Example 61 Step B, one would obtain the title compound.

Step K

[0667] If one were to treat the title compound from Step J above as described in Preparative Example 61 Step C, one would obtain the title compound.

Preparative Example 851

[0668]



Step A

[0669] If one were to treat the title compound from Preparative Example 851 as described in Preparative Example 71 Step A one would obtain the title compound.

Step B

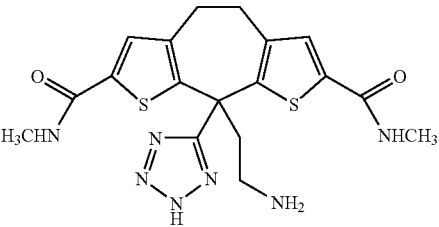
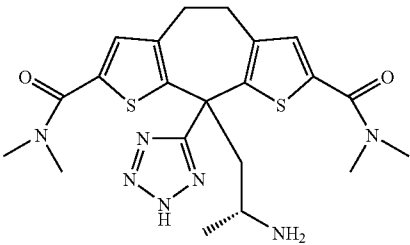
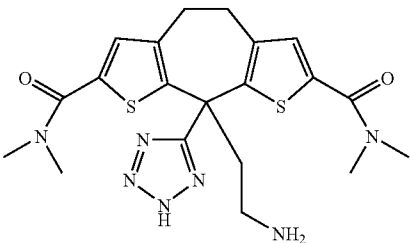
[0670] If one were to treat the title compound from Step A above as described in Preparative Example 71 Step B, one would obtain the title compound.

Preparative Example 852-859

[0671] If one were to follow a similar procedure as that described in Preparative Example 850, except using the sulfamides in Step I, and treat the product obtained according to Preparative Example 851 with the amine as indicated in the table below, one would obtain the desired title compound as HCl salt.

Preparative Example	Sulfamide	Amine	Title compound
852	21	NH ₃	
853	24	NH ₃	
854	22	NH ₃	
855	21	CH ₃ NH ₂	
856	24	CH ₃ NH ₂	

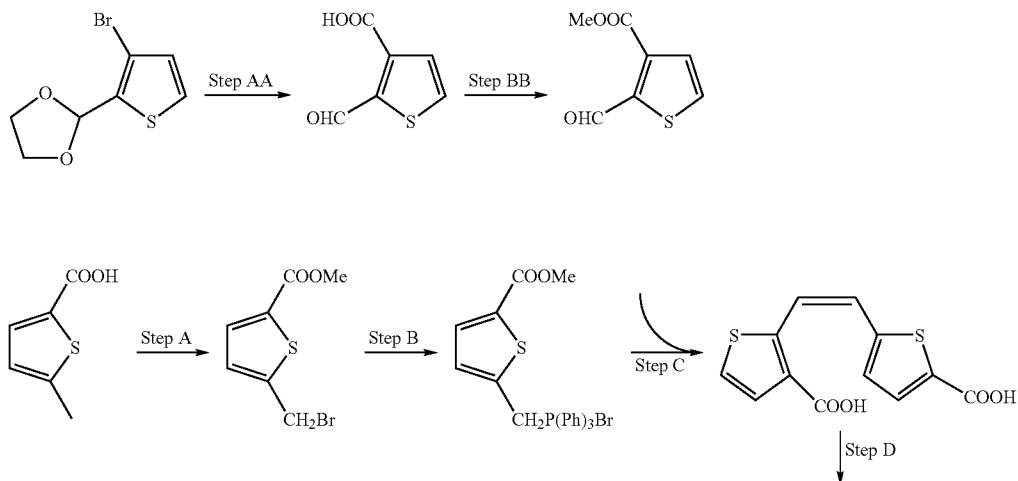
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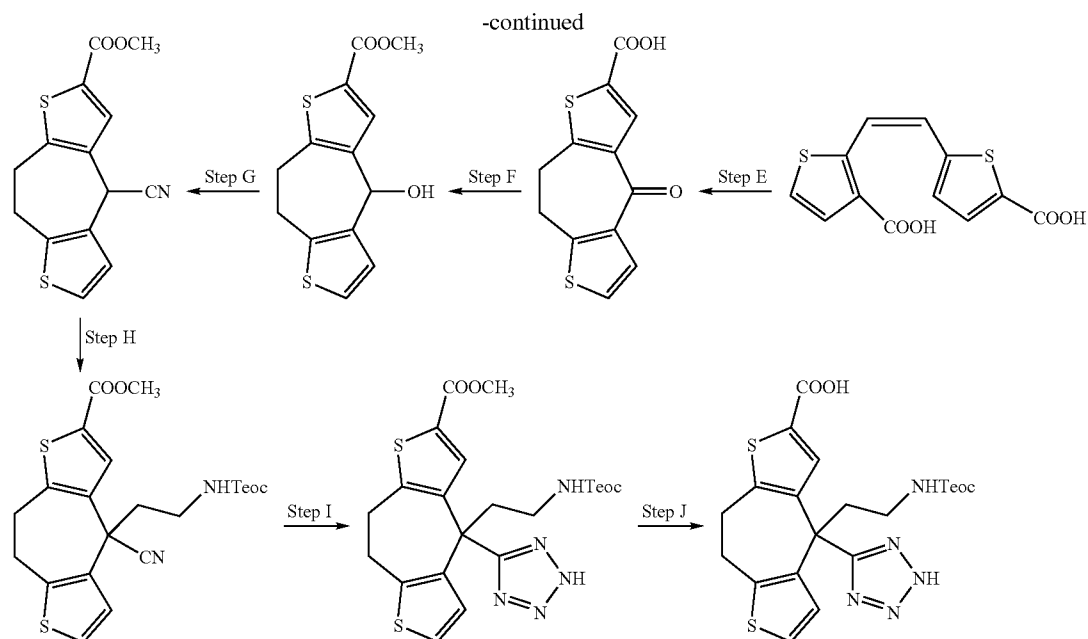
Preparative Example	Sulfamidate	Amine	Title compound
857	22	CH_3NH_2	
858	24	$(\text{CH}_3)_2\text{NH}$	
859	22	$(\text{CH}_3)_2\text{NH}$	

[0672] Examples 860-899 have been intentionally excluded.

Preparative Example 900

[0673]





Step AA

[0674] If one were to add a solution of commercially available 2-(3-bromo-2-thienyl)-1,3-dioxolane in dry diethylether with stirring to 1.05 N butyl lithium in diethylether at -70°C ., followed by addition of the mixture to solid CO_2 covered with diethylether. Hydrolysis, followed by extraction with diluted aqueous sodium hydroxide, acidification, then extraction with diethylether afford the title compound.

Step BB

[0675] If one were to add H_2SO_4 and methanol to a solution of the title compound from step AA above in dichloroethane, one would obtain the title compound.

Step A

[0676] If one were to treat a solution of commercially available 5-methylthiophene-2-carboxylic acid in benzene and methanol at 0°C . dropwise with 2.0 M trimethylsilyldiazomethane in hexanes, one would obtain the methyl ester. If one were to treat a solution of that ester intermediate in CCl_4 with NBS and 2,2'-azobisisobutyronitrile (AIBN) and heat the solution to reflux for 2 h, followed by cooling down to room temperature, filtration and concentration in vacuo one would obtain the title compound.

Step B

[0677] If one were to treat the title compound from Step A above with triphenylphosphine according to Preparative Example 49 Step C, one would obtain the title compound.

Step C

[0678] If one were to treat the title compound from Step B above with the title compound from Step BB above as described in Preparative Example 54 Step A, one would obtain the title compound.

Step D

[0679] If one were to heat a mixture of the title compound from Step C, red phosphorous and hydroiodic acid in acetic

acid at 110°C . for 1 h, one would obtain a solution after filtration of the hot mixture. After cooling to room temperature and pouring in ice water one would obtain the title compound by suction.

Step E

[0680] If one were to heat a mixture of the title compound from Step D above and polyphosphoric acid at 115°C . for 1.5 h one would obtain a mixture, which was poured on ice. After extraction with Ether washing the organic phases with water, drying (MgSO_4) and removing of the solvent one would obtain the title compound.

Step F

[0681] If one were to treat the title compound from Step E above as described in Preparative Example 59 Step G, one would obtain the title compound.

Step G

[0682] If one were to treat the title compound from Step F above as described in Preparative Example 59 Step H and Step I, one would obtain the title compound.

Step H

[0683] If one were to treat the title compound from Step G above with the compound from Preparative Example 22 as described in Preparative Example 61 Step A, one would obtain the title compound.

Step I

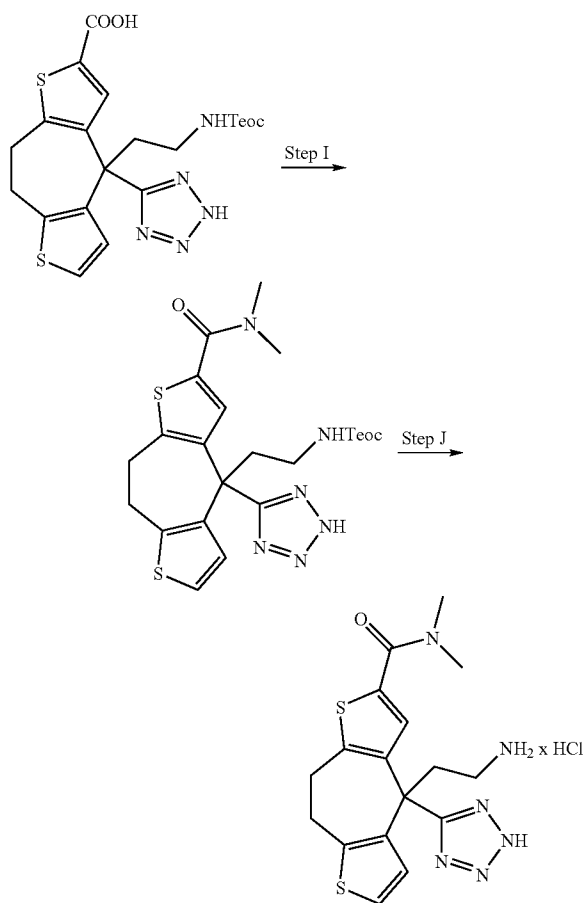
[0684] If one were to treat the title compound from Step H above as described in Preparative Example 61 Step B, one would obtain the title compound.

Step J

[0685] If one were to treat the title compound from Step I above as described in Preparative Example 61 Step C, one would obtain the title compound.

Preparative Example 901

[0686]



Step A

[0687] If one were to treat the title compound from Preparative Example 900 as described in Preparative Example 71 Step A, one would obtain the title compound.

Step B

[0688] If one were to treat the title compound from Step A above as described in Preparative Example 71 Step B, one would obtain the title compound.

Preparative Example 902-909

[0689] If one were to follow a similar procedure as that described in Preparative Example 900, except using the sulfamides in Step H, and treat the product obtained according to Preparative Example 901 with the amines as indicated in the table below, one would obtain the desired title compound as HCl salt.

Preparative Example	Sulfamide	Amine	Title compound
902	21	NH ₃	
903	24	NH ₃	
904	22	NH ₃	
905	21	CH ₃ NH ₂	
906	24	CH ₃ NH ₂	

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Preparative Example	Sulfamidate	Amine	Title compound
907	22	CH_3NH_2	
908	24	$(\text{CH}_3)_2\text{NH}$	

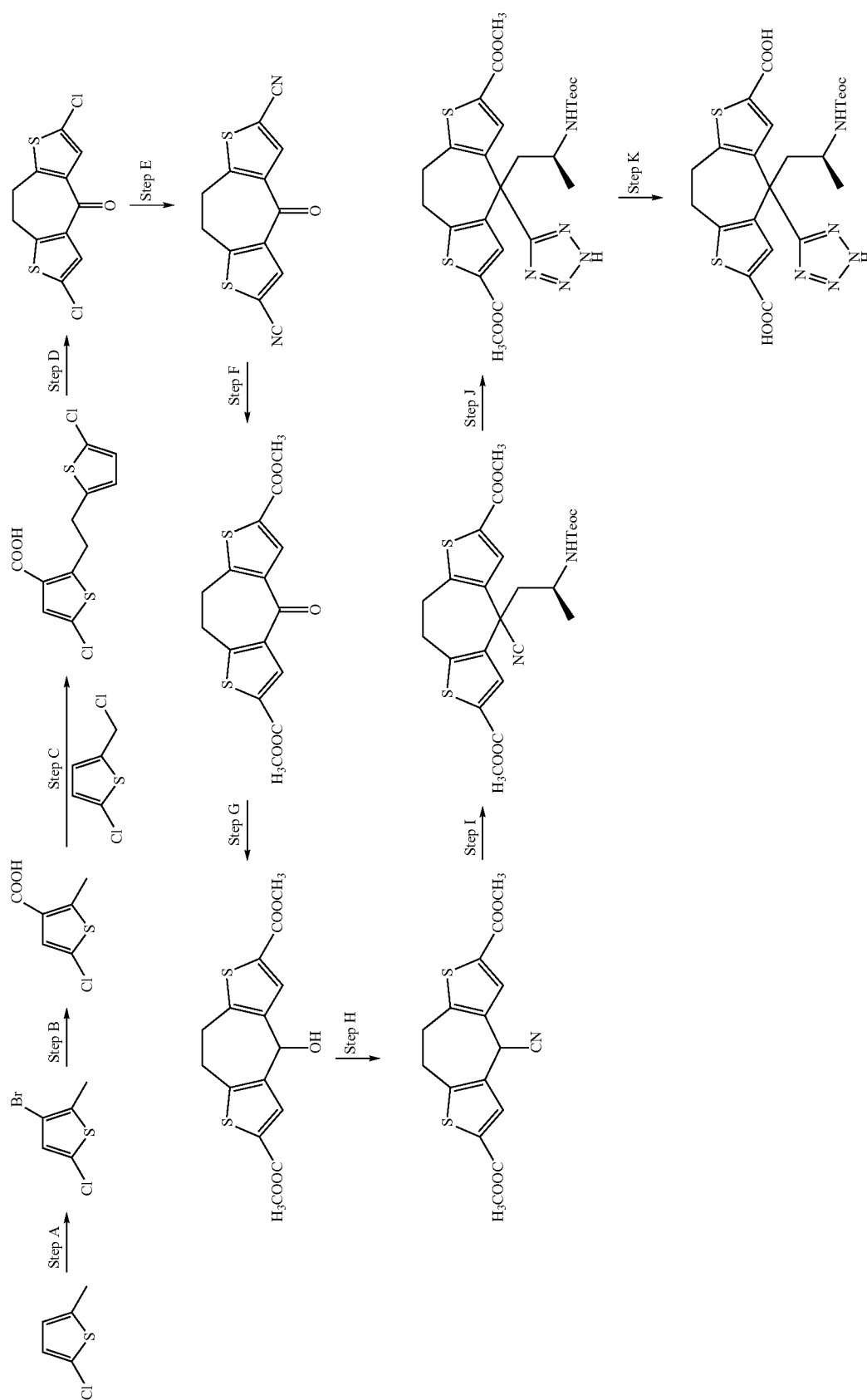
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Preparative Example	Sulfamidate	Amine	Title compound
909	22	$(\text{CH}_3)_2\text{NH}$	

[0690] Examples 910-919 have been intentionally excluded.

Preparative Example 920

[0691]



Step A

[0692] If one were to add a solution of bromine in CHCl_3 slowly to an ice-cooled solution of commercially available 2-chloro-5-methylthiophene in CHCl_3 one would obtain a reaction mixture which was stirred for 2 h at room temperature, and subsequently poured into H_2O . If one were to extract than the mixture with dichloromethane combine the organic extracts dry filter and evaporate the solvent, one would obtain a yellow/brown oil.

Step B

[0693] If one were to treat the title compound from Step A above as described in Preparative Example 59 Step A, one would obtain the title compound.

Step C

[0694] If one were to treat the title compound from Step B above with commercially available 2-chloro-5-chloromethyl-thiophene as described in Preparative Example 59 Step B, one would obtain the title compound.

Step D

[0695] If one were to treat the title compound from Step C above as described in Preparative Example 59 Step C, one would obtain the title compound.

Step E

[0696] If one were to treat the title compound from Step D above as described in Preparative Example 59 Step D, one would obtain the title compound.

Step F

[0697] If one were to treat the title compound from Step E above as described in Preparative Example 59 Step E and Step F, one would obtain the title compound.

Step G

[0698] If one were to treat the title compound from Step F above as described in Preparative Example 59 Step G, one would obtain the title compound.

Step H

[0699] If one were to treat the title compound from Step G above as described in Preparative Example 59 Step H and Step I, one would obtain the title compound.

Step I

[0700] If one were to treat the title compound from Step H above as described in Preparative Example 61 Step A, one would obtain the title compound.

Step J

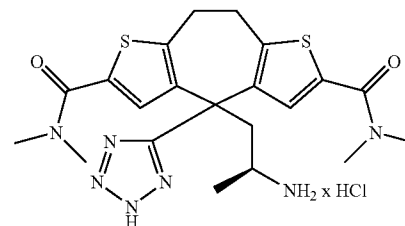
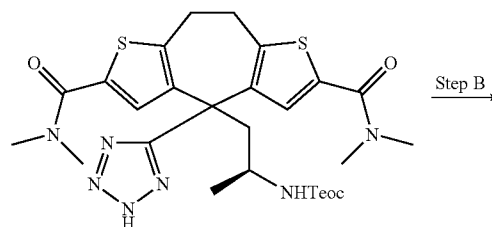
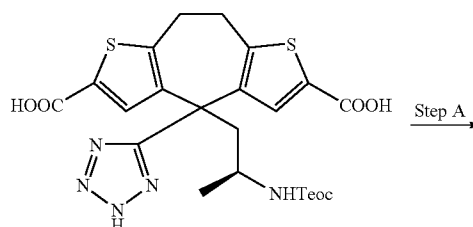
[0701] If one were to treat the title compound from Step I above as described in Preparative Example 61 Step B, one would obtain the title compound.

Step K

[0702] If one were to treat the title compound from Step J above as described in Preparative Example 61 Step C, one would obtain the title compound.

Preparative Example 921

[0703]



Step A

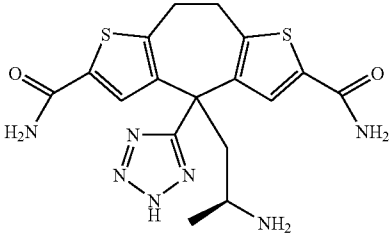
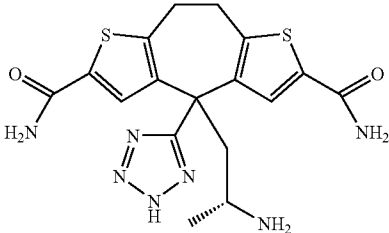
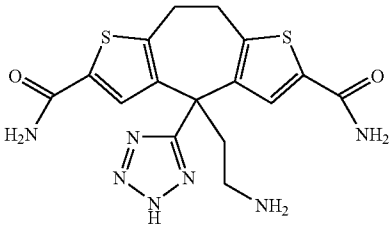
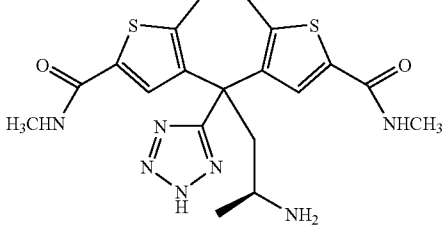
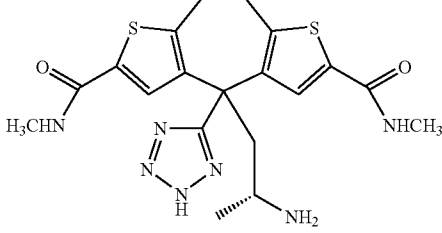
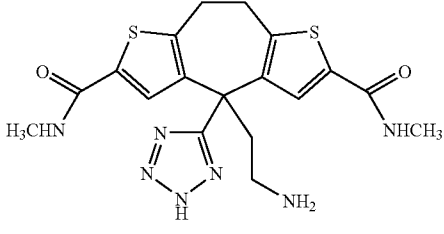
[0704] If one were to treat the title compound from Preparative Example 920 as described in Preparative Example 71 Step A one would obtain the title compound.

Step B

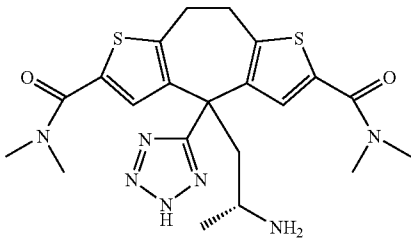
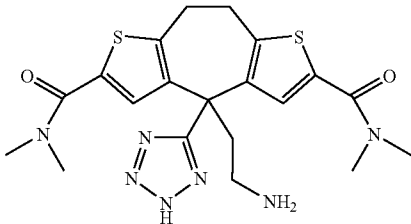
[0705] If one were to treat the title compound from Step A above as described in Preparative Example 71 Step B, one would obtain the title compound.

Preparative Example 922-929

[0706] If one were to follow a similar procedure as that described in Preparative Example 920, except using the sulfamidates in Step I, and treat the product obtained according to Preparative Example 921 with the amine as indicated in the table below, one would obtain the desired title compound as HCl salt.

Preparative Example	Sulfamidate	Amine	Title compound
922	21	NH ₃	
923	24	NH ₃	
924	22	NH ₃	
925	21	CH ₃ NH ₂	
926	24	CH ₃ NH ₂	
927	22	CH ₃ NH ₂	

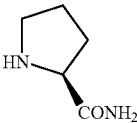
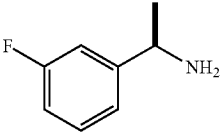
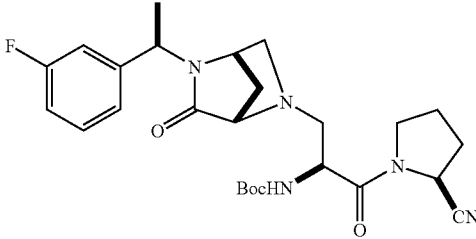
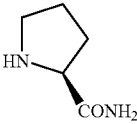
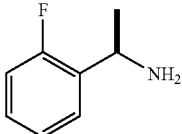
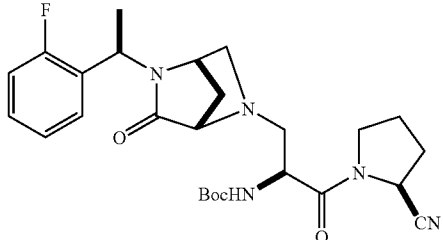
-continued

Preparative Example	Sulfamidate	Amine	Title compound
928	24	$(\text{CH}_3)_2\text{NH}$	
929	22	$(\text{CH}_3)_2\text{NH}$	

[0707] Examples 930-999 have been intentionally excluded.

Preparative Example 1000-1209

[0708] If one were to follow similar procedure as described in Preparative Examples 92 and 93, except using the amides and amines as indicated in the Table below, the following title compound would be obtained.

Prep Example	Amide	Amines	Title compound
1000			
1001			

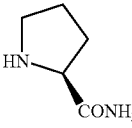
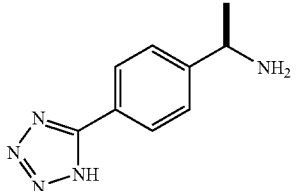
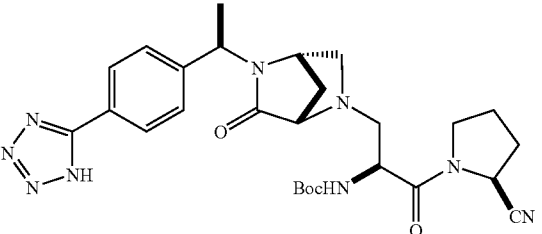
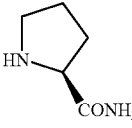
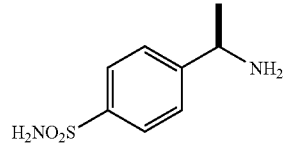
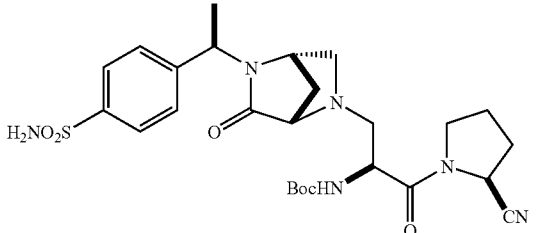
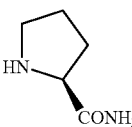
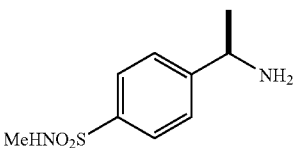
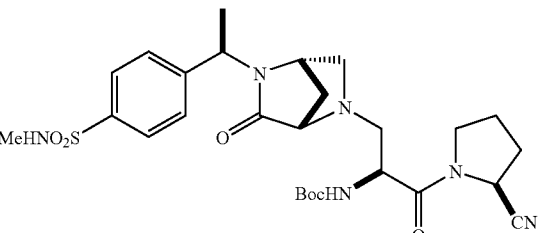
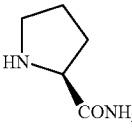
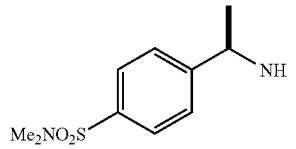
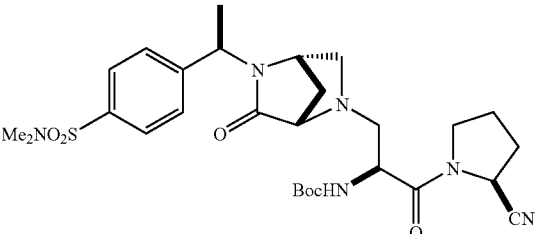
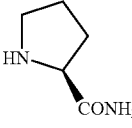
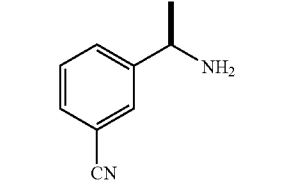
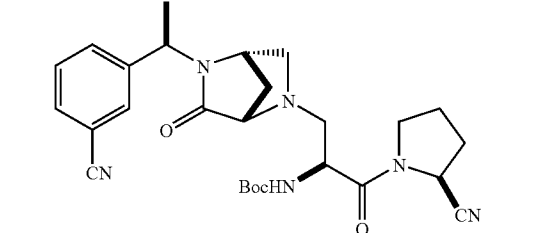
-continued

Prep Example	Amide	Amines	Title compound
1002			
1003			
1004			
1005			
1006			

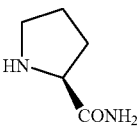
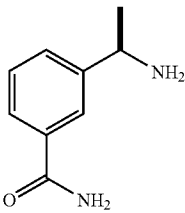
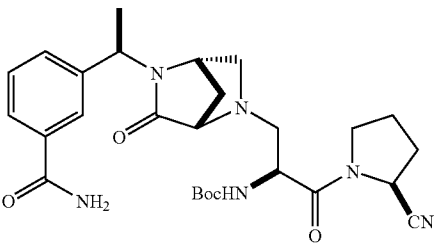
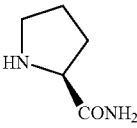
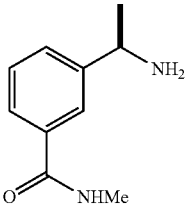
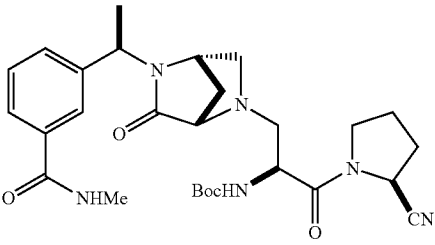
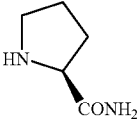
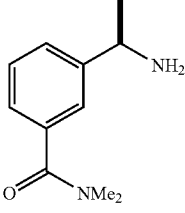
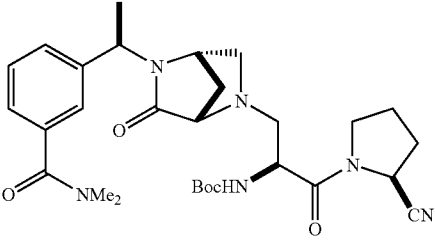
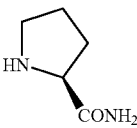
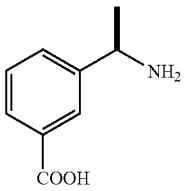
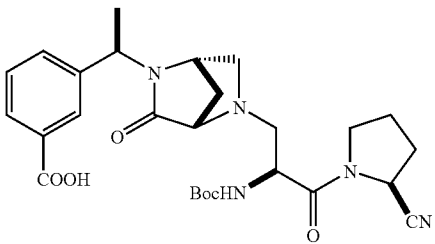
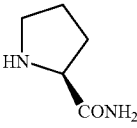
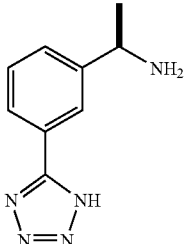
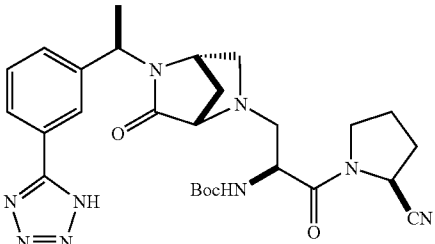
-continued

Prep Example	Amide	Amines	Title compound
1007			
1008			
1009			
1010			
1011			

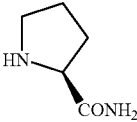
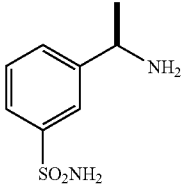
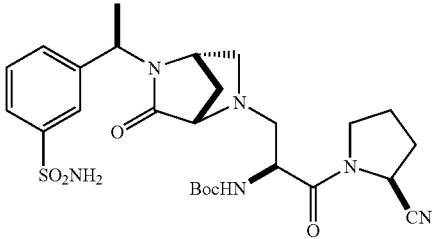
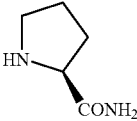
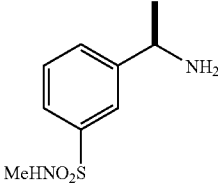
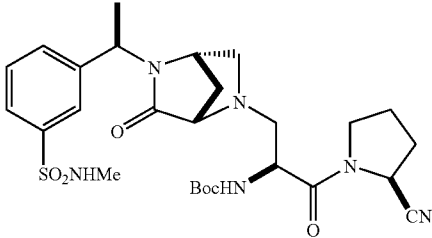
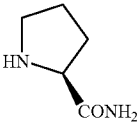
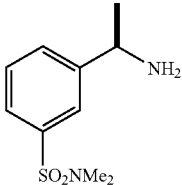
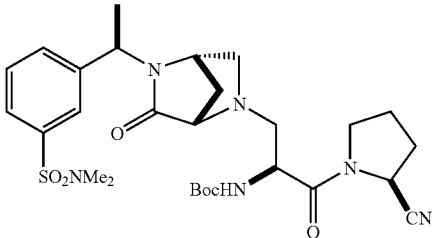
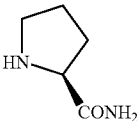
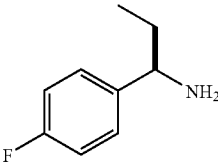
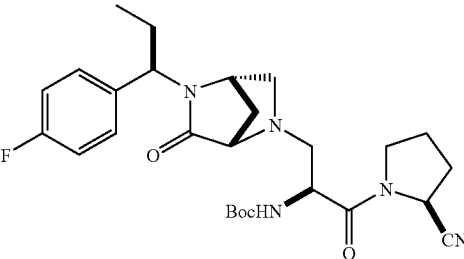
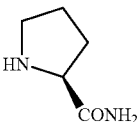
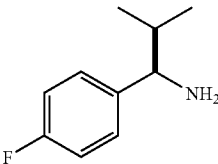
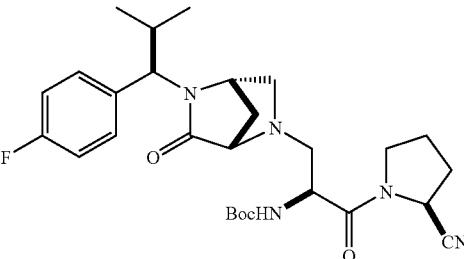
-continued

Prep Example	Amide	Amines	Title compound
1012			
1013			
1014			
1015			
1016			

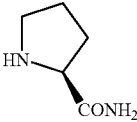
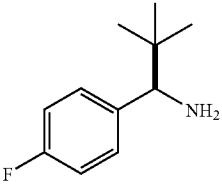
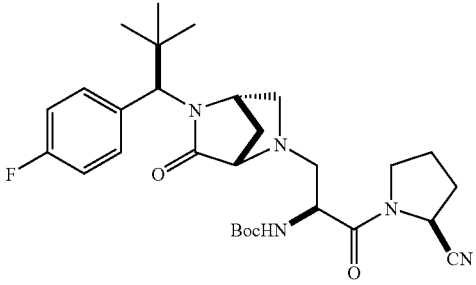
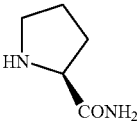
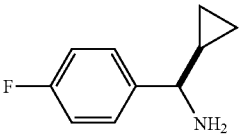
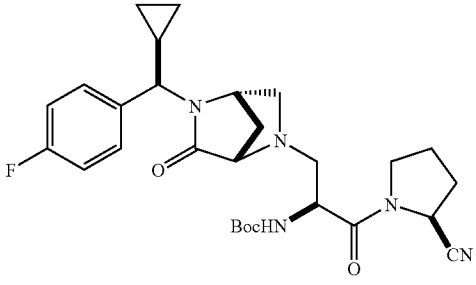
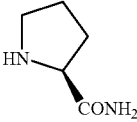
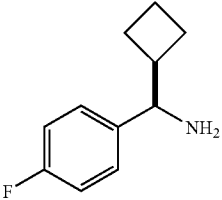
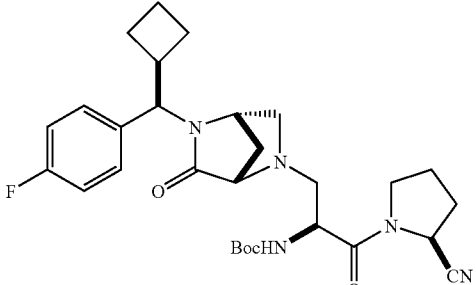
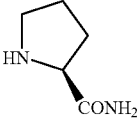
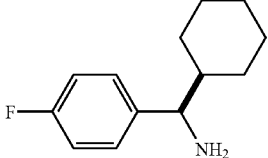
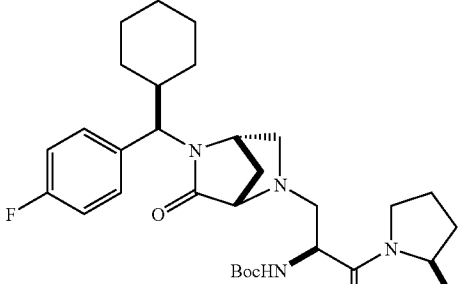
-continued

Prep Example	Amide	Amines	Title compound
1017			
1018			
1019			
1020			
1021			

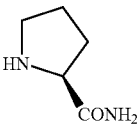
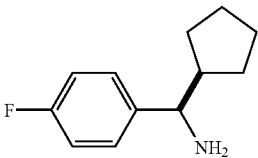
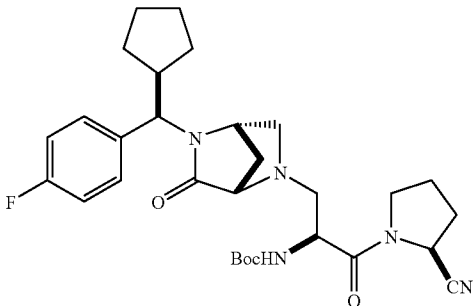
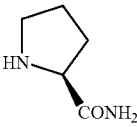
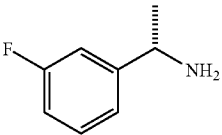
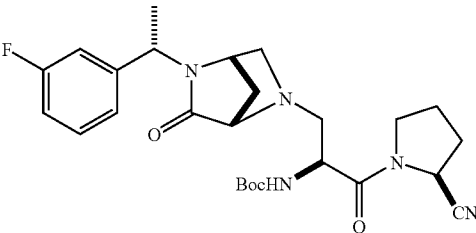
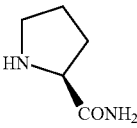
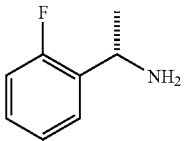
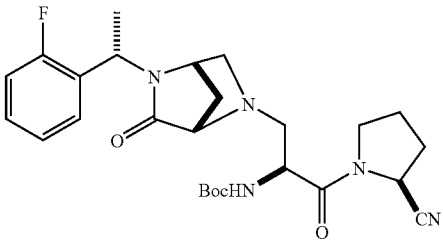
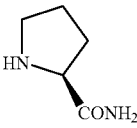
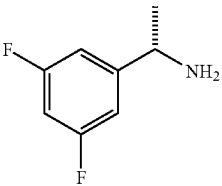
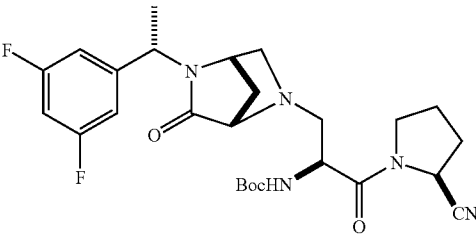
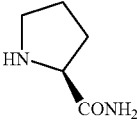
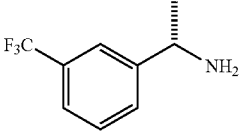
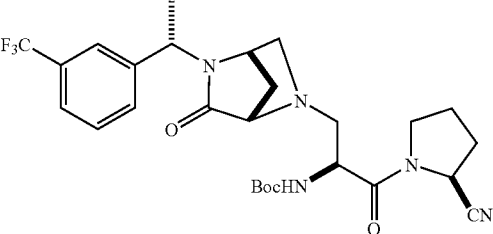
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Prep Example	Amide	Amines	Title compound
1022			
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1024			
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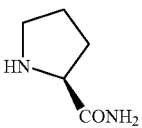
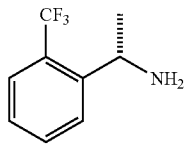
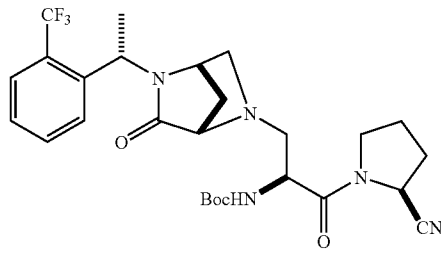
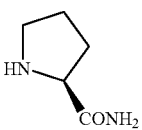
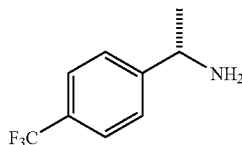
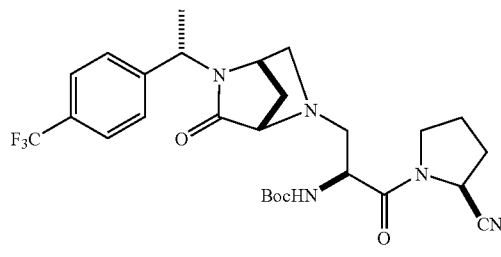
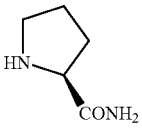
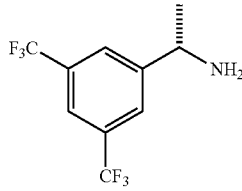
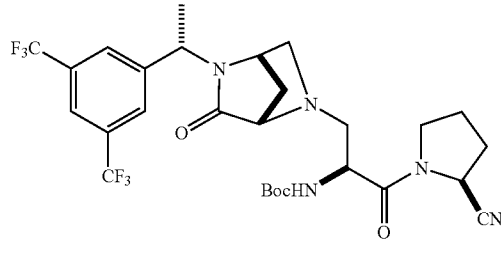
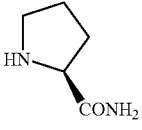
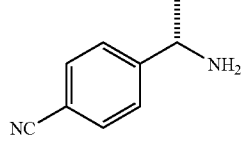
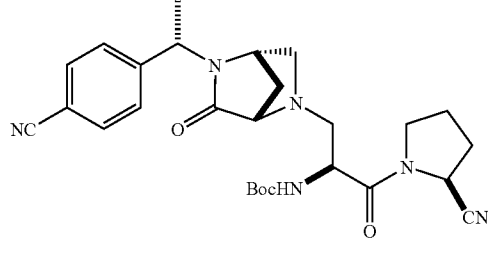
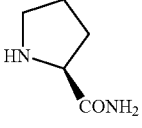
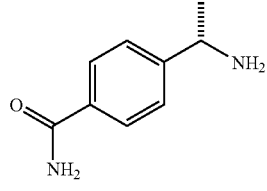
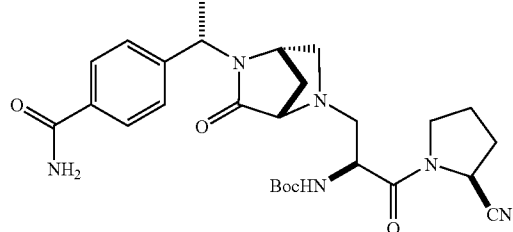
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Prep Example	Amide	Amines	Title compound
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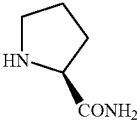
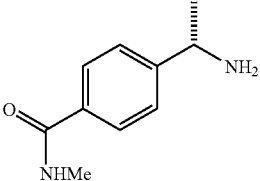
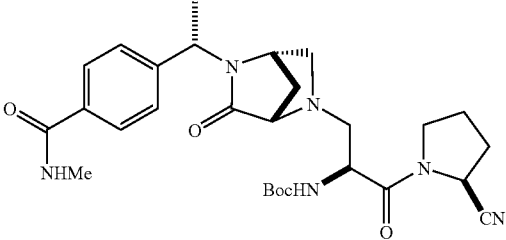
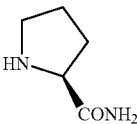
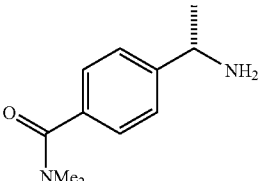
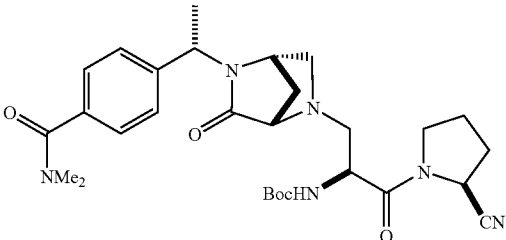
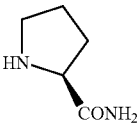
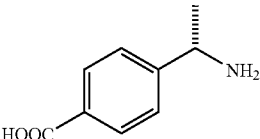
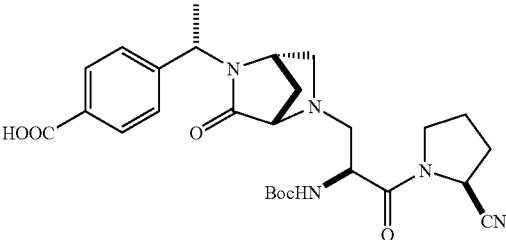
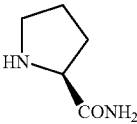
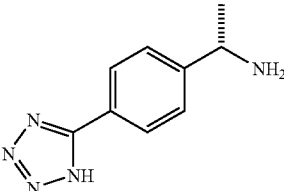
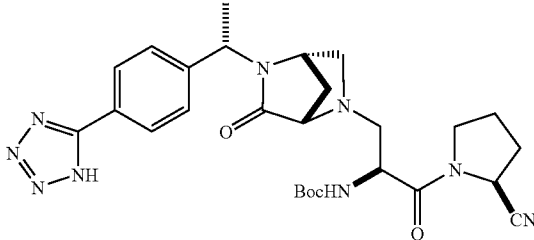
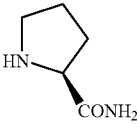
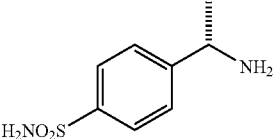
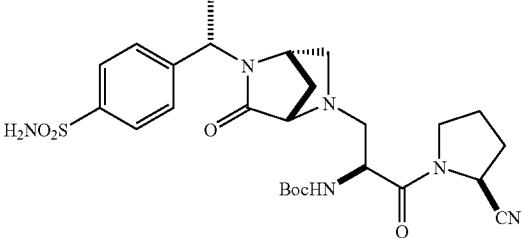
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Prep Example	Amide	Amines	Title compound
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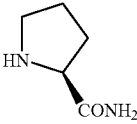
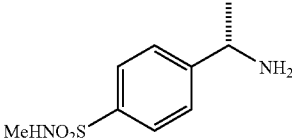
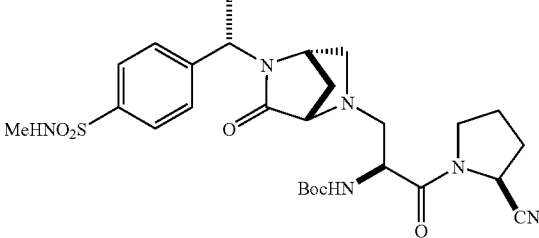
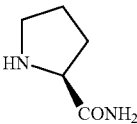
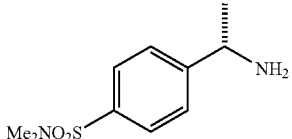
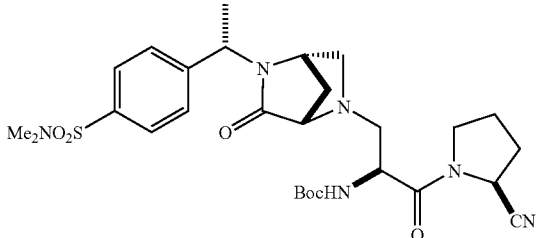
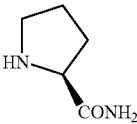
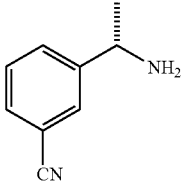
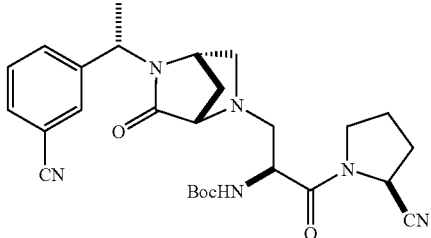
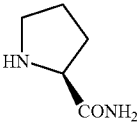
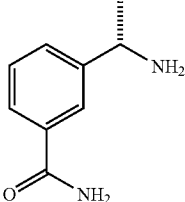
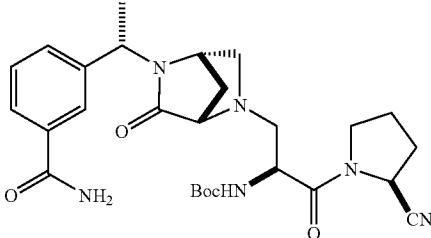
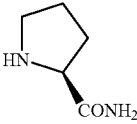
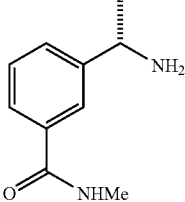
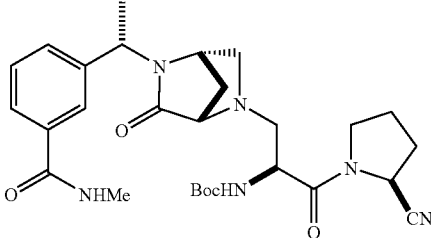
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Prep Example	Amide	Amines	Title compound
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1038			
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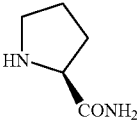
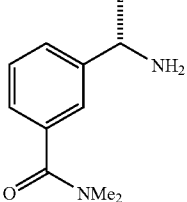
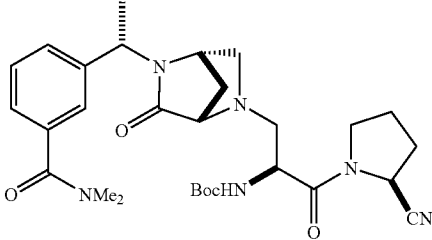
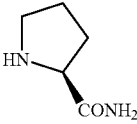
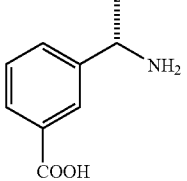
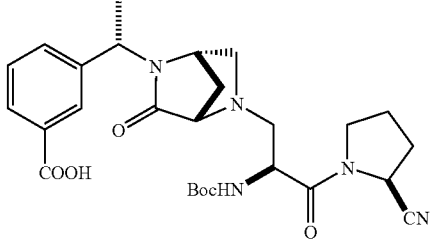
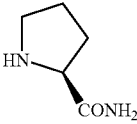
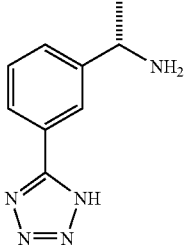
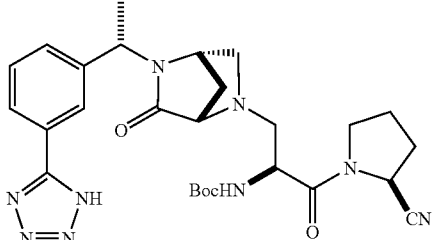
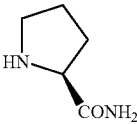
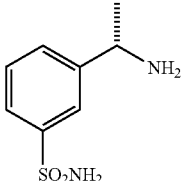
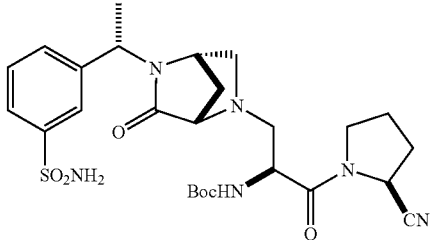
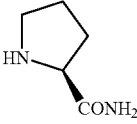
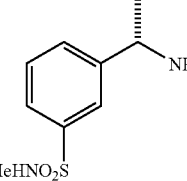
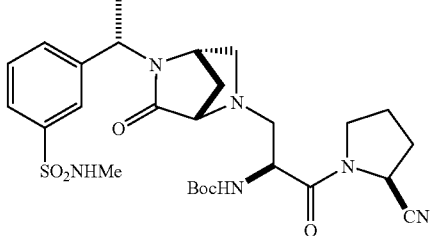
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Prep Example	Amide	Amines	Title compound
1041			
1042			
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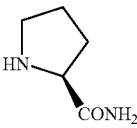
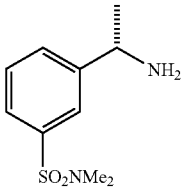
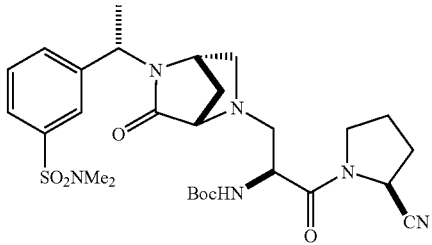
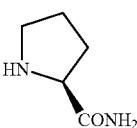
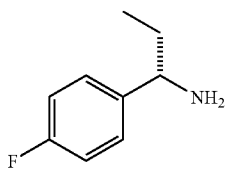
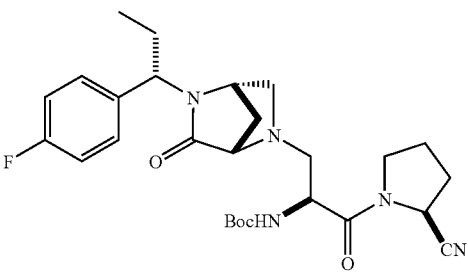
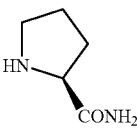
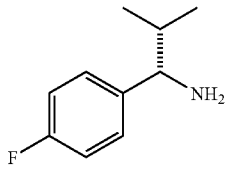
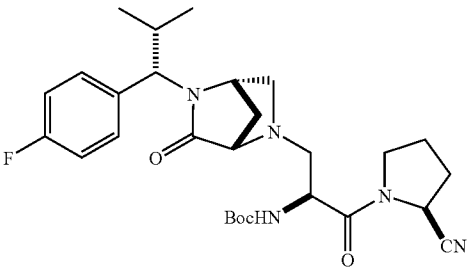
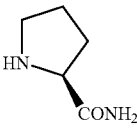
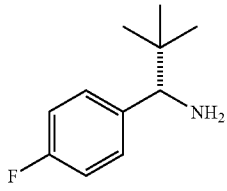
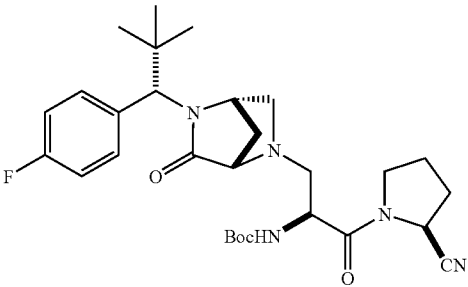
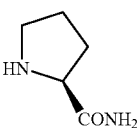
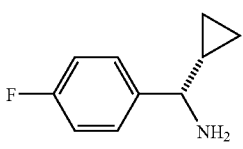
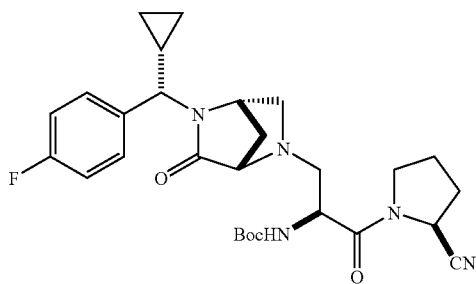
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Prep Example	Amide	Amines	Title compound
1046			
1047			
1048			
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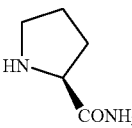
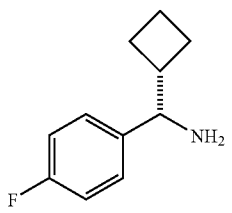
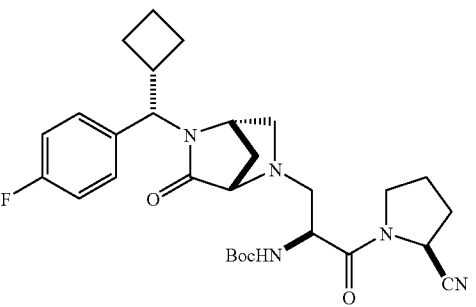
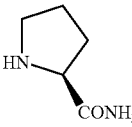
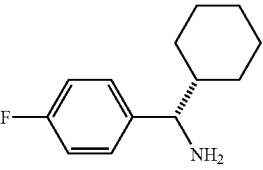
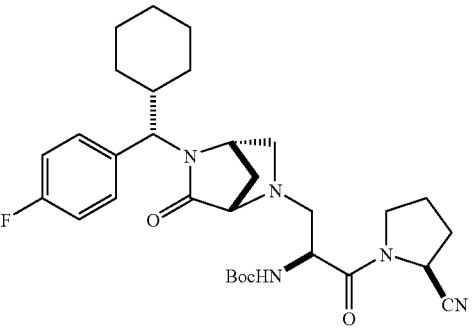
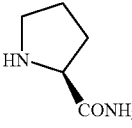
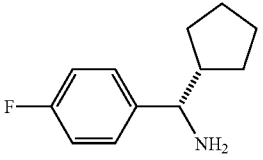
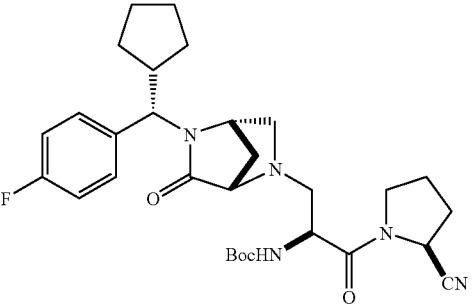
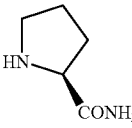
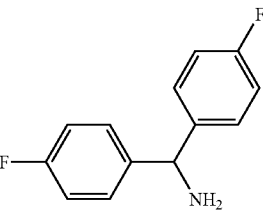
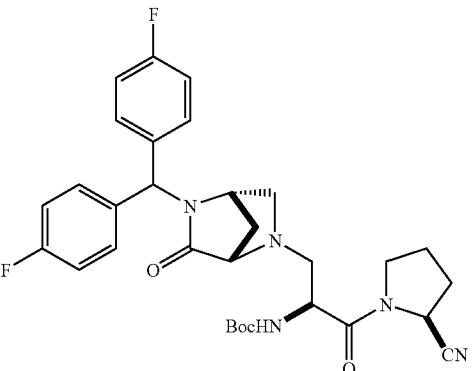
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Prep Example	Amide	Amines	Title compound
1051			
1052			
1053			
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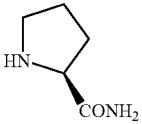
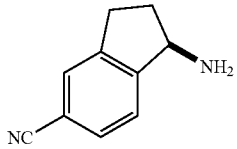
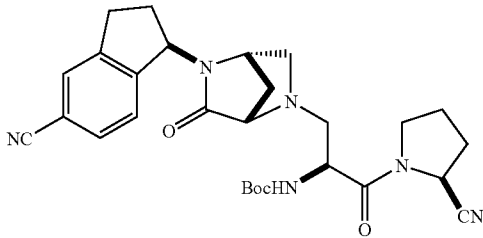
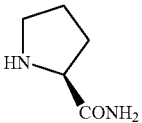
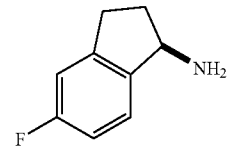
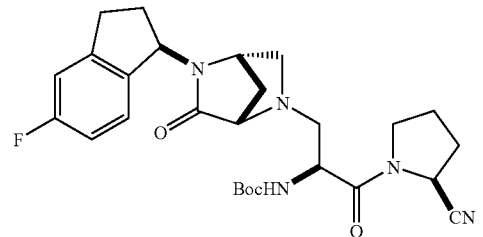
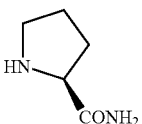
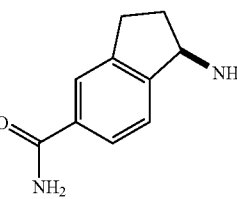
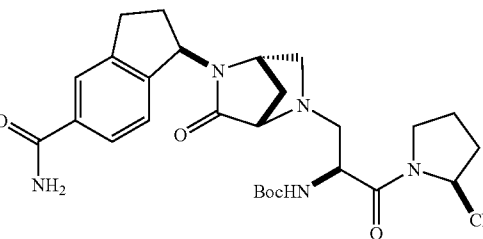
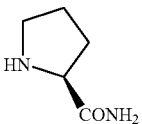
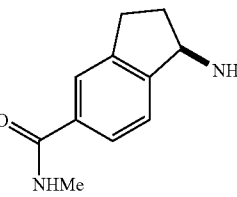
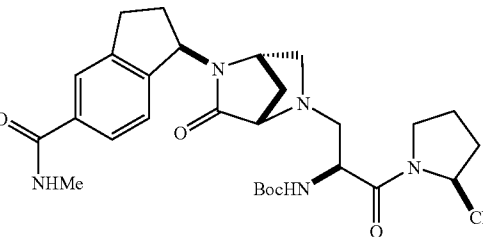
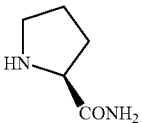
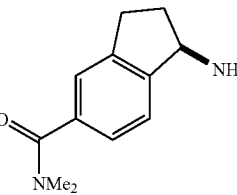
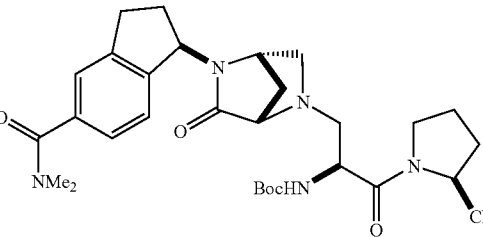
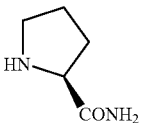
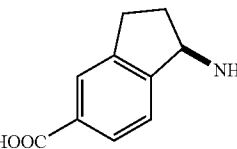
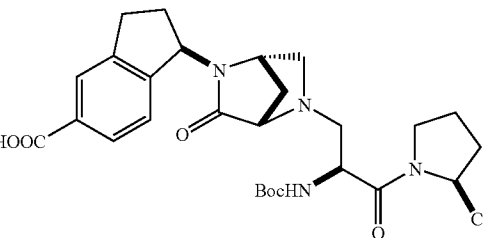
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Prep Example	Amide	Amines	Title compound
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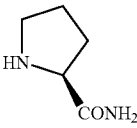
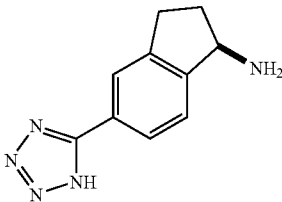
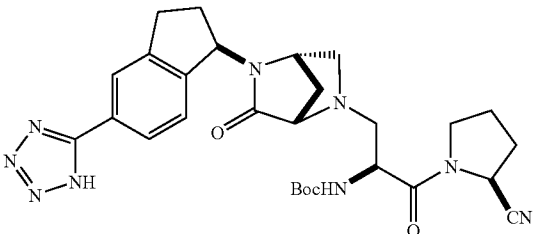
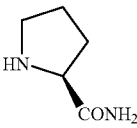
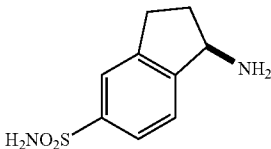
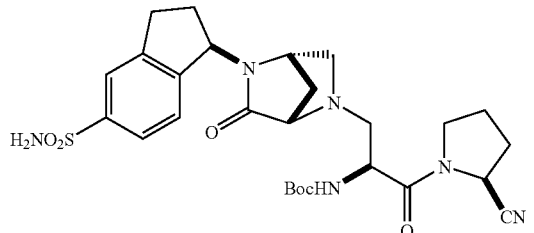
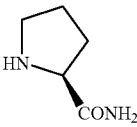
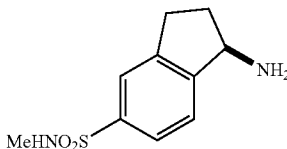
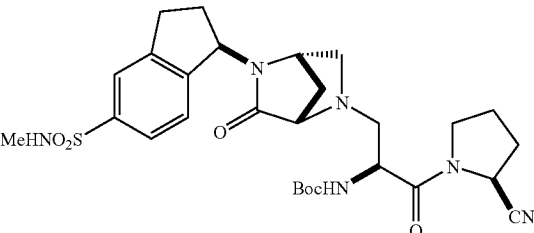
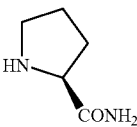
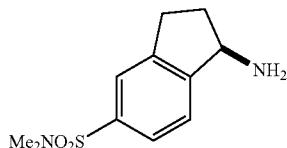
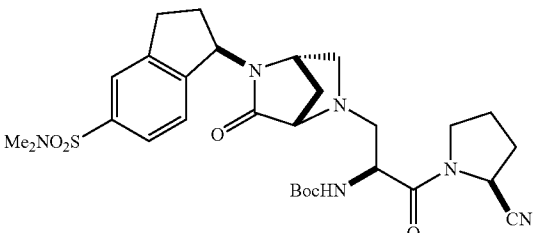
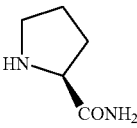
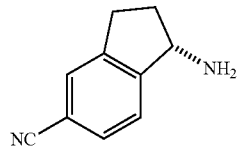
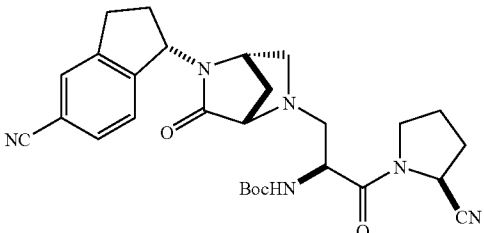
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Prep Example	Amide	Amines	Title compound
1061			
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Prep Example	Amide	Amines	Title compound
1065			
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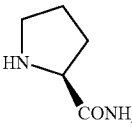
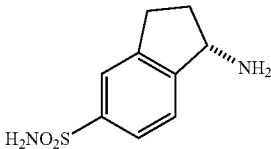
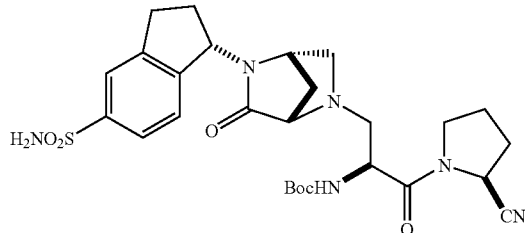
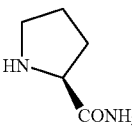
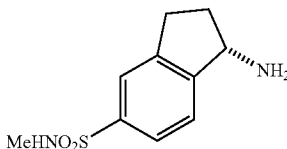
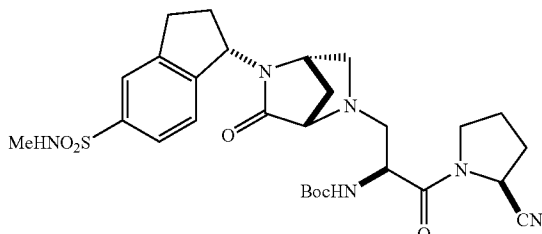
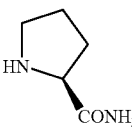
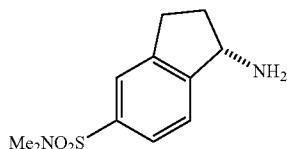
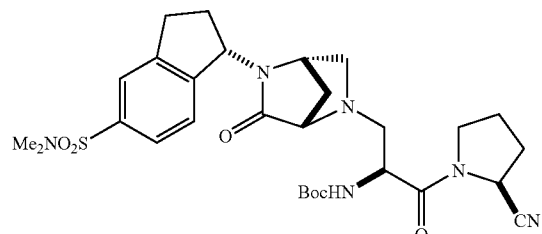
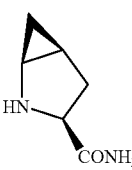
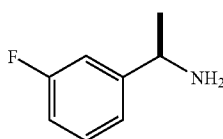
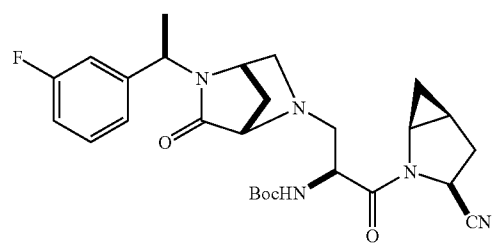
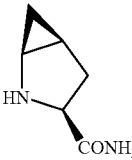
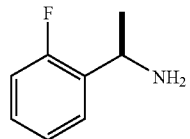
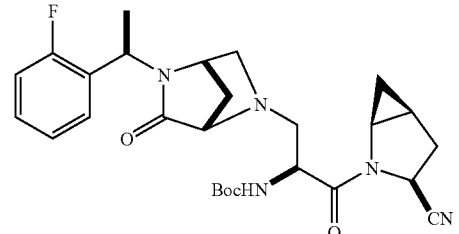
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Prep Example	Amide	Amines	Title compound
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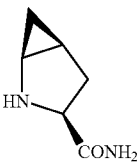
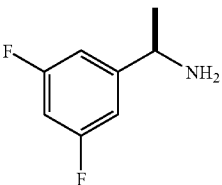
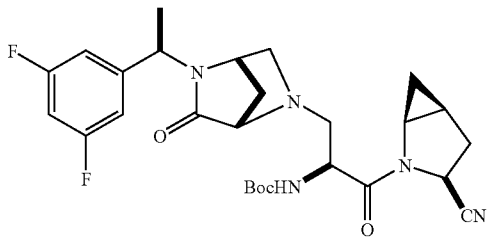
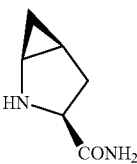
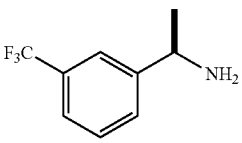
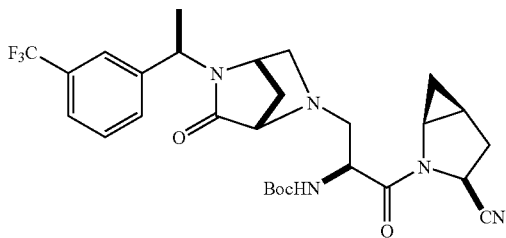
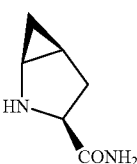
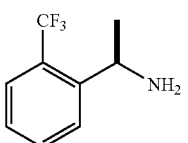
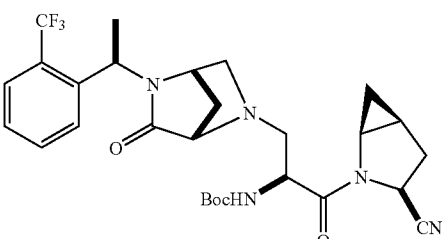
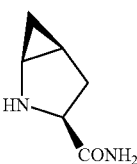
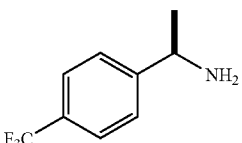
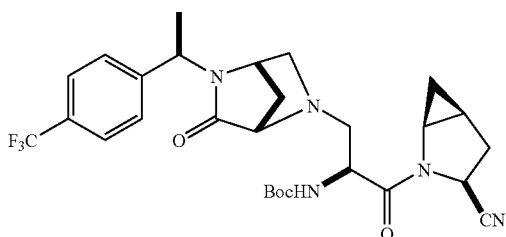
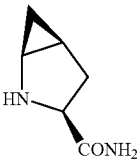
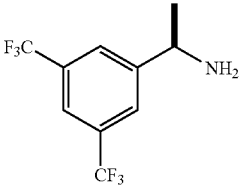
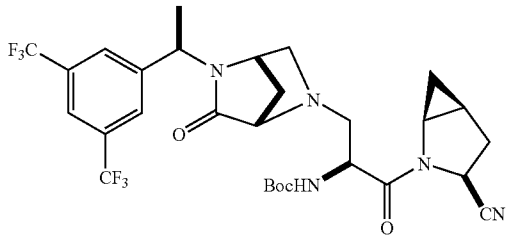
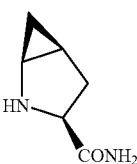
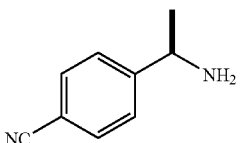
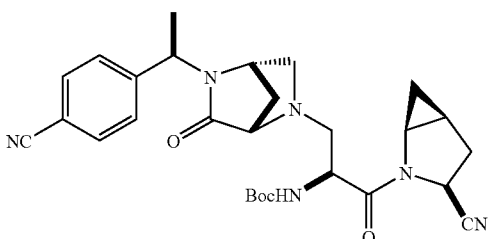
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Prep Example	Amide	Amines	Title compound
1076			
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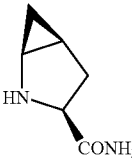
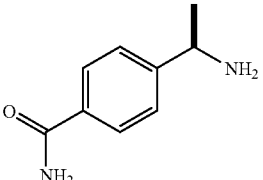
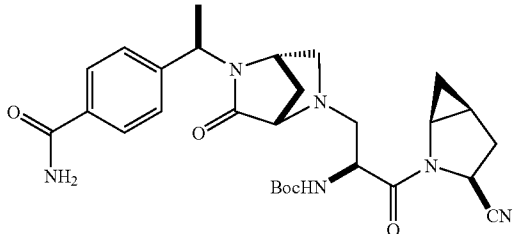
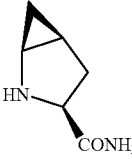
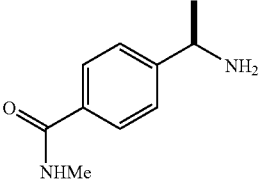
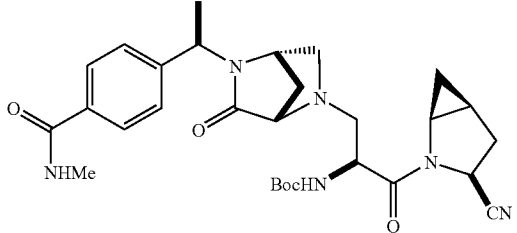
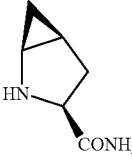
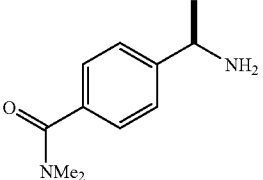
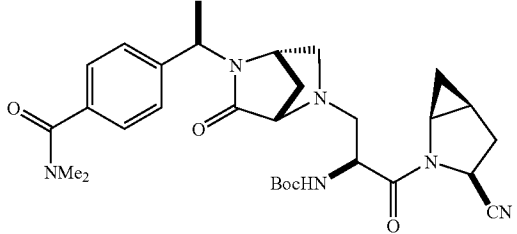
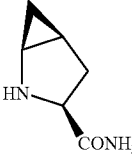
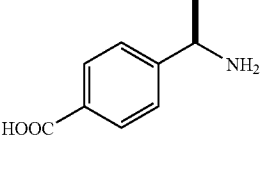
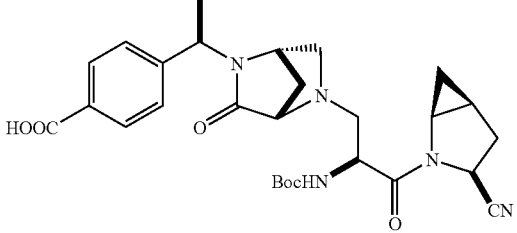
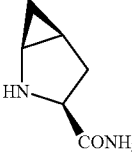
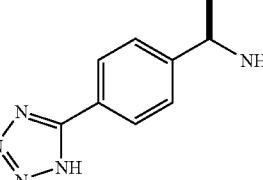
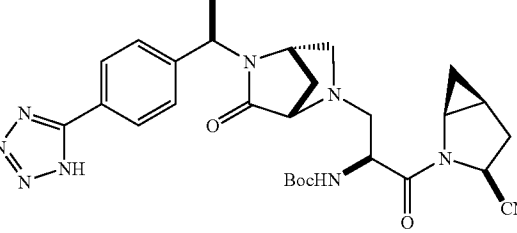
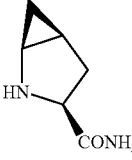
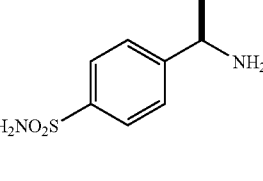
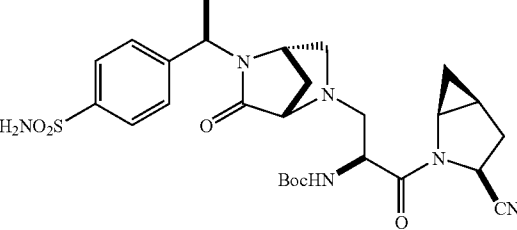
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Prep Example	Amide	Amines	Title compound
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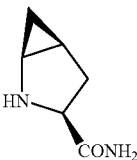
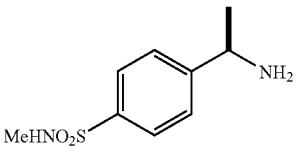
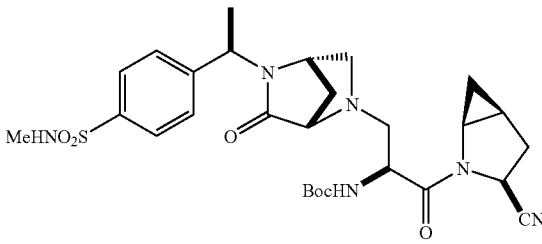
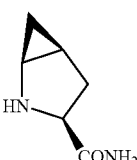
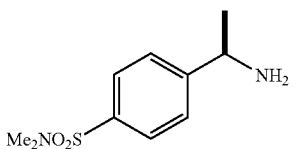
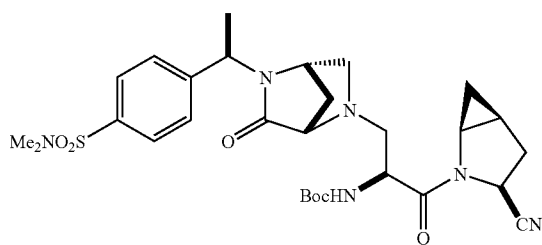
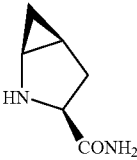
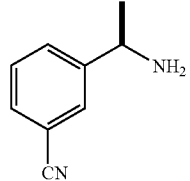
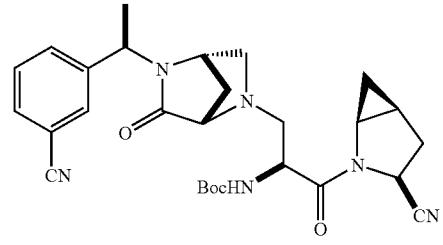
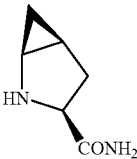
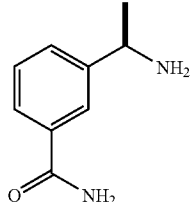
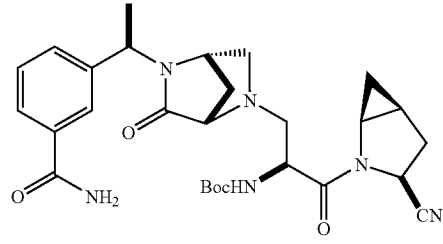
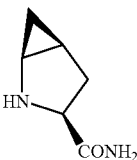
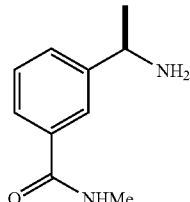
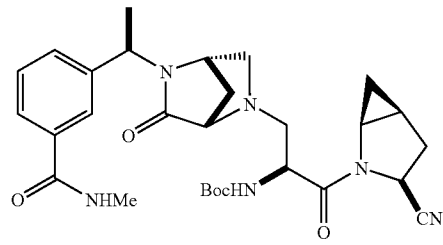
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Prep Example	Amide	Amines	Title compound
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1088			
1089			
1090			
1091			
1092			

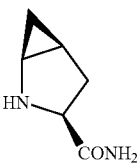
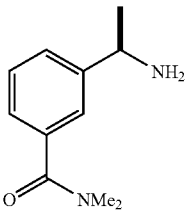
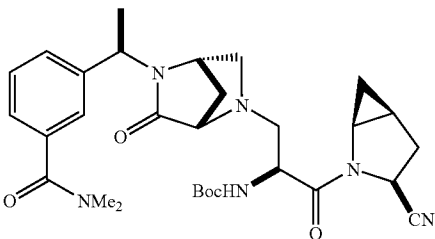
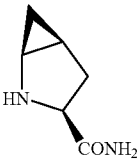
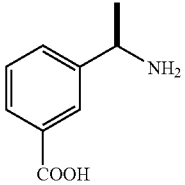
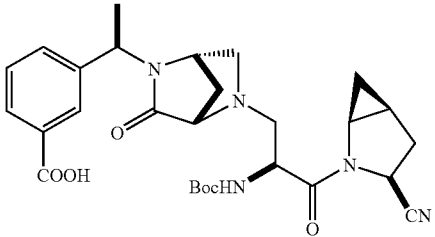
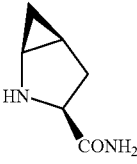
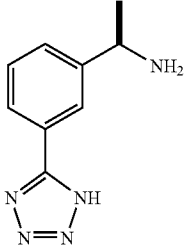
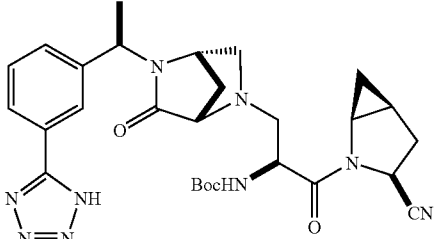
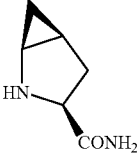
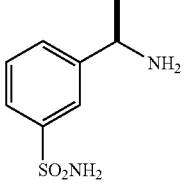
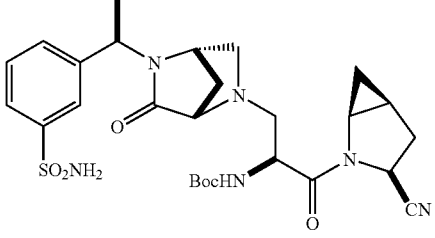
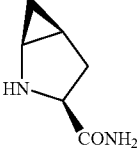
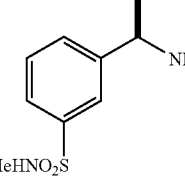
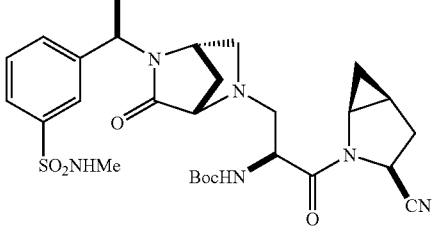
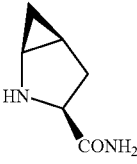
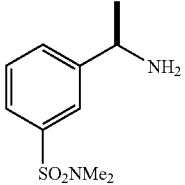
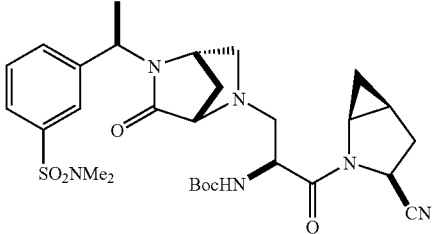
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Prep Example	Amide	Amines	Title compound
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1094			
1095			
1096			
1097			
1098			

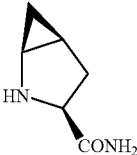
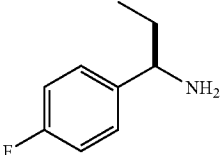
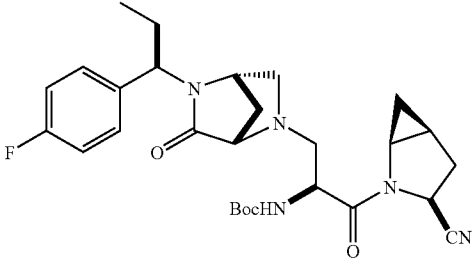
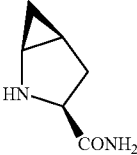
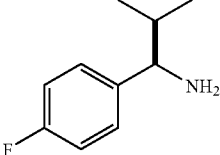
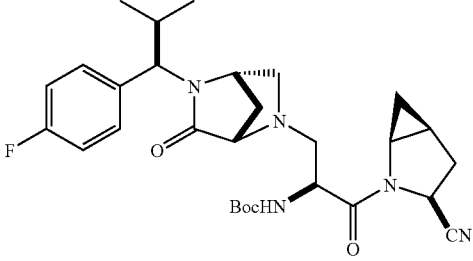
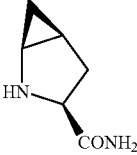
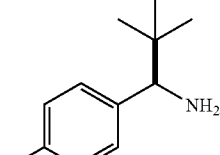
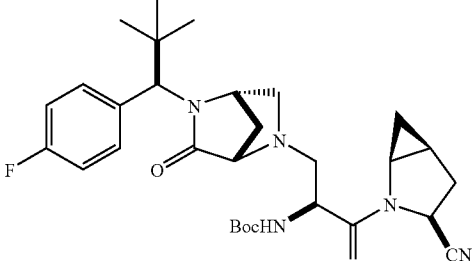
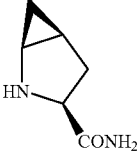
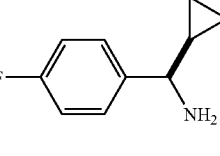
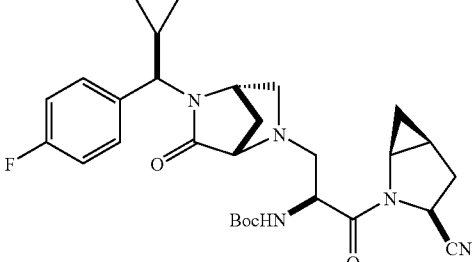
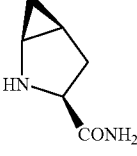
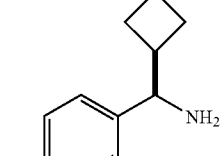
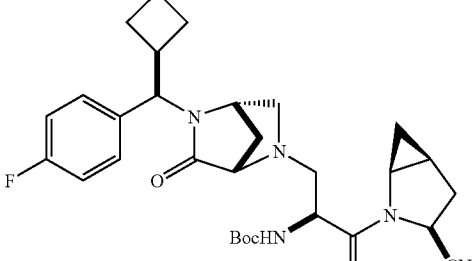
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Prep Example	Amide	Amines	Title compound
1099			
1100			
1101			
1102			
1103			

-continued

Prep Example	Amide	Amines	Title compound
1104			
1105			
1106			
1107			
1108			
1109			

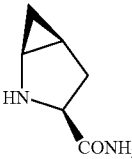
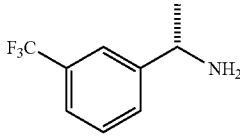
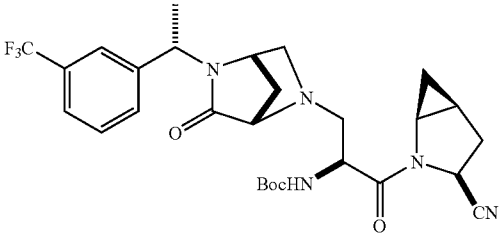
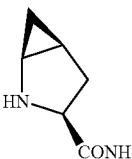
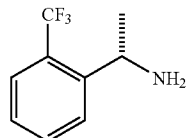
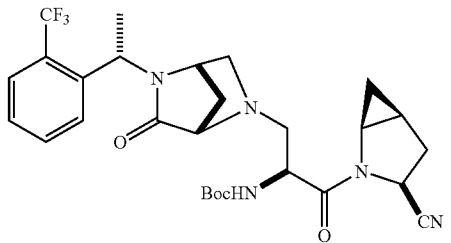
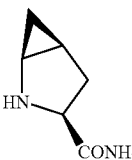
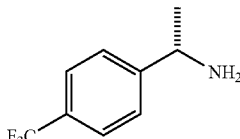
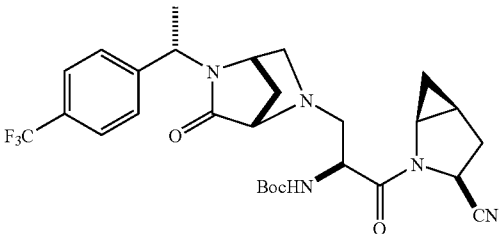
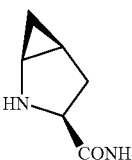
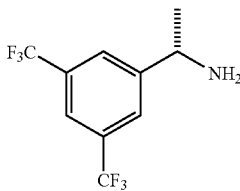
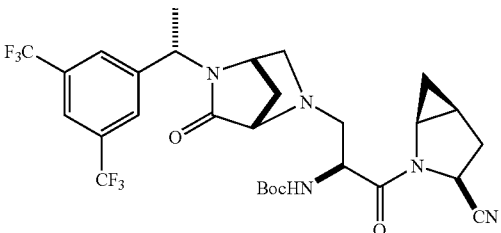
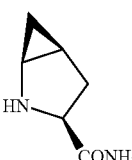
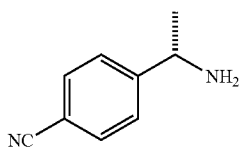
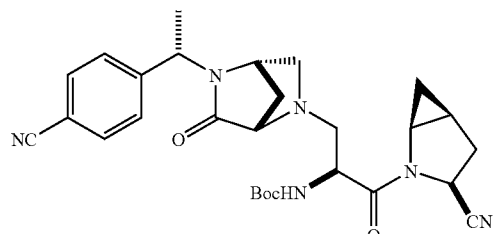
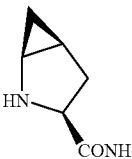
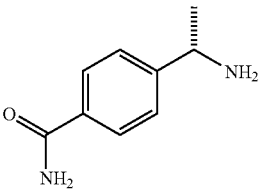
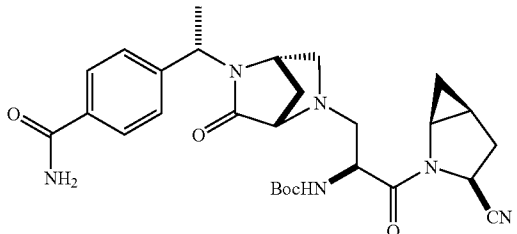
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Prep Example	Amide	Amines	Title compound
1110			
1111			
1112			
1113			
1114			

-continued

Prep Example	Amide	Amines	Title compound
1115			
1116			
1117			
1118			
1119			

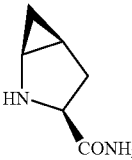
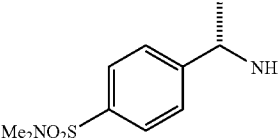
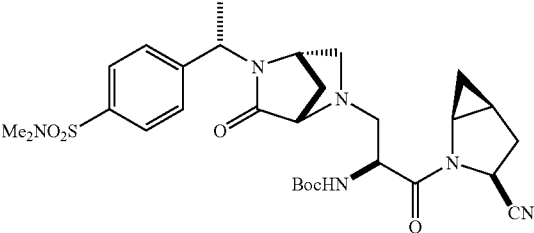
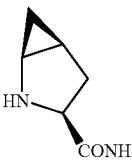
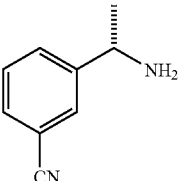
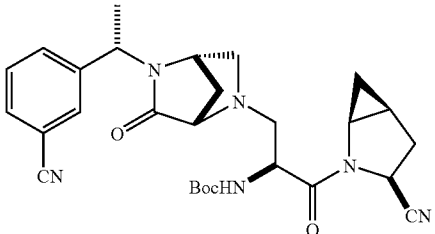
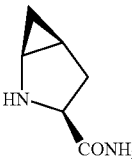
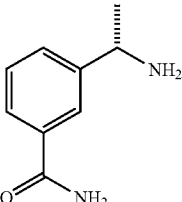
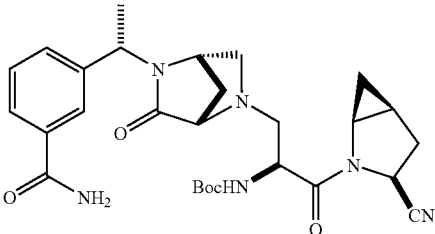
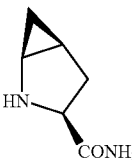
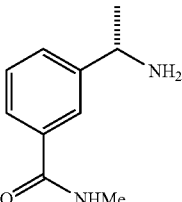
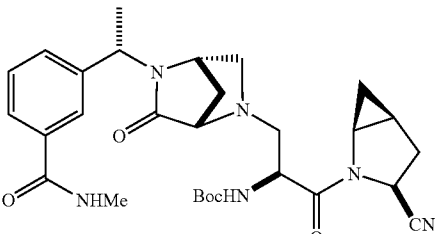
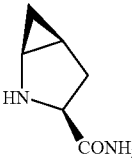
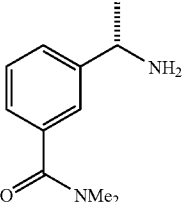
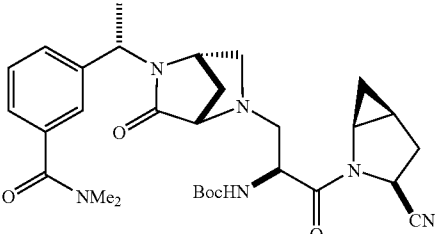
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Prep Example	Amide	Amines	Title compound
1120			
1121			
1122			
1123			
1124			
1125			

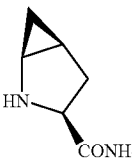
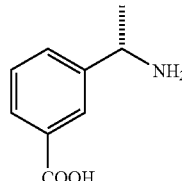
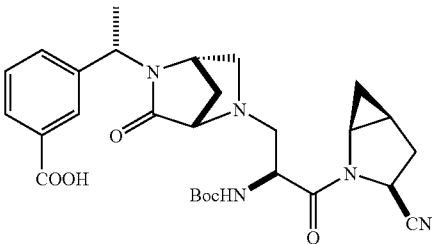
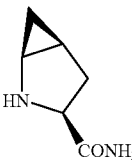
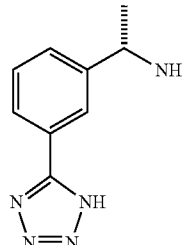
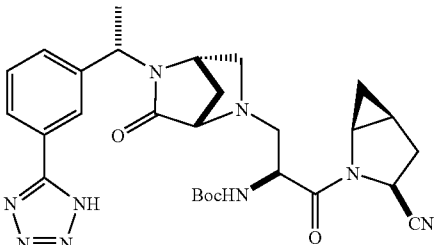
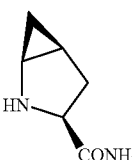
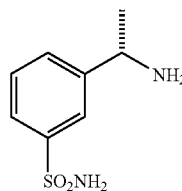
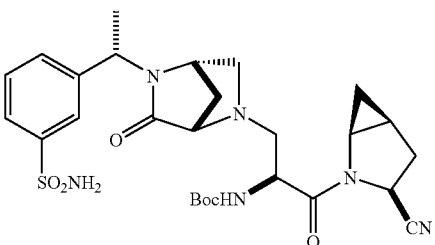
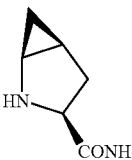
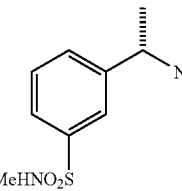
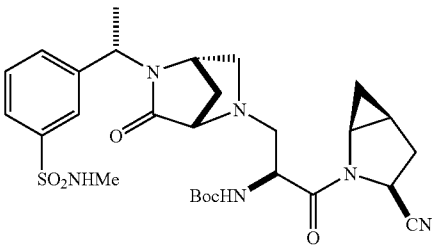
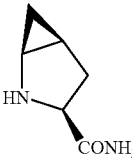
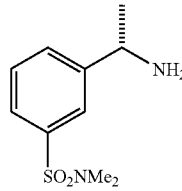
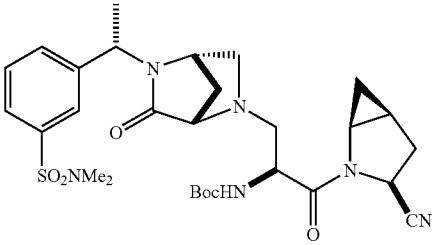
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Prep Example	Amide	Amines	Title compound
1126			
1127			
1128			
1129			
1130			
1131			

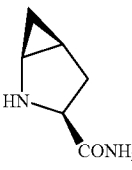
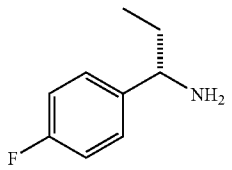
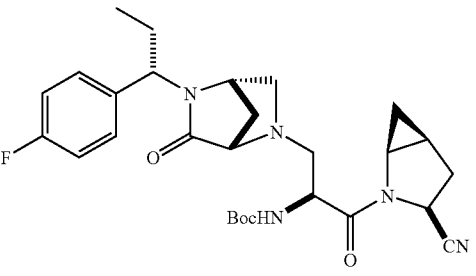
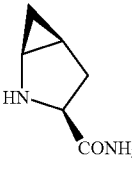
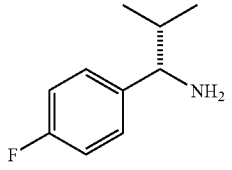
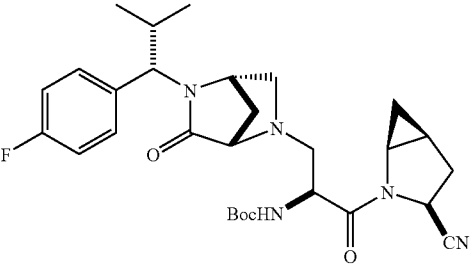
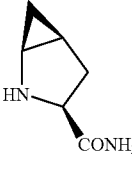
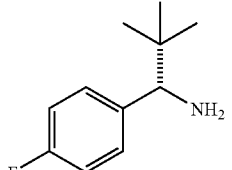
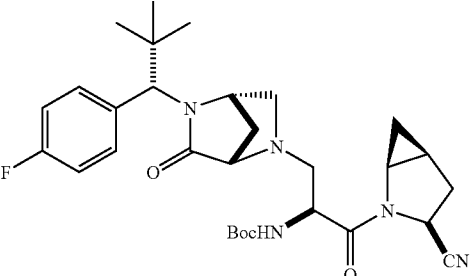
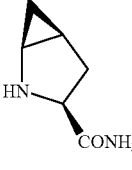
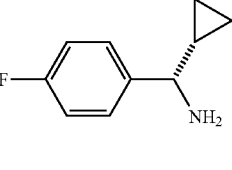
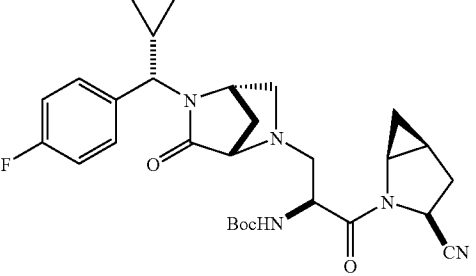
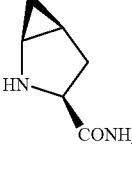
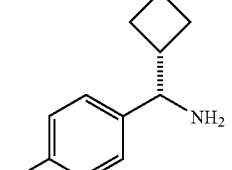
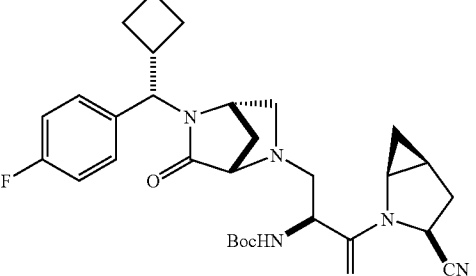
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Prep Example	Amide	Amines	Title compound
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1133			
1134			
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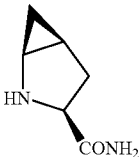
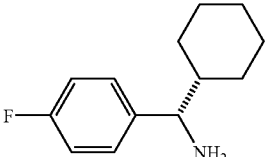
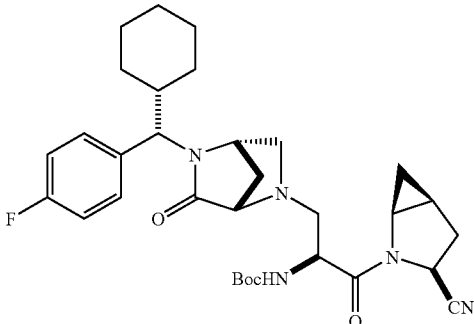
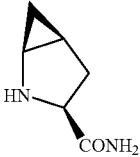
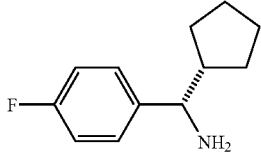
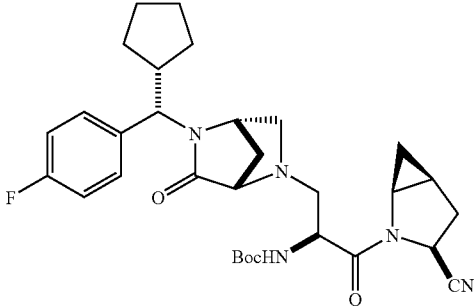
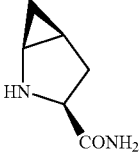
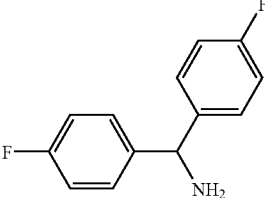
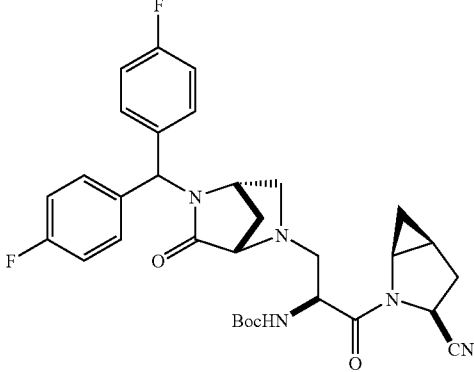
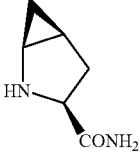
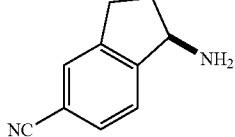
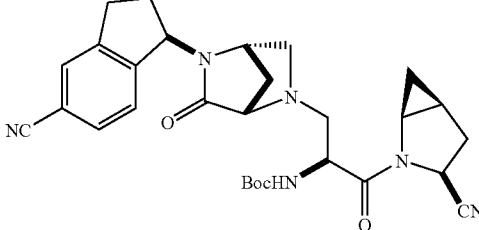
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Prep Example	Amide	Amines	Title compound
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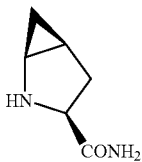
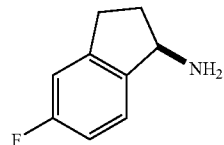
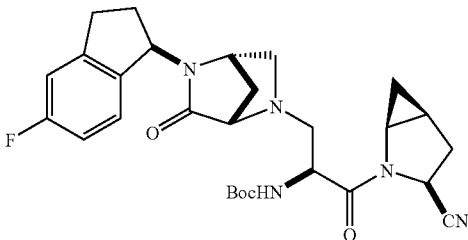
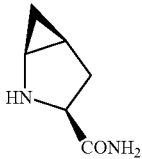
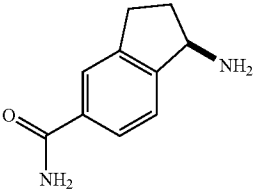
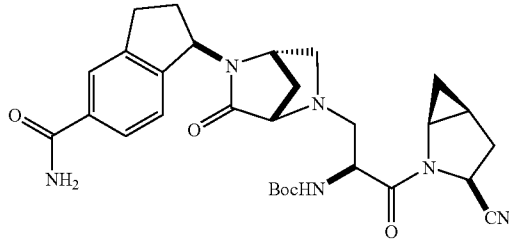
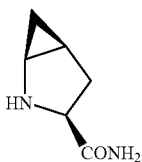
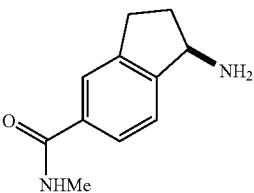
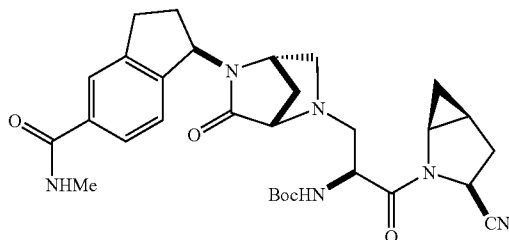
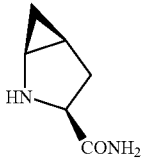
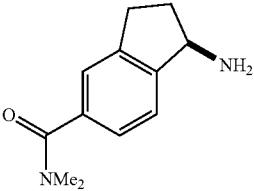
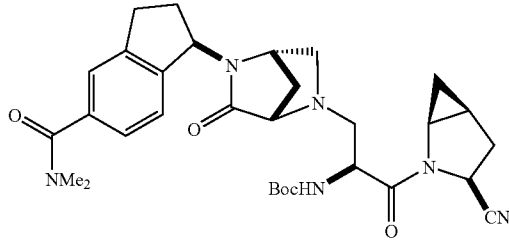
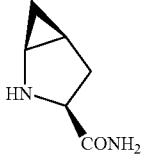
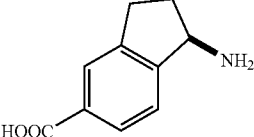
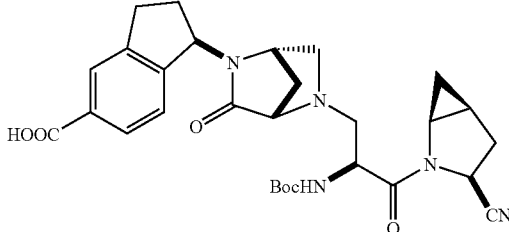
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Prep Example	Amide	Amines	Title compound
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1143			
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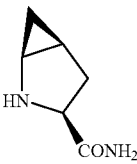
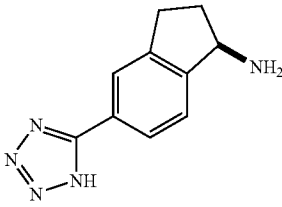
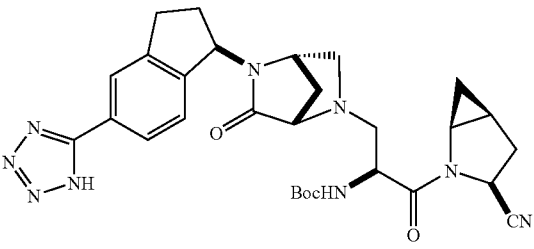
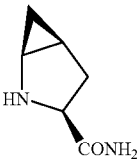
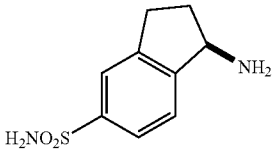
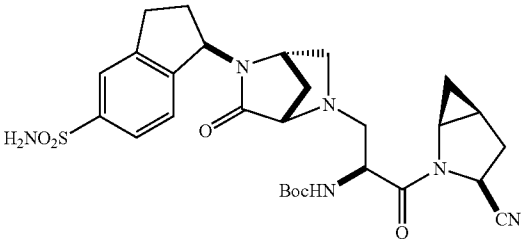
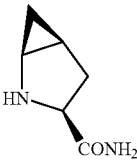
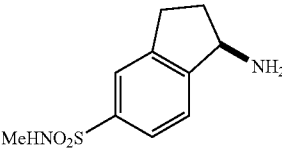
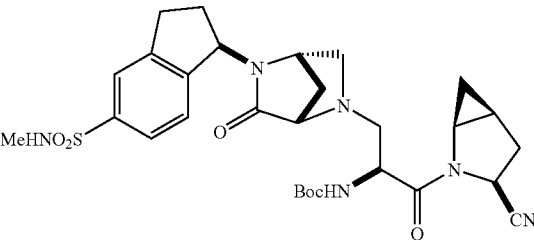
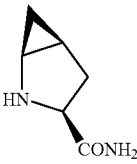
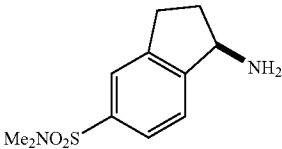
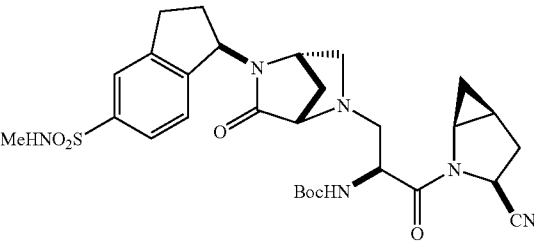
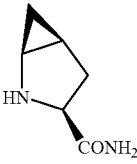
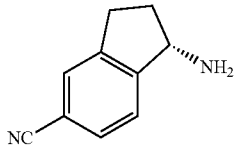
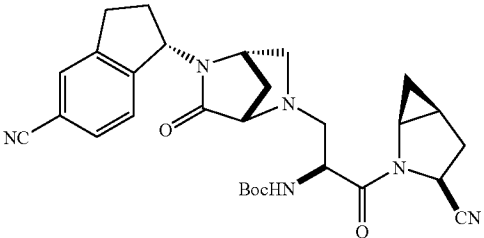
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Prep Example	Amide	Amines	Title compound
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1148			
1149			
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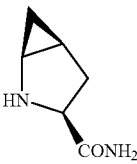
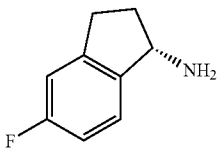
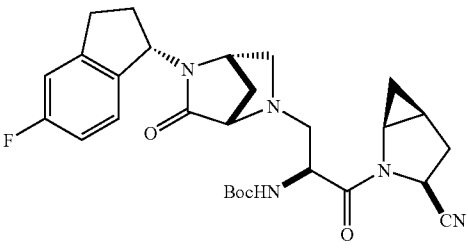
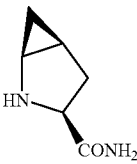
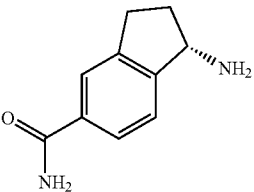
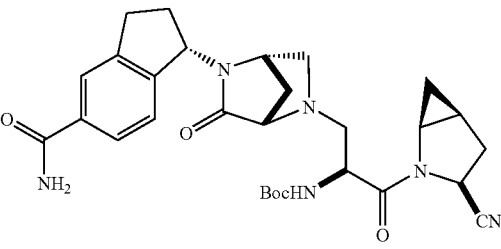
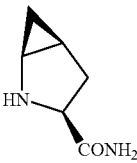
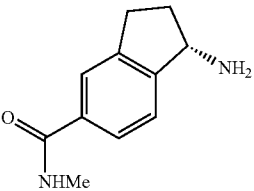
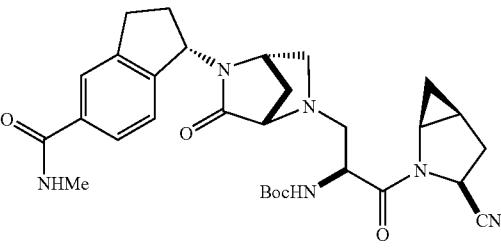
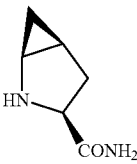
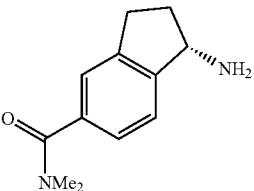
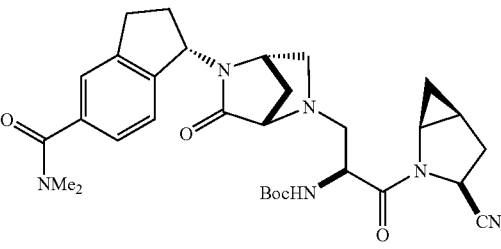
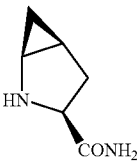
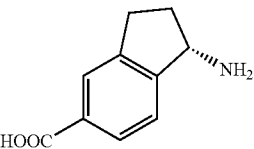
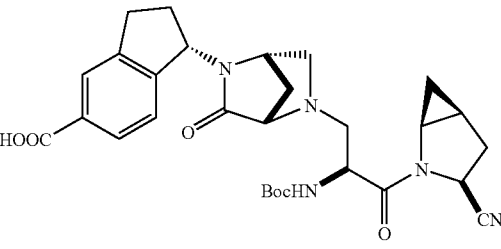
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Prep Example	Amide	Amines	Title compound
1151			
1152			
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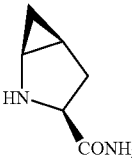
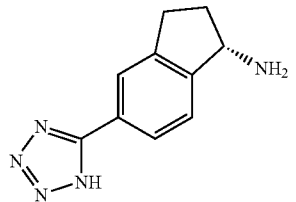
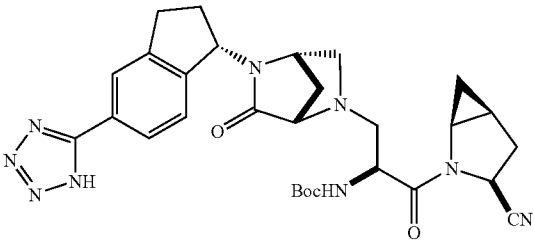
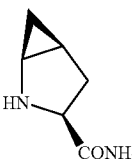
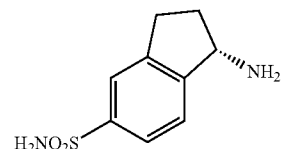
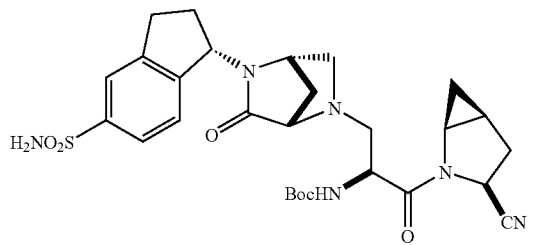
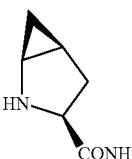
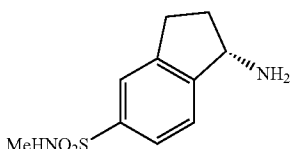
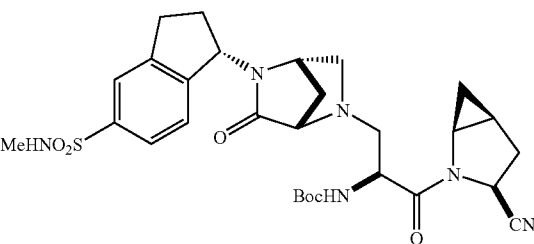
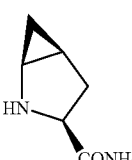
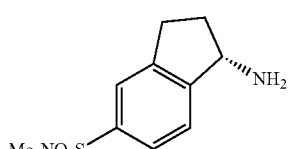
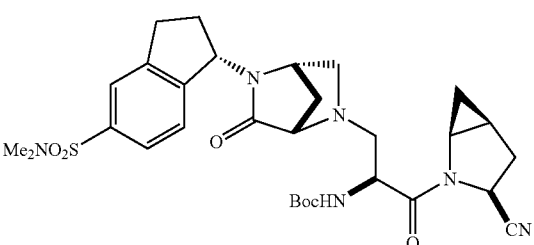
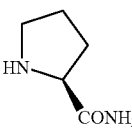
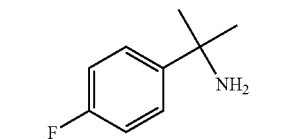
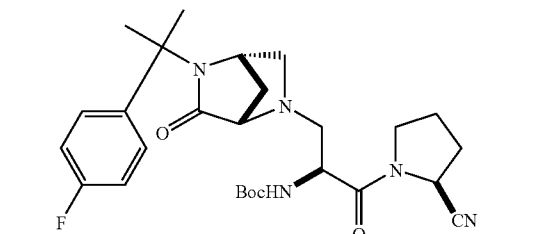
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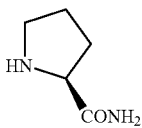
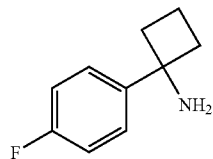
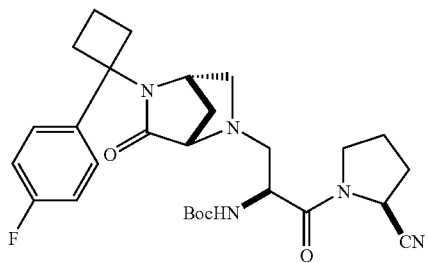
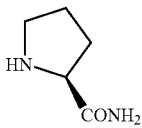
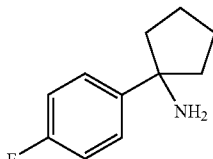
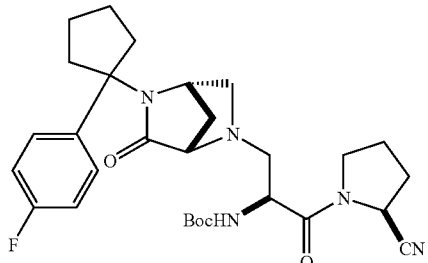
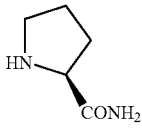
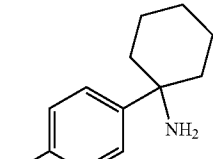
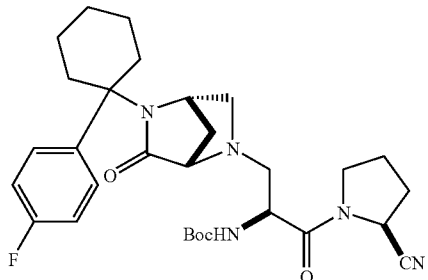
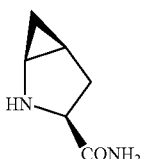
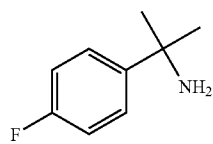
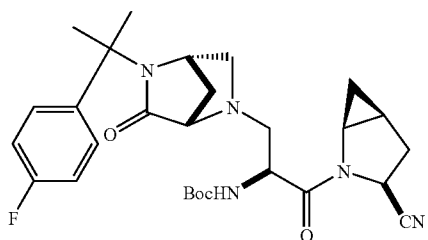
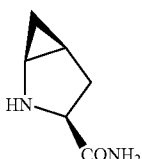
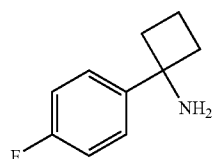
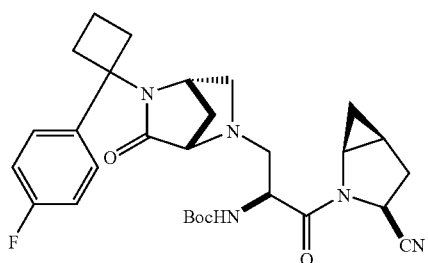
Prep Example	Amide	Amines	Title compound
1156			
1157			
1158			
1159			
1160			

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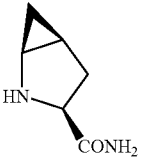
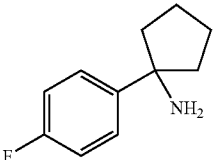
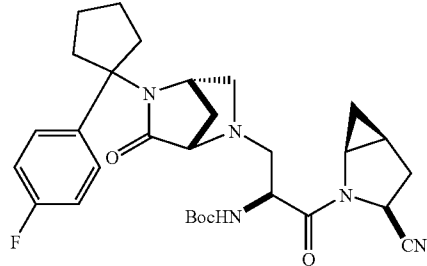
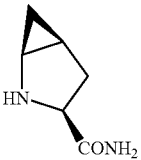
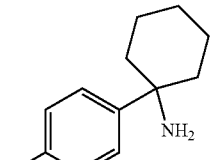
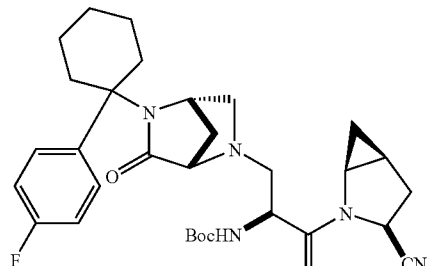
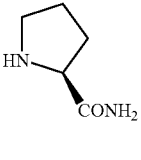
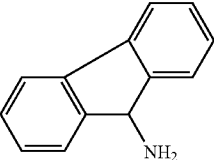
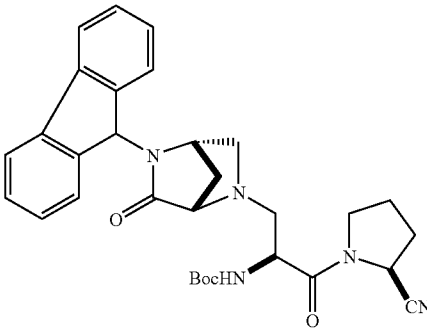
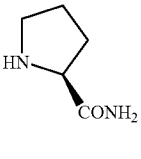
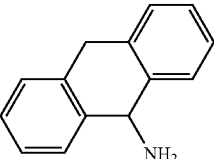
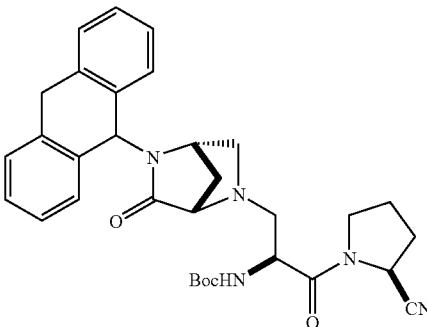
Prep Example	Amide	Amines	Title compound
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1162			
1163			
1164			
1165			

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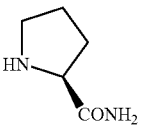
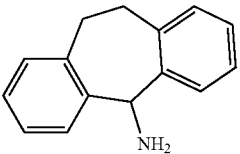
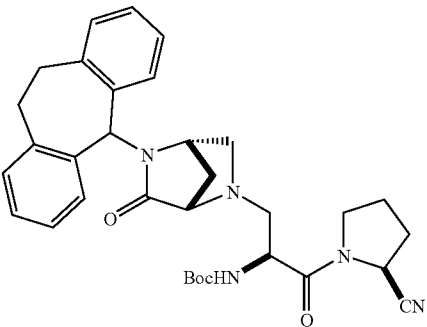
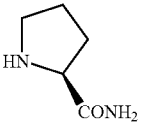
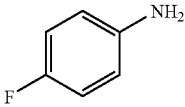
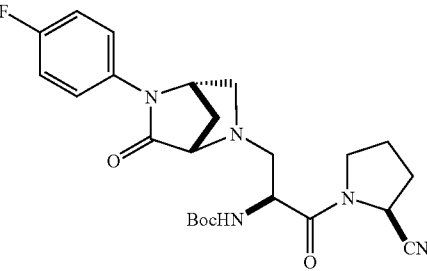
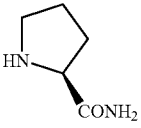
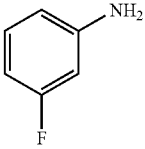
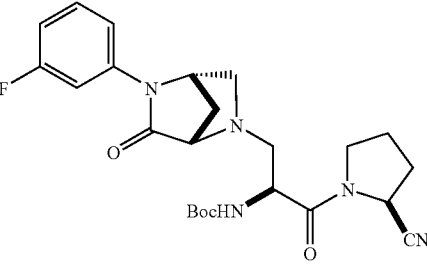
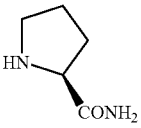
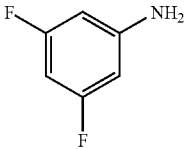
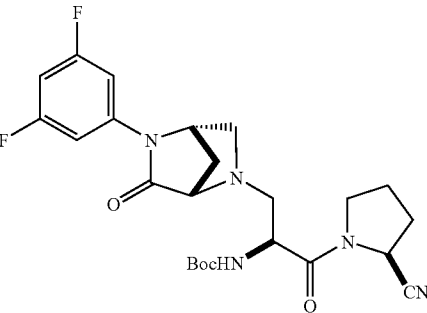
Prep Example	Amide	Amines	Title compound
1166			
1167			
1168			
1169			
1170			

Prep Example	Amide	Amines	Title compound
1171			
1172			
1173			
1174			
1175			

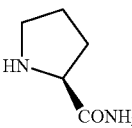
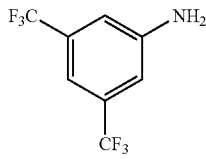
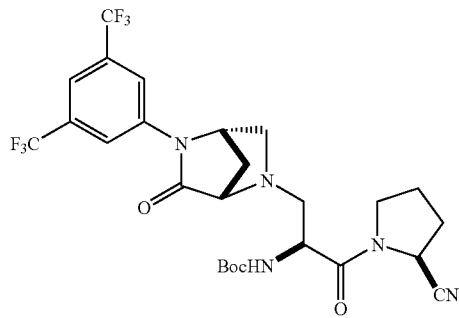
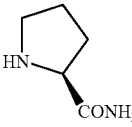
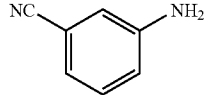
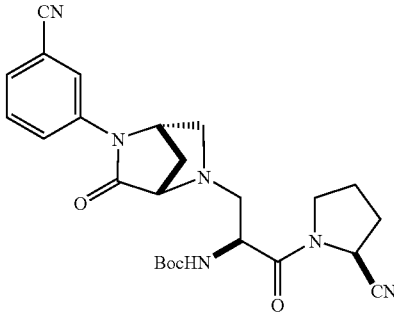
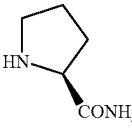
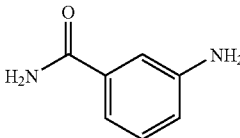
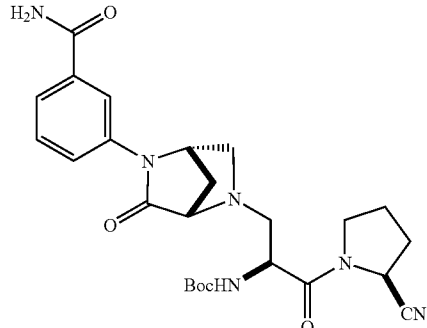
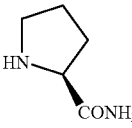
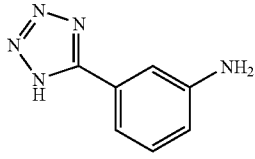
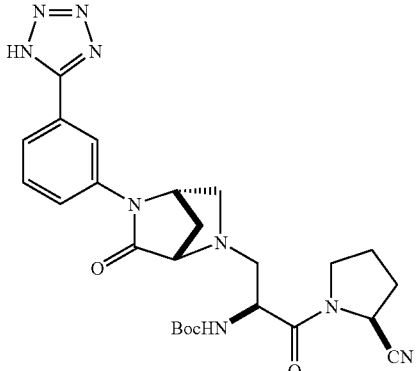
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Prep Example	Amide	Amines	Title compound
1176			
1177			
1178			
1179			

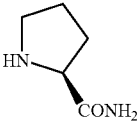
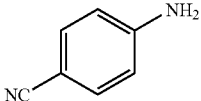
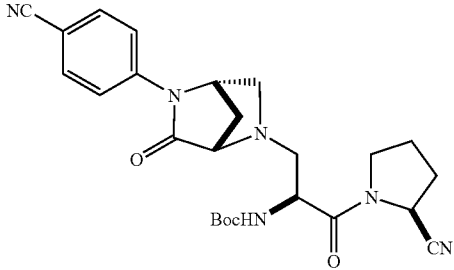
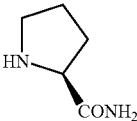
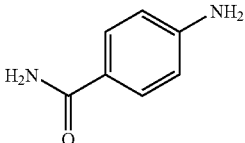
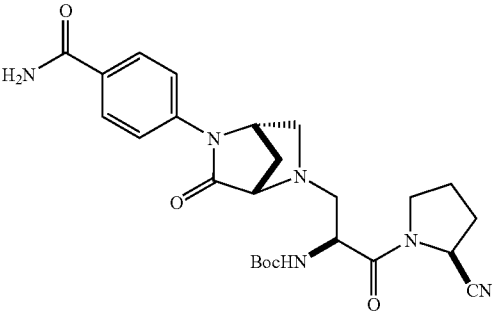
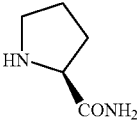
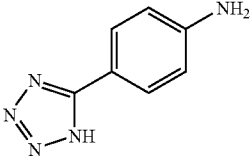
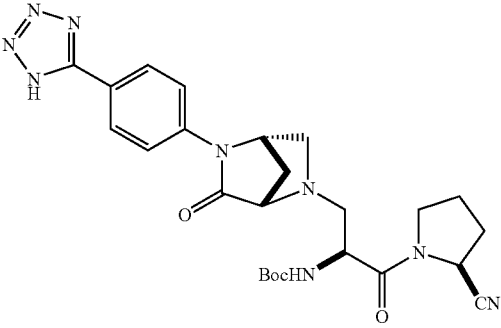
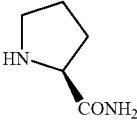
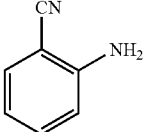
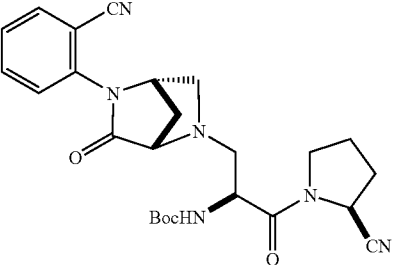
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Prep Example	Amide	Amines	Title compound
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1181			
1182			
1183			

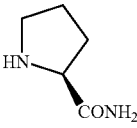
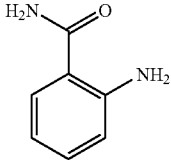
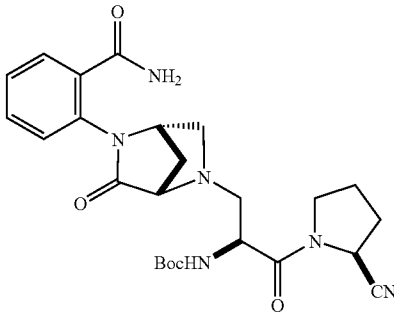
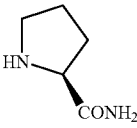
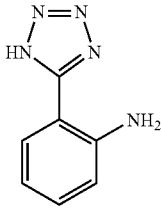
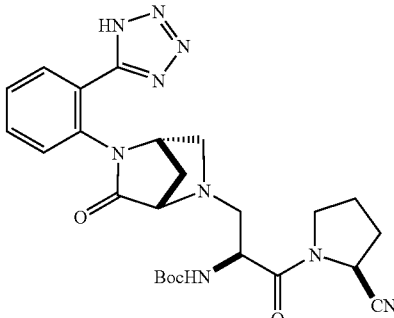
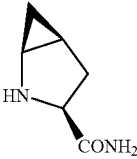
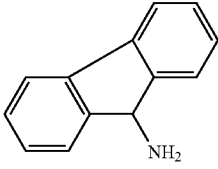
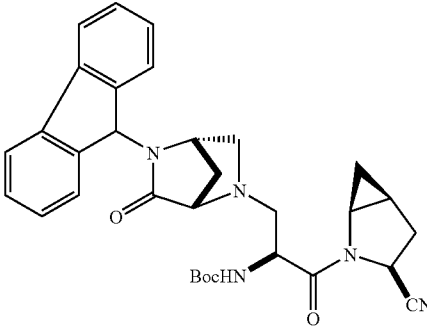
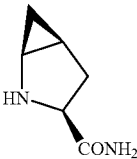
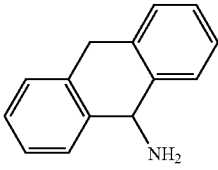
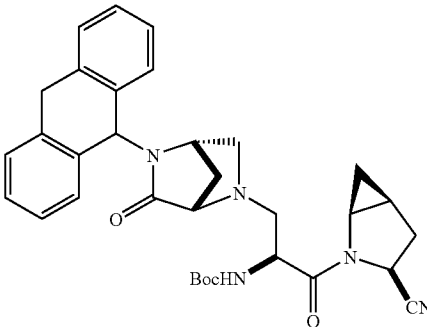
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Prep Example	Amide	Amines	Title compound
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1185			
1186			
1187			

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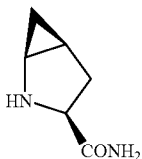
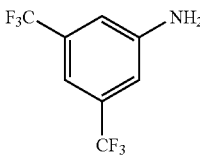
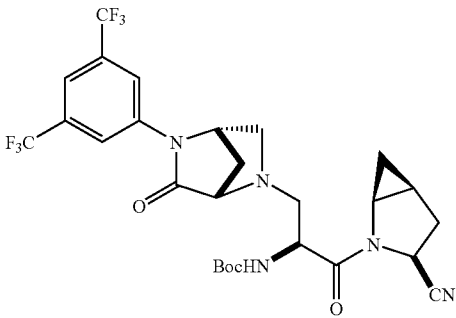
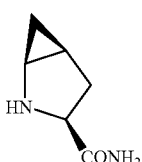
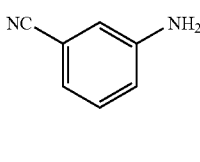
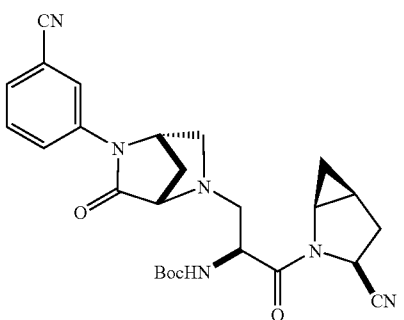
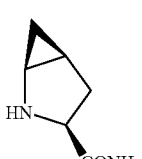
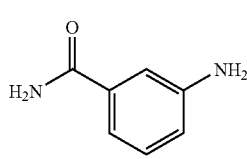
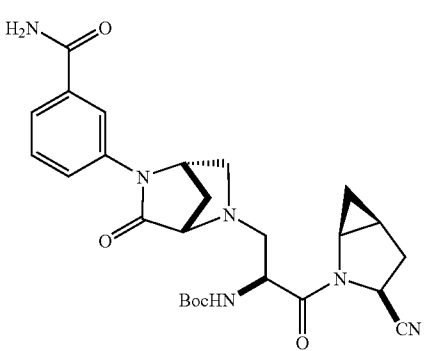
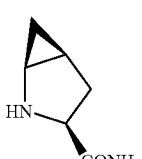
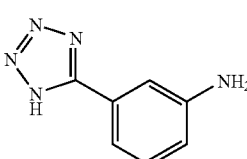
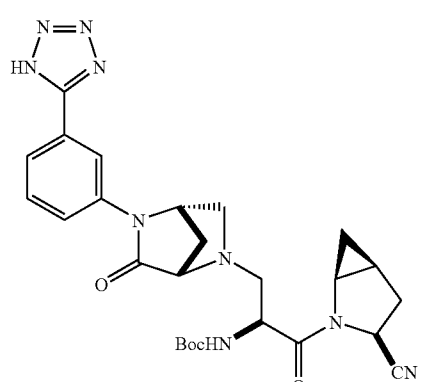
Prep Example	Amide	Amines	Title compound
1188			
1189			
1190			
1191			

-continued

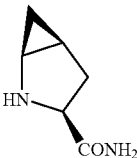
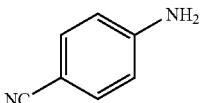
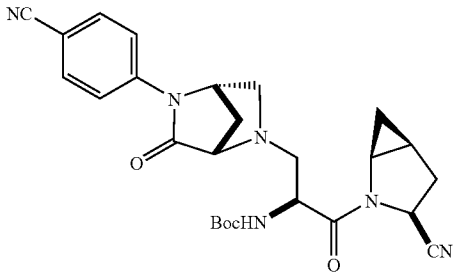
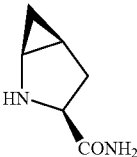
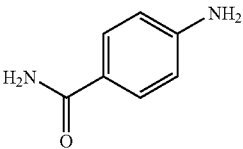
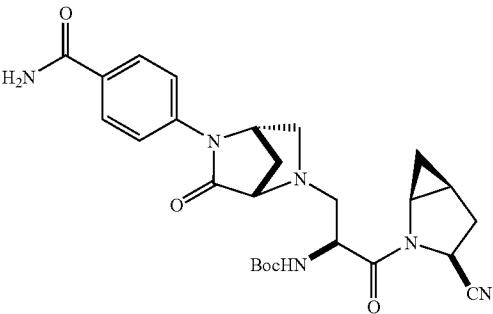
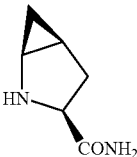
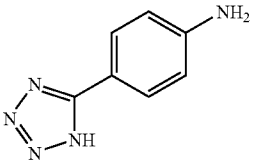
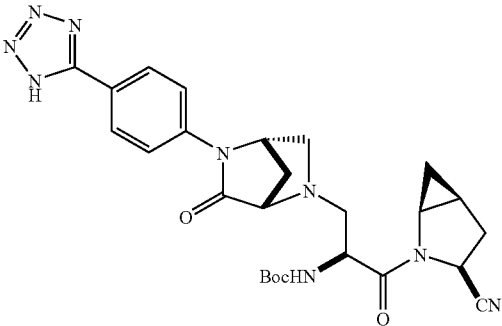
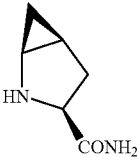
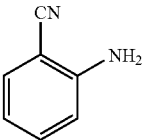
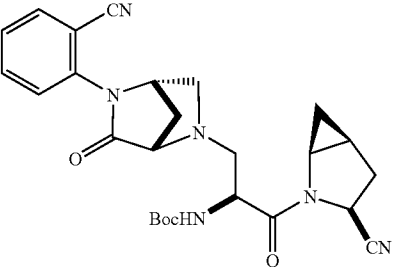
Prep Example	Amide	Amines	Title compound
1192			
1193			
1194			
1195			

-continued

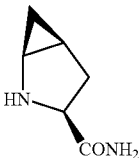
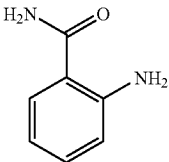
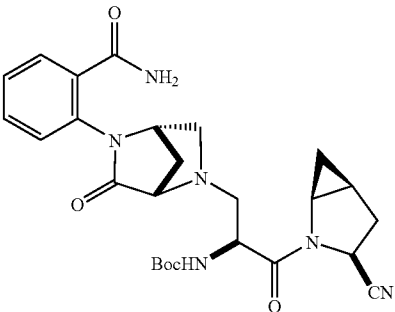
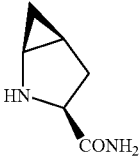
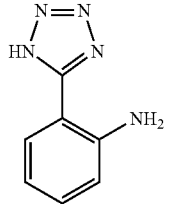
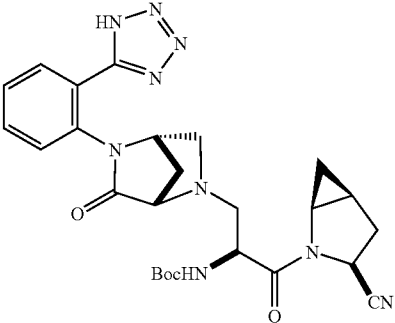
Prep Example	Amide	Amines	Title compound
1196			
1197			
1198			
1199			

Prep Example	Amide	Amines	Title compound
1200			
1201			
1202			
1203			

-continued

Prep Example	Amide	Amines	Title compound
1204			
1205			
1206			
1207			

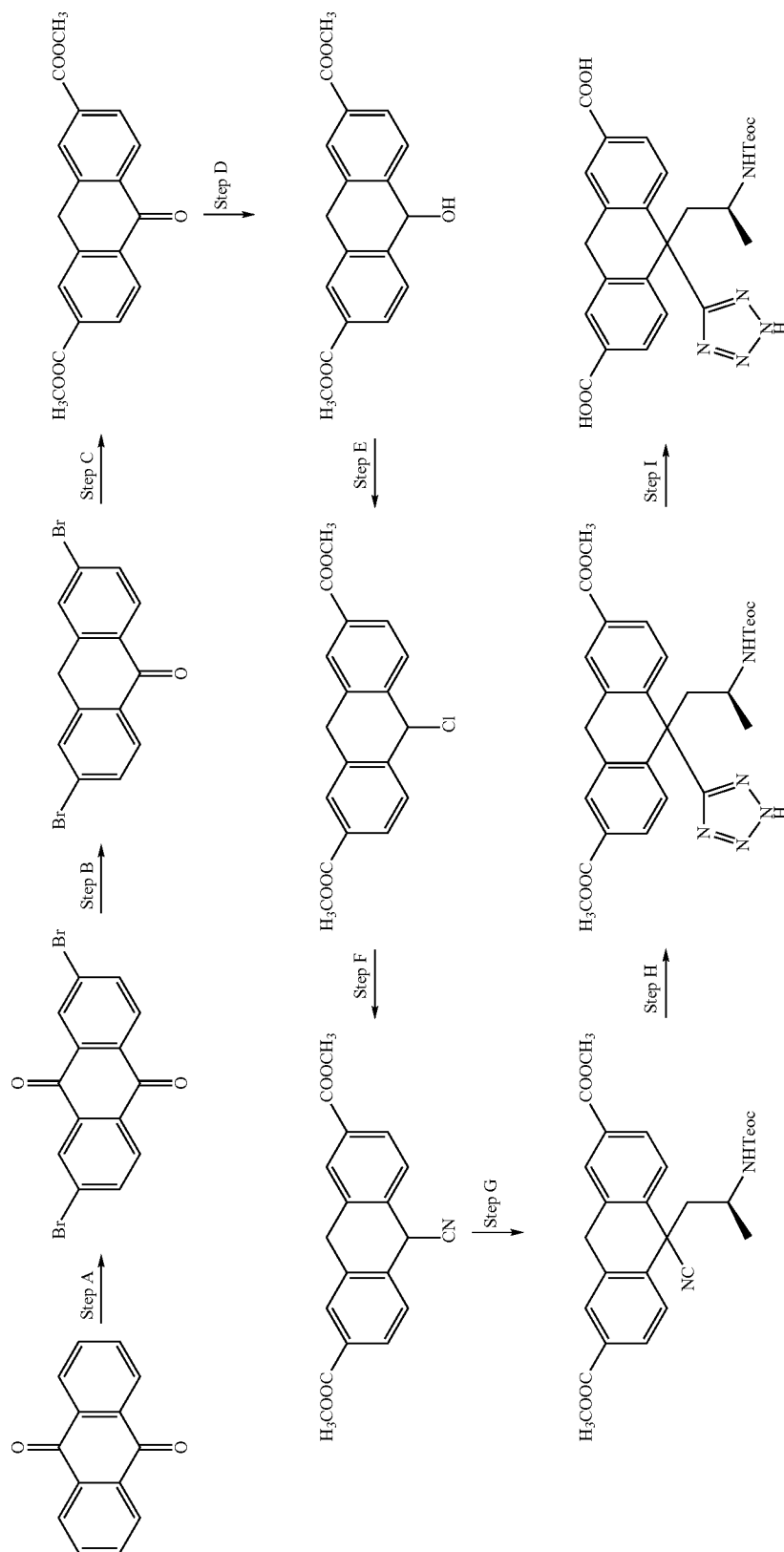
-continued

Prep Example	Amide	Amines	Title compound
1208			
1209			

[0709] Examples 1210-1299 have been intentionally excluded.

Preparative Example 1300

[0710]



Step A

[0711] If one were to treat commercially available anthraquinone with 1.5-2 equivalents of bromine and some iodine at 160° C., and then treat the mixture with aqueous sodium hydroxide at reflux, one would obtain the title compound, after crystallisation from glacial acetic acid.

Step B

[0712] If one were to treat the title compound from Step A above with hot concentrated H₂SO₄, treat the obtained solution with Al powder at rt and stir the mixture at rt for 3 h, one would obtain the title compound, after aqueous workup and chromatography on silica gel.

Step C

[0713] If one were to treat the title compound from Step B above as described in Preparative Example 59 Step D, Step E and Step F, one would obtain the title compound.

Step D

[0714] If one were to treat the title compound from Step C above as described in Preparative Example 59 Step G, one would obtain the title compound.

Step E

[0715] If one were to treat the title compound from Step D above as described in Preparative Example 59 Step H, one would obtain the title compound.

Step F

[0716] If one were to treat the title compound from Step E above as described in Preparative Example 59 Step I, one would obtain the title compound.

Step G

[0717] If one were to treat the title compound from Step F above as described in Preparative Example 61 Step A, one would obtain the title compound.

Step H

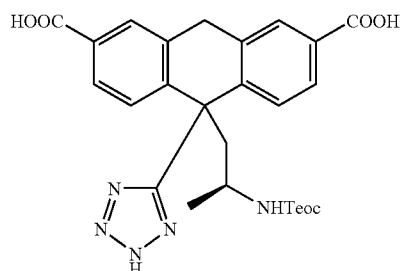
[0718] If one were to treat the title compound from Step G above as described in Preparative Example 61 Step B, one would obtain the title compound.

Step I

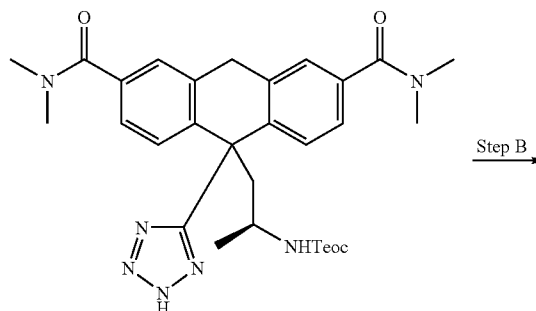
[0719] If one were to treat the title compound from Step H above as described in Preparative Example 61 Step C, one would obtain the title compound.

Preparative Example 1301

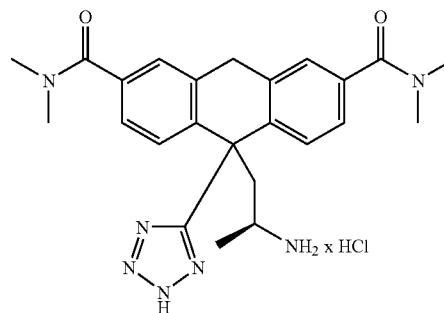
[0720]



Step A



Step B



Step A

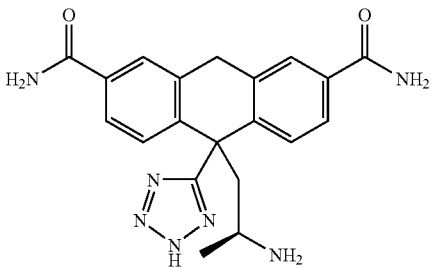
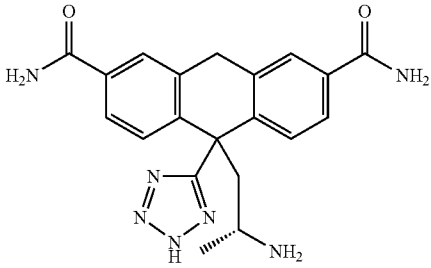
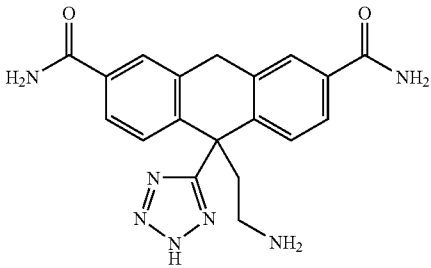
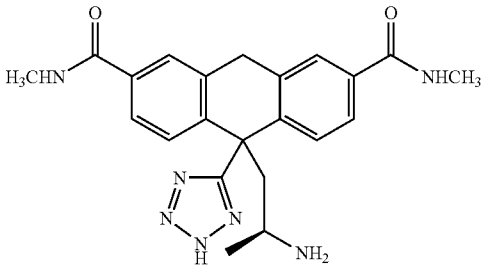
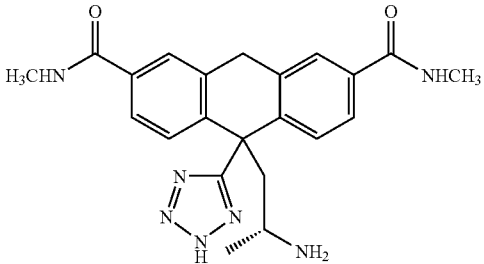
[0721] If one were to treat the title compound from Preparative Example 1300 as described in Preparative Example 71 Step A one would obtain the title compound.

Step B

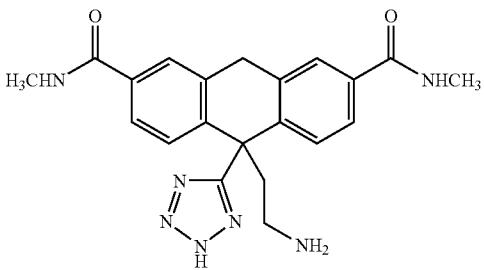
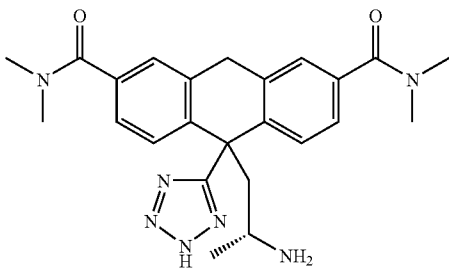
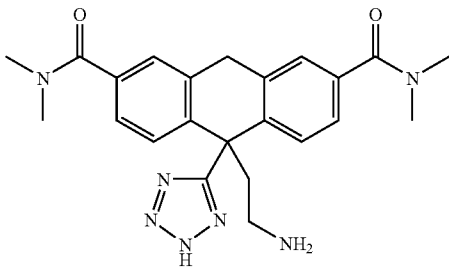
[0722] If one were to treat the title compound from Step A above as described in Preparative Example 71 Step B, one would obtain the title compound.

Preparative Example 1302-1309

[0723] If one were to follow a similar procedure as that described in Preparative Example 1300, except using the sulfamides in Step G, and treat the product obtained according to Preparative Example 1301 with the amine as indicated in the table below, one would obtain the desired title compound as HCl salt.

Preparative			
Example	Sulfamidate	Amine	Title compound
1302	21	NH ₃	
1303	24	NH ₃	
1304	22	NH ₃	
1305	21	CH ₃ NH ₂	
1306	24	CH ₃ NH ₂	

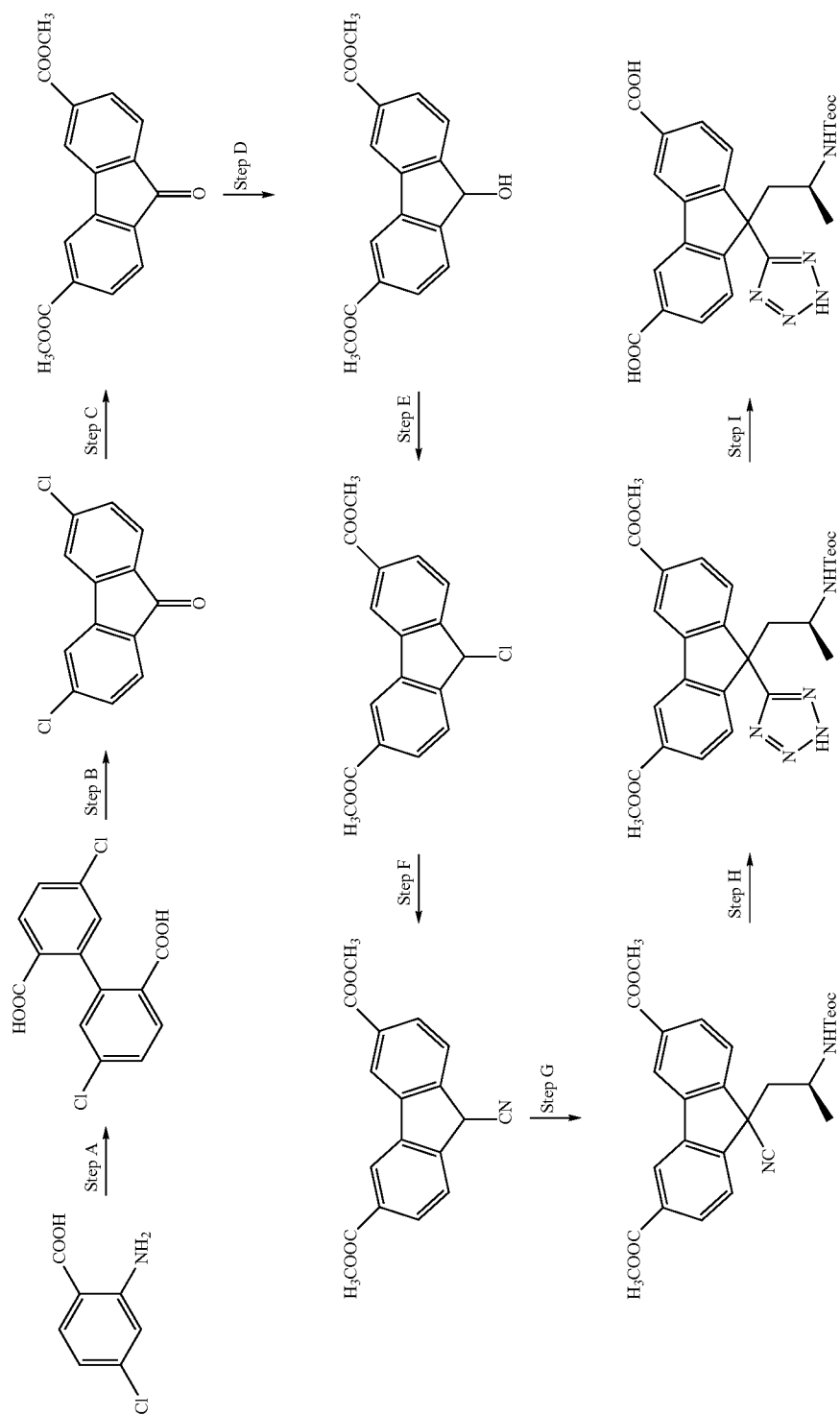
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Preparative Example	Sulfamidate	Amine	Title compound
1307	22	CH_3NH_2	
1308	24	$(\text{CH}_3)_2\text{NH}$	
1309	22	$(\text{CH}_3)_2\text{NH}$	

[0724] Examples 1310-1349 have been intentionally excluded.

Preparative Example 1350

[0725]



Step A

[0726] If one were to treat a solution of commercially available 4-chloroanthranilic acid in water and concentrated hydrochloric acid at 0° C. with a solution of sodium nitrate in water over 45 min and stir the resulting mixture at 0° C. for 1 h, one would obtain the diazonium salt solution after filtration. If one were to treat a solution of commercially available hydroxylamine hydrochloride in water at 10° C. with an aqueous solution of sodium hydroxide and carefully pour the mixture into an aqueous solution of hydrated copper(II) sulfate and concentrated ammonia solution, one would obtain a blue solution after filtration. If one were to carefully add the diazonium salt solution from above to the blue solution over a period of 1 h and then heat the mixture at reflux, followed by the addition of concentrated hydrochloric acid, one would obtain a precipitate after 3 h. If one were to collect the precipitate by filtration, wash it with water and dissolved it in a solution of sodium bicarbonate, one would obtain a clear solution after treatment with charcoal and filtration. If one were to add an excess of 6 M aqueous hydrochloric acid and collect the precipitate, one would obtain the title compound after crystallisation from EtOH.

Step B

[0727] If one were to treat the title compound of Step A above at 400° C. for twenty-five minutes and then sublime the mixture at 250° C. under a pressure of 2 mm, one would obtain the title compound after crystallization from benzene.

Step C

[0728] If one were to treat the title compound from Step B above as described in Preparative Example 59 Step D, Step E and Step F, one would obtain the title compound.

Step D

[0729] If one were to treat the title compound from Step C above as described in Preparative Example 59 Step G, one would obtain the title compound.

Step E

[0730] If one were to treat the title compound from Step D above as described in Preparative Example 59 Step H, one would obtain the title compound.

Step F

[0731] If one were to treat the title compound from Step E above as described in Preparative Example 59 Step I, one would obtain the title compound.

Step G

[0732] If one were to treat the title compound from Step F above as described in Preparative Example 61 Step A, one would obtain the title compound.

Step H

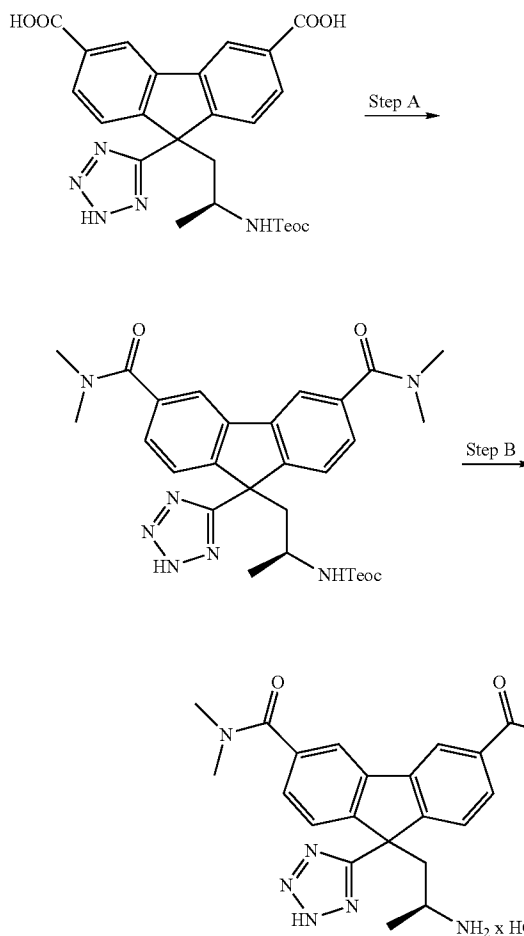
[0733] If one were to treat the title compound from Step G above as described in Preparative Example 61 Step B, one would obtain the title compound.

Step I

[0734] If one were to treat the title compound from Step H above as described in Preparative Example 61 Step C, one would obtain the title compound.

Preparative Example 1351

[0735]



Step A

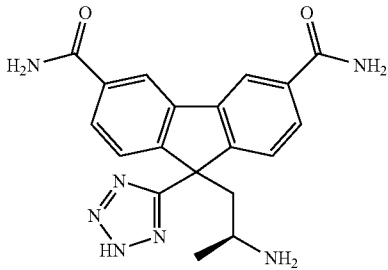
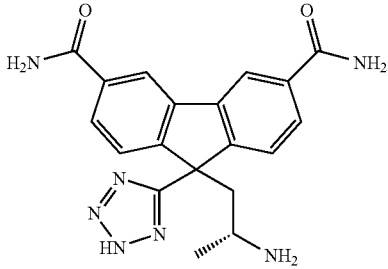
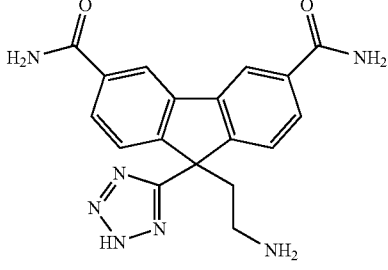
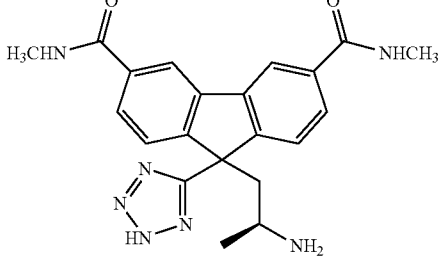
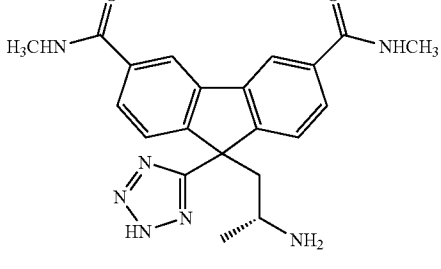
[0736] If one were to treat the title compound from Preparative Example 1350 as described in Preparative Example 71 Step A one would obtain the title compound.

Step B

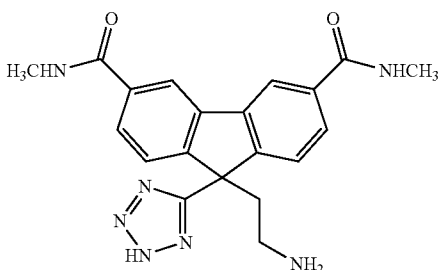
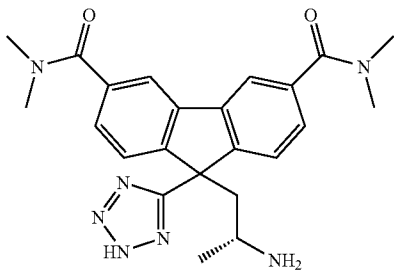
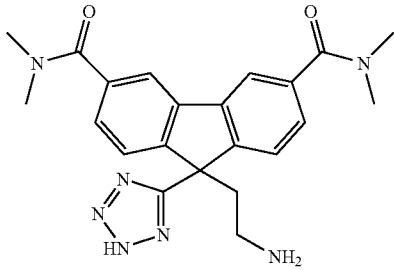
[0737] If one were to treat the title compound from Step A above as described in Preparative Example 71 Step B, one would obtain the title compound.

Preparative Example 1352-1359

[0738] If one were to follow a similar procedure as that described in Preparative Example 1350, except using the sulfamidates in Step G, and treat the product obtained according to Preparative Example 1351 with the amine as indicated in the table below, one would obtain the desired title compound as HCl salt.

Preparative Example	Sulfamidate	Amine	Title compound
1352	21	NH ₃	
1353	24	NH ₃	
1354	22	NH ₃	
1355	21	CH ₃ NH ₂	
1356	24	CH ₃ NH ₂	

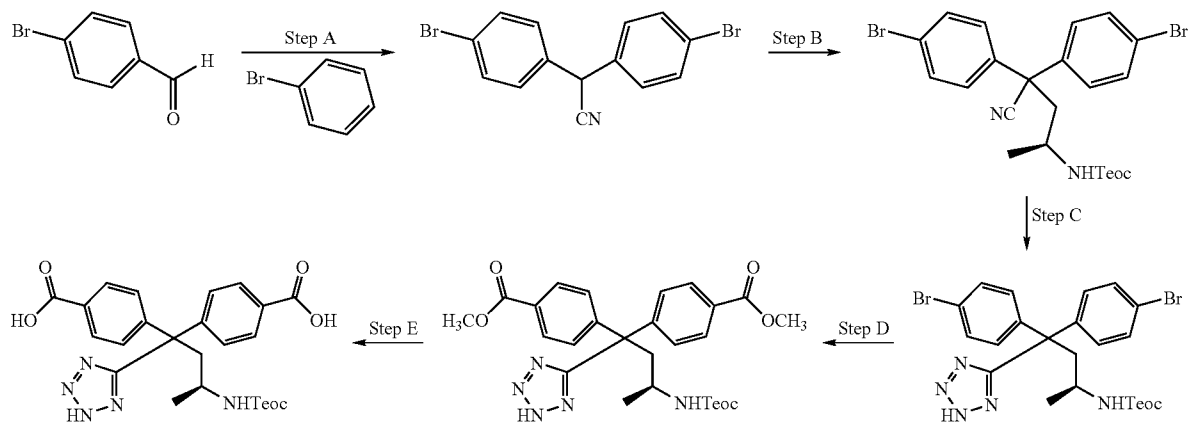
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Preparative Example	Sulfamidate	Amine	Title compound
1357	22	CH_3NH_2	
1358	24	$(\text{CH}_3)_2\text{NH}$	
1359	22	$(\text{CH}_3)_2\text{NH}$	

[0739] Examples 1360-1399 have been intentionally excluded.

Preparative Example 1400

[0740]



Step A

[0741] If one were to treat commercially available 4-bromo benzaldehyde dissolved in ether at 0° C. over a period of two hours portion-wise with KCN and concentrated HCl and maintain the temperature of the reaction below 10° C., followed by stirring for 1 h after complete addition, while permitting the temperature to rise to 15° C., subsequently the resultant two-phase system is filtered off and washed with ether, separating the combined organic solutions one would obtain the intermediate after washing with saturated aqueous sodium bisulfide, drying over MgSO₄, and concentrating in vacuo. If one were to dilute the residue with benzene and slowly add this mixture over a period of one hour to concentrated H₂SO₄, which would maintained under stirring in an ice bath at a temperature below 15° C. until completion of the addition, followed by stirring for an additional hour, allowing the mixture to warm to room temperature one would obtain after pouring the reaction mixture onto ice and the mixture is being extracted with benzene, the title compound.

Step B

[0742] If one were to treat the title compound from Step A above as described in Preparative Example 61 Step A, one would obtain the title compound.

Step C

[0743] If one were to treat the title compound from Step B above as described in Preparative Example 61 Step B, one would obtain the title compound.

Step D

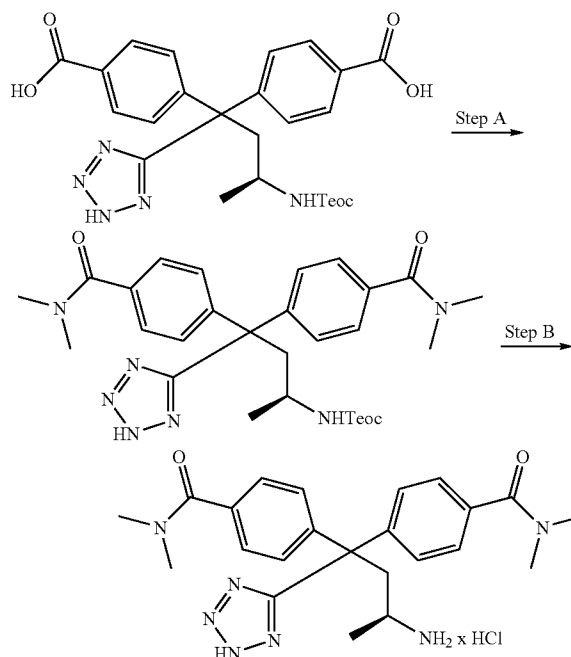
[0744] If one were to treat the title compound from Step C above as described in Preparative Example 59 Step D, Step E and Step F, one would obtain the title compound.

Step E

[0745] If one were to treat the title compound from Step D above as described in Preparative Example 61 Step C, one would obtain the title compound.

Preparative Example 1401

[0746]



Step A

[0747] If one were to treat the title compound from Preparative Example 1400 as described in Preparative Example 71 Step A one would obtain the title compound.

Step B

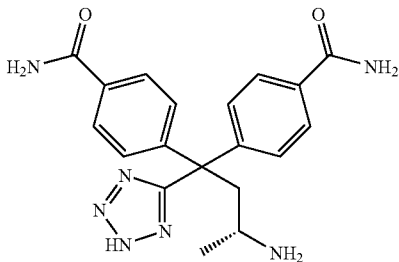
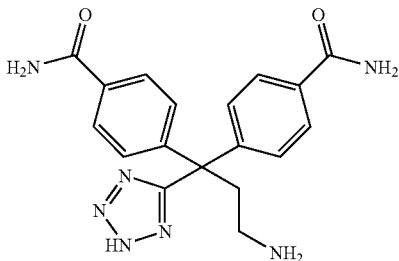
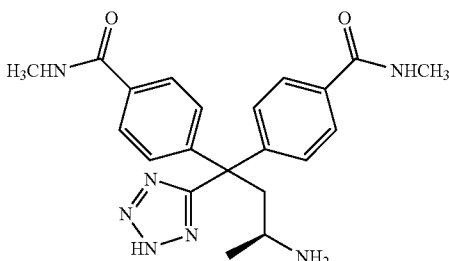
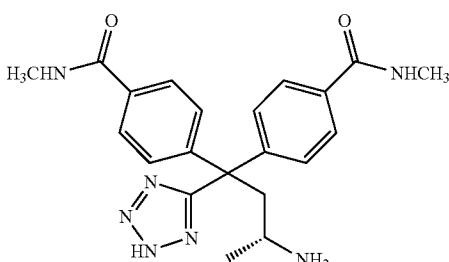
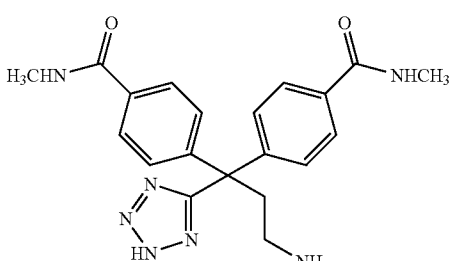
[0748] If one were to treat the title compound from Step A above as described in Preparative Example 71 Step B, one would obtain the title compound.

Preparative Example 1402-1409

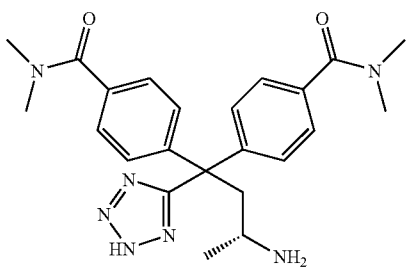
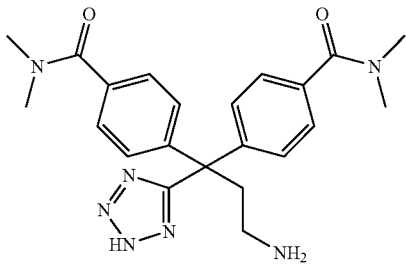
[0749] If one were to follow a similar procedure as that described in Preparative Example 1400, except using the sulfamides in Step B, and treat the product obtained according to Preparative Example 1401 with the amine as indicated in the table below, one would obtain the desired title compound as HCl salt.

Preparative Example	Sulfamide	Amine	Title compound
1402	21	NH ₃	

-continued

Preparative			
Example	Sulfamidate	Amine	Title compound
1403	24	NH ₃	
1404	22	NH ₃	
1405	21	CH ₃ NH ₂	
1406	24	CH ₃ NH ₂	
1407	22	CH ₃ NH ₂	

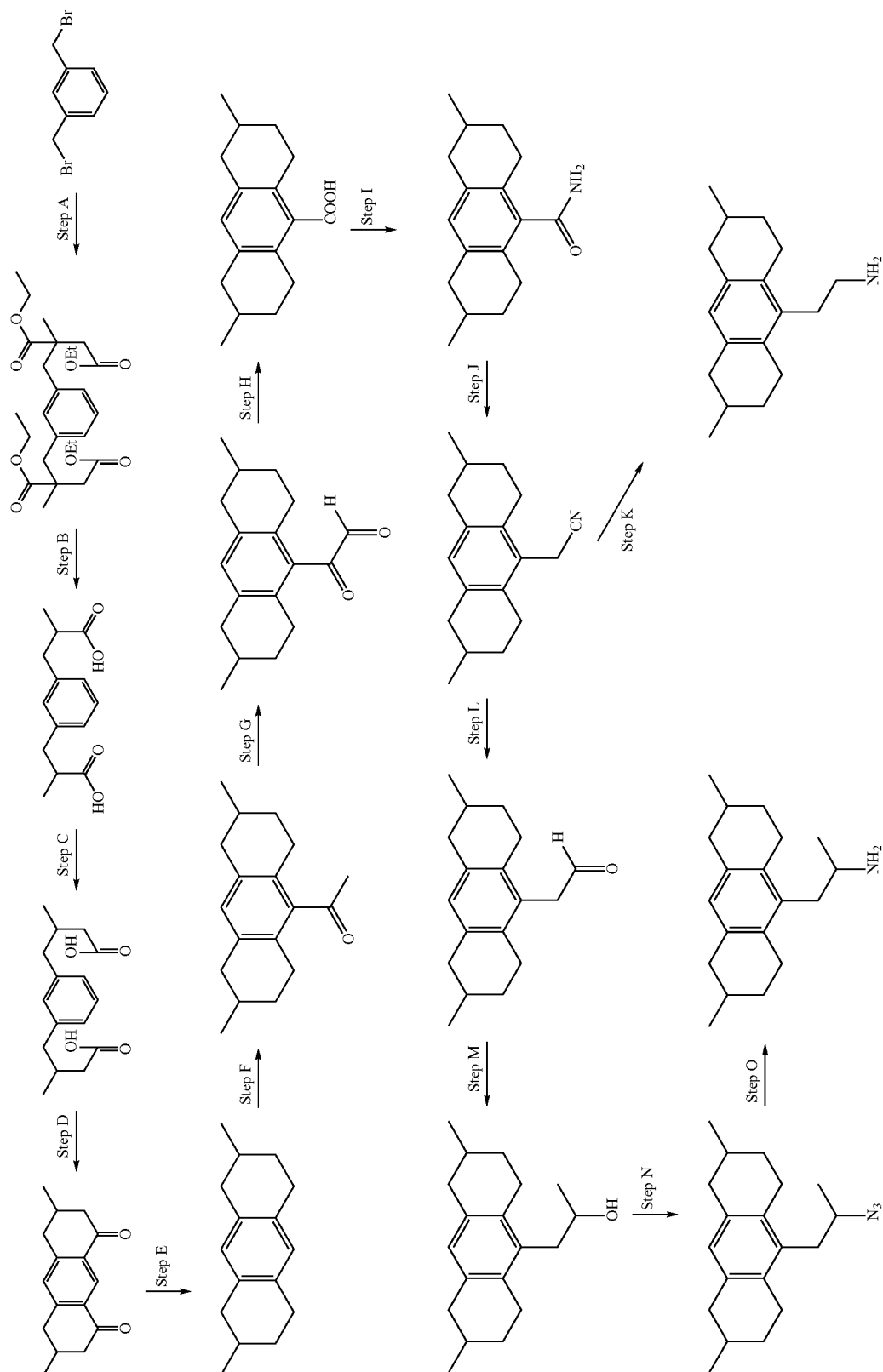
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Preparative Example	Sulfamidate	Amine	Title compound
1408	24	$(\text{CH}_3)_2\text{NH}$	
1409	22	$(\text{CH}_3)_2\text{NH}$	

[0750] Examples 1410-1449 have been intentionally excluded.

Preparative Example 1450

[0751]



Step A

[0752] If one were to add commercially available diethyl-methylmalonate to a solution of sodium ethoxide in EtOH, and then add a solution of α,α' -dibromo-m-xylene in benzene to the above solution and boil the mixture at reflux for 1 h, one would obtain the title compound after distillation and crystallisation.

Step B

[0753] If one were to treat the title compound from Step A above with aqueous-ethanolic potassium hydroxide, one would obtain the crude tetracarboxylic acid. If one were to decarboxylate the crude tetracarboxylic acid at 210° C., one would obtain the title compound.

Step C

[0754] If one were to convert the title compound from Step B above to its bis-acid chloride with thionyl chloride in benzene and treat the bis-acid chloride with a solution of diazomethane in ether, one would obtain the diazoketone intermediate after 12 h and evaporation of the solvents. If one were to treat the diazoketone with benzyl alcohol- γ -collidine (1:1) in an oil-bath maintained at 180° C. for 10 Min, one would obtain the crude title compound. If one were to treat the crude title compound with MeOH and HCl, one would obtain the dimethylester. If one were to treat the dimethylester with KOH in EtOH, one would obtain the title compound.

Step D

[0755] If one were to treat the title compound from Step C above with phosphorus pentachloride in benzene for 1 h and warm the mixture on a steam-bath for 5 min, one would obtain the crude bis-acid chloride. If one were to dissolve the bis-acid chloride in nitrobenzene, add a solution of aluminium chloride in nitrobenzene at 0° C. and then allow the mixture to stand at rt for 6 h, one would obtain the title compound, after removal of the nitrobenzene by steam distillation and crystallisation of the residue with EtOH.

Step E

[0756] If one were to treat the title compound from Step D above with hydrazine hydrate and potassium hydroxide in diethylene glycol for 4 h at 180° C., followed by purification by chromatography on alumina one would obtain the title compound.

Step F

[0757] If one were to treat the title compound from Step E with 10 eq. of aluminium chloride by adding the compound to the reagent in tetrachloroethane at low temperature, add dropwise 2.0 eq. of acetic anhydride to the mixture, pour onto ice and hydrochloric acid and extract with an appropriate solvent, wash with water, evaporate, recrystallize from methanol, one would obtain the title compound.

Step G

[0758] If one were to treat the title compound from Step F above with selenium dioxide in water and dioxane and

refluxed for 4 h, followed by removal of precipitated selenium one would obtain after recrystallization the title compound.

Step H

[0759] If one were to treat the title compound from Step G above with hydrogen peroxide and drop wise with 10% NaOH in ethanol at 80° C., followed by dilution with water, treatment with norite, filtration and acidifying with HCl, one would obtain after recrystallization the title compound.

Step I

[0760] If one were to treat the title compound from Step H above as described in Preparative Example 70 Step A, one would obtain the title compound

Step J

[0761] If one were to treat the title compound from Step I above as described in Preparative Example 93 Step C, one would obtain the title compound.

Step K

[0762] If one were to treat the title compound from Step J above as described in Preparative Example 13 Step B, one would obtain the title compound.

Step L

[0763] If one were to treat the title compound from Step K above with diisobutylaluminum hydride in CH_2Cl_2 at -78° C., add 10% aq AcOH, extract with ether:hexane, wash with H_2O , sat. aq NaHCO_3 , and brine, dry over Na_2SO_4 , evaporate, purify the crude product through chromatography on silica gel, one would obtain the title compound.

Step M

[0764] If one were to treat the title compound from Step L above with 1.2 eq. commercially available methylmagnesium bromide in Et_2O at room temperature, heat the mixture to reflux, add ice and half concentrated hydrochloric acid, extract with Et_2O , wash the organic layer with H_2O , sat. aq NaHCO_3 , and brine, dry over Na_2SO_4 , evaporate, purify the crude product through chromatography on silica gel, one would obtain the title compound.

Step N

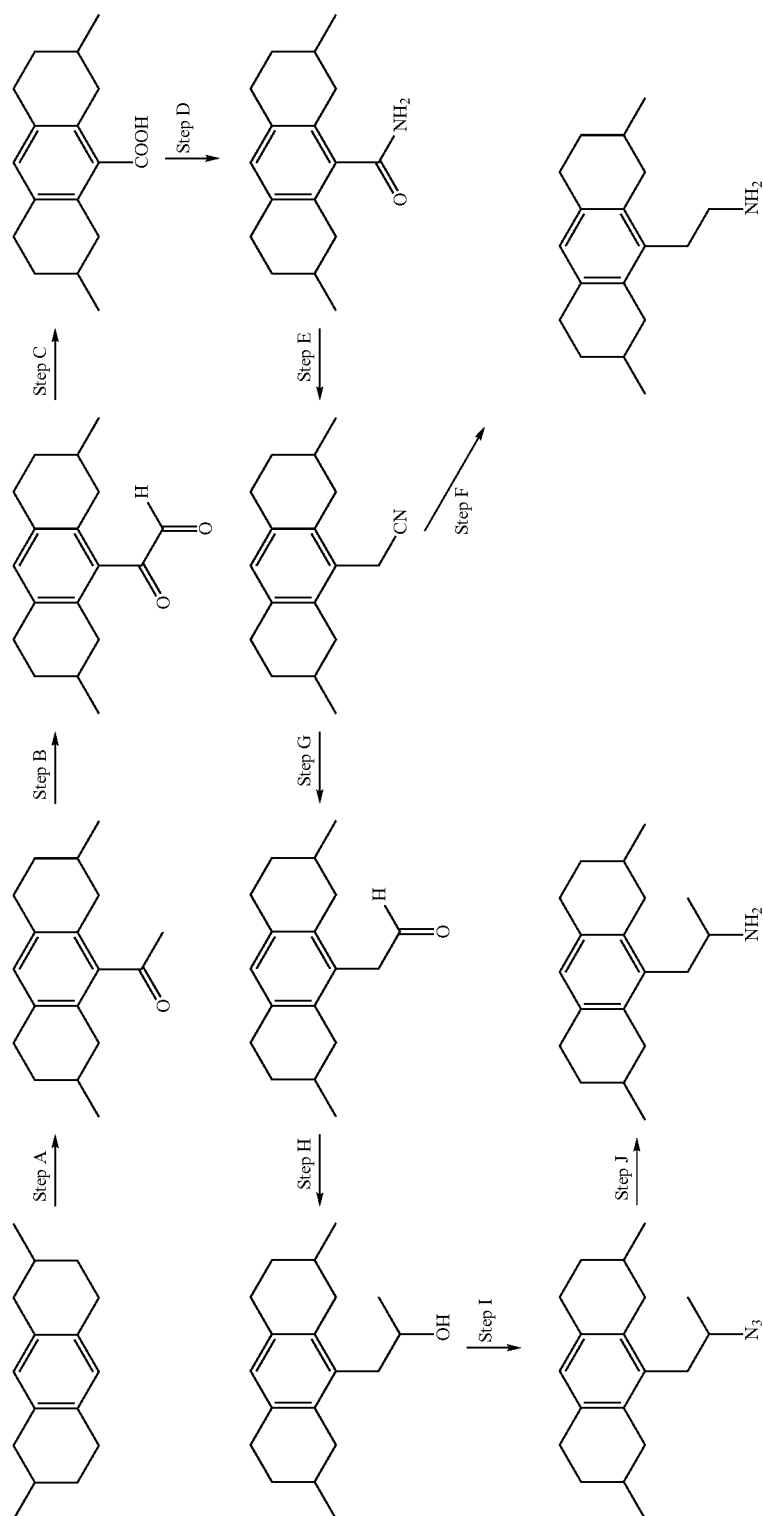
[0765] If one were to treat the title compound from Step M above with methylsulfonyl chloride and triethylamine in CH_2Cl_2 at 0° C., evaporate, add water and ethyl acetate to the residue, extract with ethyl acetate, wash the organic layer with H_2O , sat. aq NaHCO_3 , and brine, dry over Na_2SO_4 , evaporate and then the obtained intermediate with NaN_3 in DMA as described in Preparative Example 17 Step C, one would obtain the title compound.

Step O

[0766] If one were to treat the title compound from Step N above as described in Preparative Example 17 Step D, one would obtain the title compound.

Preparative Example 1451

[0767]



Step A

[0768] If one were to treat the title compound from Preparative Example 1450 Step E with 10 eq. of aluminium chloride by adding the compound to the reagent in tetrachloroethane at low temperature, add dropwise 2.0 eq. of acetic anhydride to the mixture, pour onto ice and hydrochloric acid and extract with an appropriate solvent, wash with water, evaporate, recrystallize from methanol, one would obtain the title compound.

Step B

[0769] If one were to treat the title compound from Step F above with selenium dioxide in water and dioxane and refluxed for 4 h, followed by removal of precipitated selenium one would obtain after recrystallization the title compound.

Step C

[0770] If one were to treat the title compound from Step G above with hydrogen peroxide and drop wise with 10% NaOH in ethanol at 80° C., followed by dilution with water, treatment with norite, filtration and acidifying with HCl, one would obtain after recrystallization the title compound.

Step D

[0771] If one were to treat the title compound from Step H above as described in Preparative Example 70 Step A, one would obtain the title compound

Step E

[0772] If one were to treat the title compound from Step I above as described in Preparative Example 93 Step C, one would obtain the title compound.

Step F

[0773] If one were to treat the title compound from Step J above as described in Preparative Example 13 Step B, one would obtain the title compound.

Step G

[0774] If one were to treat the title compound from Step K above with diisobutylaluminium hydride in CH₂Cl₂ at -78°

C., add 10% aq AcOH, extract with ether:hexane, wash with H₂O, sat. aq NaHCO₃, and brine, dry over Na₂SO₄, evaporate, purify the crude product through chromatography on silica gel, one would obtain the title compound.

Step H

[0775] If one were to treat the title compound from Step L above with 1.2 eq. commercially available methylmagnesium bromide in Et₂O at room temperature, heat the mixture to reflux, add ice and half concentrated hydrochloric acid, extract with Et₂O, wash the organic layer with H₂O, sat. aq NaHCO₃, and brine, dry over Na₂SO₄, evaporate, purify the crude product through chromatography on silica gel, one would obtain the title compound.

Step I

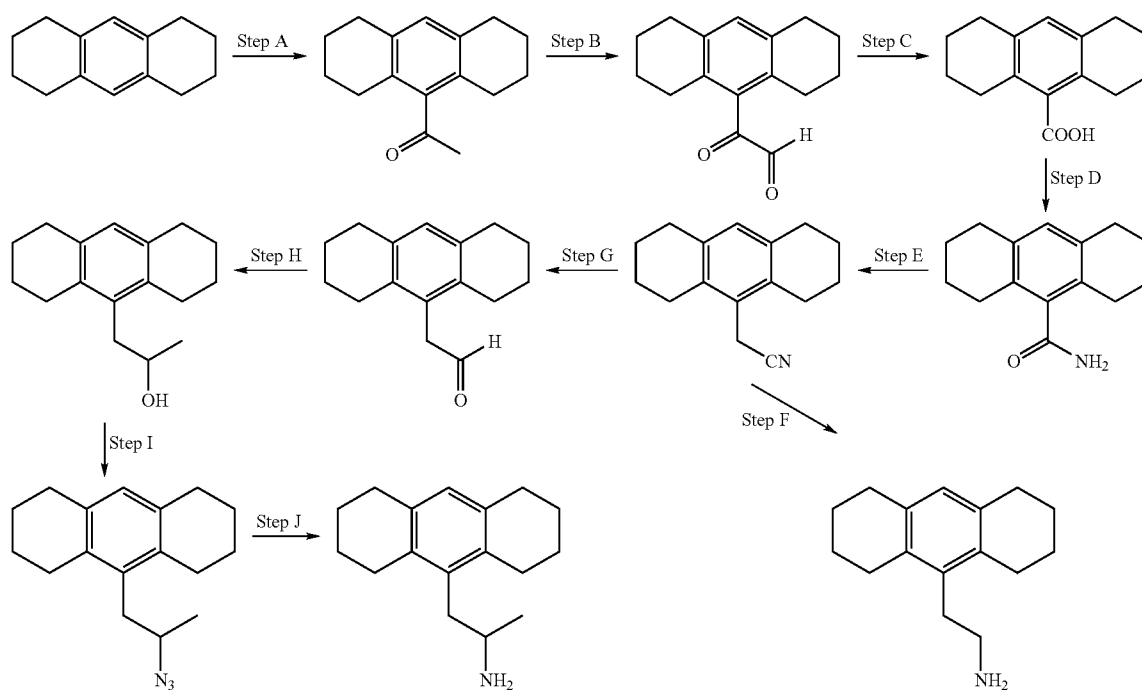
[0776] If one were to treat the title compound from Step M above with methylsulfonyl chloride and triethylamine in CH₂Cl₂ at 0° C., evaporate, add water and ethyl acetate to the residue, extract with ethyl acetate, wash the organic layer with H₂O, sat. aq NaHCO₃, and brine, dry over Na₂SO₄, evaporate and then the obtained intermediate with NaN₃ in DMA as described in Preparative Example 17 Step C, one would obtain the title compound.

Step J

[0777] If one were to treat the title compound from Step N above as described in Preparative Example 17 Step D, one would obtain the title compound.

Preparative Example 1452

[0778]



Step A

[0779] If one were to treat commercially available 1,2,3,4,5,6,7,8-octahydro-anthracene with 10 eq. of aluminium chloride by adding the compound to the reagent in tetrachloroethane at low temperature, add dropwise 2.0 eq. of acetic anhydride to the mixture, pour onto ice and hydrochloric acid and extract with an appropriate solvent, wash with water, evaporate, recrystallize from methanol, one would obtain the title compound.

Step B

[0780] If one were to treat the title compound from Step A above with selenium dioxide in water and dioxane and refluxed for 4 h, followed by removal of precipitated selenium one would obtain after recrystallization the title compound.

Step C

[0781] If one were to treat the title compound from Step B above with hydrogen peroxide and drop wise with 10% NaOH in ethanol at 80° C., followed by dilution with water, treatment with norite, filtration and acidifying with HCl, one would obtain after recrystallization the title compound.

Step D

[0782] If one were to treat the title compound from Step C above as described in Preparative Example 70 Step A, one would obtain the title compound

Step E

[0783] If one were to treat the title compound from Step D above as described in Preparative Example 93 Step C, one would obtain the title compound.

Step F

[0784] If one were to treat the title compound from Step E above as described in Preparative Example 13 Step B, one would obtain the title compound.

Step G

[0785] If one were to treat the title compound from Step F above with diisobutylaluminium hydride in CH₂Cl₂ at -78°

C., add 10% aq AcOH, extract with ether:hexane, wash with H₂O, sat. aq NaHCO₃, and brine, dry over Na₂SO₄, evaporate, purify the crude product through chromatography on silica gel, one would obtain the title compound.

Step H

[0786] If one were to treat the title compound from Step G above with 1.2 eq. commercially available methylmagnesium bromide in Et₂O at room temperature, heat the mixture to reflux, add ice and half concentrated hydrochloric acid, extract with Et₂O, wash the organic layer with H₂O, sat. aq NaHCO₃, and brine, dry over Na₂SO₄, evaporate, purify the crude product through chromatography on silica gel, one would obtain the title compound.

Step I

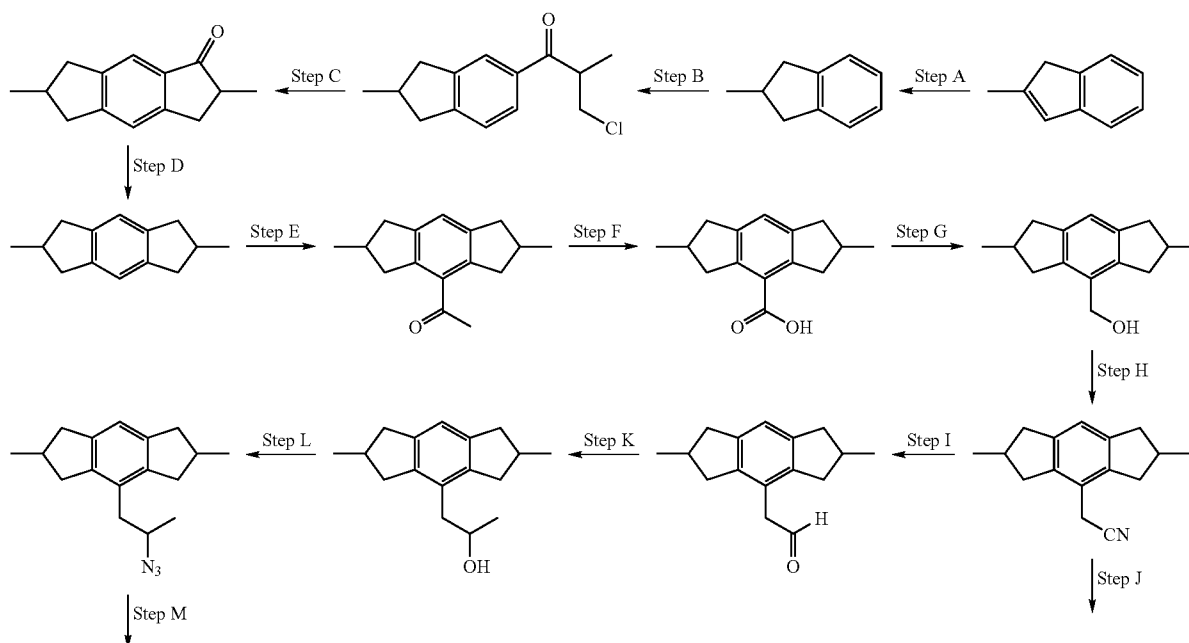
[0787] If one were to treat the title compound from Step H above with methylsulfonyl chloride and triethylamine in CH₂Cl₂ at 0° C., evaporate, add water and ethyl acetate to the residue, extract with ethyl acetate, wash the organic layer with H₂O, sat. aq NaHCO₃, and brine, dry over Na₂SO₄, evaporate and then the obtained intermediate with NaN₃ in DMA as described in Preparative Example 17 Step C, one would obtain the title compound.

Step J

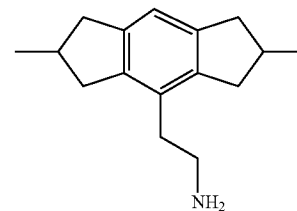
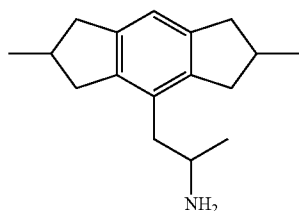
[0788] If one were to treat the title compound from Step I above as described in Preparative Example 17 Step D, one would obtain the title compound.

Preparative Example 1453

[0789]



-continued

**Step A**

[0790] If one were to treat commercially available 2-methyl-1H-indene and with 0.01 eq of platinum oxide in tetrahydrofuran and hydrogenate at 20-30 psi for 10-15 h at room temperature, filter the mixture through a pad of Celite, purify the crude product through chromatography on silica gel, one would obtain the title compound.

Step B

[0791] If one were to treat the title compound from Step A above with 1.0 eq. of 3-chloro-2-methyl-propionyl chloride and 3.0 eq. of aluminum chloride in nitromethane at room temperature, decompose the mixture with ice and hydrochloric acid, dilute with water, filter, dissolve the solid in benzene and wash with dilute hydrochloric acid, evaporate, purify with a Soxhlet extractor, one would obtain the title compound.

Step C

[0792] If one were to treat the title compound from Step B above with concentrated sulphuric acid by adding the compound in small portions to the acid at low temperature, heat on the steam-bath, pour onto ice and extract with benzene and water, evaporate, distillate at reduced pressure, recrystallize from petroleum ether, sublimate, one would obtain the title compound.

Step D

[0793] If one were to treat the title compound from Step C above with amalgamated zinc, water, acetic acid, toluene, hydrochloric acid, separate the organic layer, evaporate, distillate at reduced pressure, recrystallize, one would obtain the title compound.

Step E

[0794] If one were to treat the title compound from Step D with 10 eq. of aluminium chloride by adding the compound to the reagent in tetrachloroethane at low temperature, add dropwise 2.0 eq. of acetic anhydride to the mixture, pour onto ice and hydrochloric acid and extract with an appropriate solvent, wash with water, evaporate, recrystallize from methanol, one would obtain the title compound.

Step F

[0795] If one were to treat the title compound from Step E with an aqueous solution of potassium hypochlorite prepared from bleaching powder in methanol, separate the precipitate formed by filtration, acidify the filtrate, separate the precipi-

tate formed by filtration, recrystallize from methanol, one would obtain the title compound.

Step G

[0796] If one were to treat the title compound from Step F above as described in Preparative Example 70 Step A, one would obtain the title compound

Step H

[0797] If one were to treat the title compound from Step G above as described in Preparative Example 93 Step C, one would obtain the title compound.

Step I

[0798] If one were to treat the title compound from Step H above with diisobutylaluminium hydride in CH_2Cl_2 at -78°C ., add 10% aq AcOH, extract with ether:hexane, wash with H_2O , sat. aq NaHCO_3 , and brine, dry over Na_2SO_4 , evaporate, purify the crude product through chromatography on silica gel, one would obtain the title compound.

Step J

[0799] If one were to treat the title compound from Step H above as described in Preparative Example 13 Step B, one would obtain the title compound.

Step K

[0800] If one were to treat the title compound from Step I above with 1.2 eq. commercially available methylmagnesium bromide in Et_2O at room temperature, heat the mixture to reflux, add ice and half concentrated hydrochloric acid, extract with Et_2O , wash the organic layer with H_2O , sat. aq NaHCO_3 , and brine, dry over Na_2SO_4 , evaporate, purify the crude product through chromatography on silica gel, one would obtain the title compound.

Step L

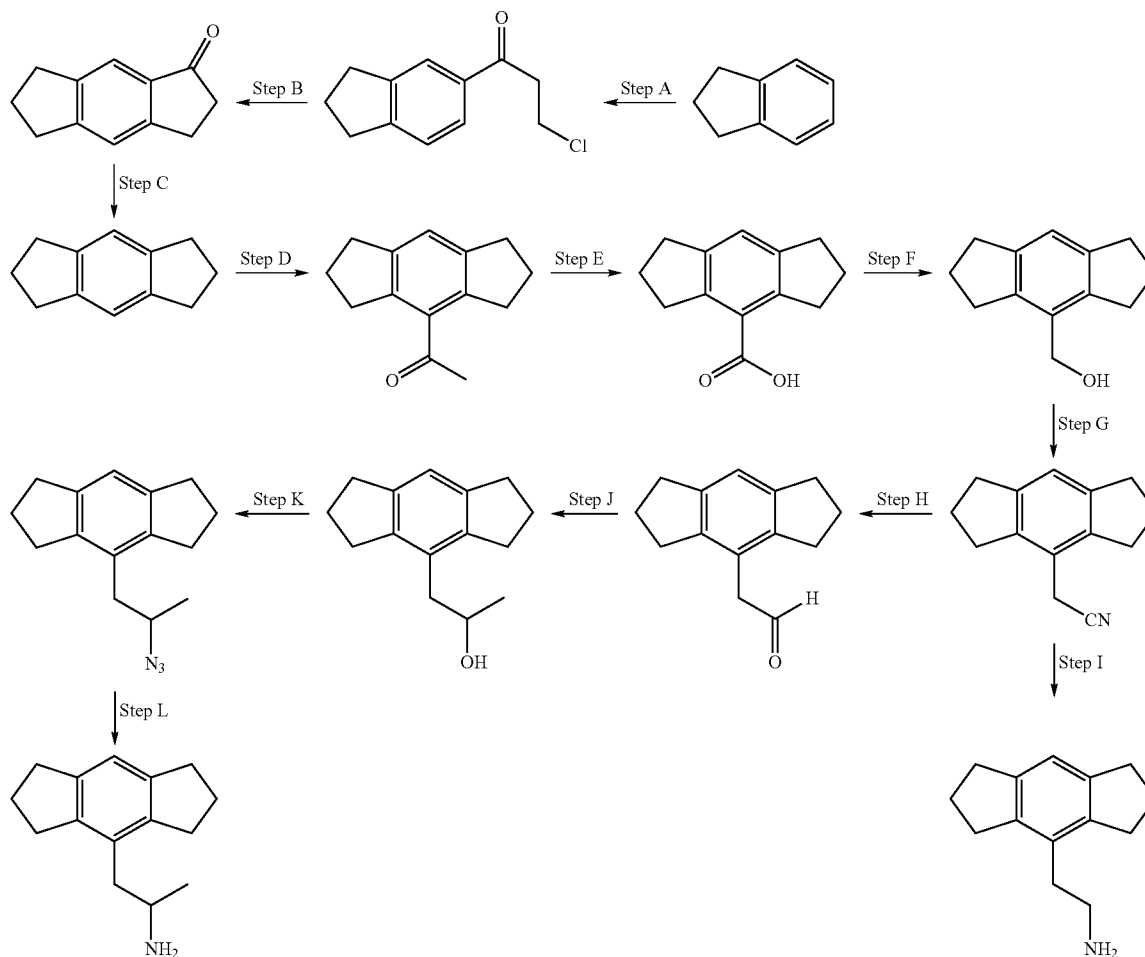
[0801] If one were to treat the title compound from Step K above with methylsulfonyl chloride and triethylamine in CH_2Cl_2 at 0°C ., evaporate, add water and ethyl acetate to the residue, extract with ethyl acetate, wash the organic layer with H_2O , sat. aq NaHCO_3 , and brine, dry over Na_2SO_4 , evaporate and then the obtained intermediate with NaN_3 in DMA as described in Preparative Example 17 Step C, one would obtain the title compound.

Step M

[0802] If one were to treat the title compound from Step L above as described in Preparative Example 17 Step D, one would obtain the title compound.

Preparative Example 1454

[0803]



Step A

[0804] If one were to treat commercially available indane with 1.0 eq. of 3-chloro-propionyl chloride and 3.0 eq. of aluminum chloride in nitromethane at room temperature, decompose the mixture with ice and hydrochloric acid, dilute with water, filter, dissolve the solid in benzene and wash with dilute hydrochloric acid, evaporate, purify with a Soxhlet extractor, one would obtain the title compound.

Step B

[0805] If one were to treat the title compound from Step A above with concentrated sulphuric acid by adding the compound in small portions to the acid at low temperature, heat on the steam-bath, pour onto ice and extract with benzene and water, evaporate, distillate at reduced pressure, recrystallize from petroleum ether, sublimate, one would obtain the title compound.

Step C

[0806] If one were to treat the title compound from Step B above with amalgamated zinc, water, acetic acid, toluene,

hydrochloric acid, separate the organic layer, evaporate, distillate at reduced pressure, recrystallize, one would obtain the title compound.

Step D

[0807] If one were to treat the title compound from Step D with 10 eq. of aluminium chloride by adding the compound to the reagent in tetrachloroethane at low temperature, add dropwise 2.0 eq. of acetic anhydride to the mixture, pour onto ice and hydrochloric acid and extract with an appropriate solvent, wash with water, evaporate, recrystallize from methanol, one would obtain the title compound.

Step E

[0808] If one were to treat the title compound from Step D with an aqueous solution of potassium hypochlorite prepared from bleaching powder in methanol, separate the precipitate formed by filtration, acidify the filtrate, separate the precipitate formed by filtration, recrystallize from methanol, one would obtain the title compound.

Step F

[0809] If one were to treat the title compound from Step E above as described in Preparative Example 70 Step A, one would obtain the title compound.

Step G

[0810] If one were to treat the title compound from Step F above as described in Preparative Example 93 Step C, one would obtain the title compound.

Step H

[0811] If one were to treat the title compound from Step G above with diisobutylaluminum hydride in CH_2Cl_2 at -78°C ., add 10% aq AcOH, extract with ether:hexane, wash with H_2O , sat. aq NaHCO_3 , and brine, dry over Na_2SO_4 , evaporate, purify the crude product through chromatography on silica gel, one would obtain the title compound.

Step I

[0812] If one were to treat the title compound from Step G above as described in Preparative Example 13 Step B, one would obtain the title compound.

Step J

[0813] If one were to treat the title compound from Step H above with 1.2 eq. commercially available methylmagnesium

bromide in Et_2O at room temperature, heat the mixture to reflux, add ice and half concentrated hydrochloride acid, extract with Et_2O , wash the organic layer with H_2O , sat. aq NaHCO_3 , and brine, dry over Na_2SO_4 , evaporate, purify the crude product through chromatography on silica gel, one would obtain the title compound.

Step K

[0814] If one were to treat the title compound from Step J above with methylsulfonyl chloride and triethylamine in CH_2Cl_2 at 0°C ., evaporate, add water and ethyl acetate to the residue, extract with ethyl acetate, wash the organic layer with H_2O , sat. aq NaHCO_3 , and brine, dry over Na_2SO_4 , evaporate and then the obtained intermediate with NaN_3 in DMA as described in Preparative Example 17 Step C, one would obtain the title compound.

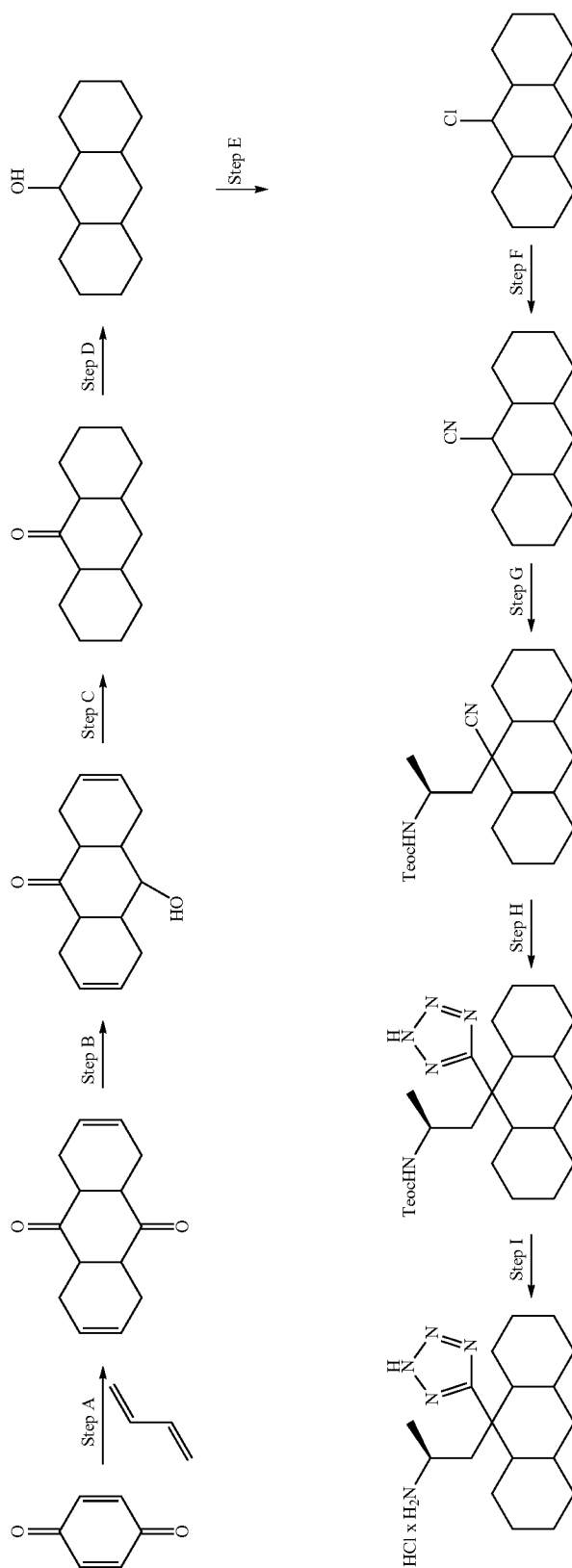
Step L

[0815] If one were to treat the title compound from Step K above as described in Preparative Example 17 Step D, one would obtain the title compound.

[0816] Examples 1455-1499 have been intentionally excluded.

Preparative Example 1500

[0817]



Step A

[0818] If one were to treat commercially available 1,4-benzoquinone with buta-1,3-diene in benzene at 100° C. in an autoclave, separate the precipitate, wash it with methanol, one would obtain the title compound.

Step B

[0819] If one were to treat the title compound from Step A above with LiAlH_4 in THF at rt for 15 min and then heat to reflux for 50 min, one would obtain after removal of the solvent, followed by aqueous workup and column chromatography the title compound.

Step C

[0820] If one were to treat the title compound from Step B above with methanesulfonyl chloride in pyridine at 0° C. for 24 h, one would obtain after pouring into an ice/water mixture followed by extraction with benzene and subsequently washing the organic phase with water, cold 5% sulphuric acid, water, 2% sodium bicarbonate solution, brine and finally evaporation to dryness, the methansulfonate intermediate. If one were to treat the methansulfonate intermediate with LiAlH_4 in THF and heat to reflux for 24 h, one would obtain after removal of the solvent, followed by aqueous workup the alcohol intermediate.

[0821] If one were to treat the alcohol intermediate with CrO_3 in pyridine at 40° C. for 9 h, one would obtain after pouring into water, followed by extraction with CCl_4 and subsequently drying the organic phase and evaporating to dryness, followed by column chromatography and crystallization the alkene intermediate. If one were to treat the alkene intermediate with Pd/C in ethanol at 10 bar H_2 and room temperature, separate the crude product from the reaction mixture and then the obtained intermediate with CrO_3 in aqueous acetic acid and water, neutralize the mixture, extract with Et_2O , recrystallize from THF/ CH_2Cl_2 , one would obtain the title compound.

Step D

[0822] If one were to treat the title compound from Step C above as described in Preparative Example 59 Step G, one would obtain the title compound.

Step E

[0823] If one were to treat the title compound from Step D above as described in Preparative Example 59 Step H, one would obtain the title compound.

Step F

[0824] If one were to treat the title compound from Step E with NaCN in 90% ethanol under reflux, add water, extract with CHCl_3 , wash the organic layer with 5% sulphuric acid, sat. aq NaHCO_3 , water, brine, dry over Na_2SO_4 , distillate, one would obtain the title compound.

Step G

[0825] If one were to treat the title compound from Step F above as described in Preparative Example 61 Step A, one would obtain the title compound.

Step H

[0826] If one were to treat the title compound from Step G above as described in Preparative Example 61 Step B, one would obtain the title compound.

Step I

[0827] If one were to treat the title compound from Step H above as described in Preparative Example 70 Step B, one would obtain the title compound.

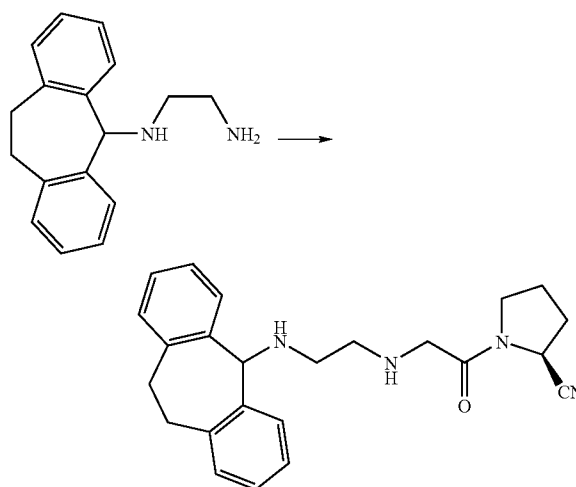
Preparative Example 1501-1502

[0828] If one were to follow a similar procedure as that described in Preparative Example 1500, except using the sulfamidates in Step G, one would obtain the desired title compound as HCl salt.

Preparative Example	Sulfamidate	Title compound
1501	22	
1502	24	

Example 1

[0829]

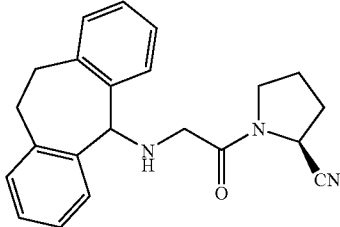
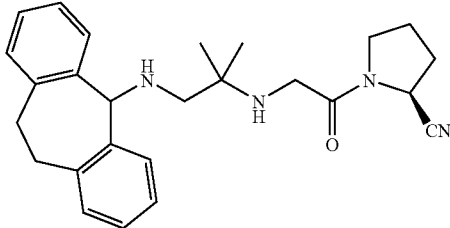
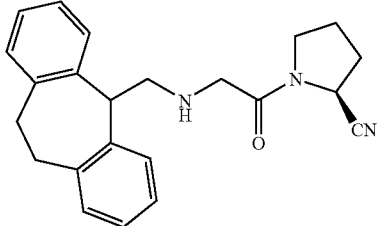
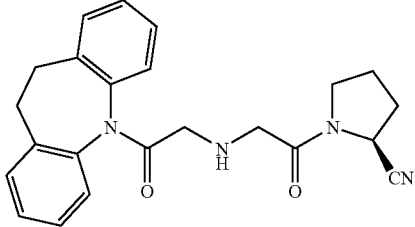
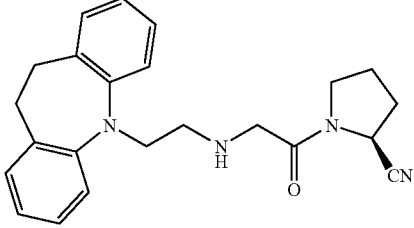


[0830] The title compound from Preparative Example 5 (378 mg) and 419 mg K_2CO_3 were suspended in 3 ml THF and cooled to 0° C. A solution of Preparative Example 1 (109 mg) in 1 ml THF was slowly added and the reaction mixture

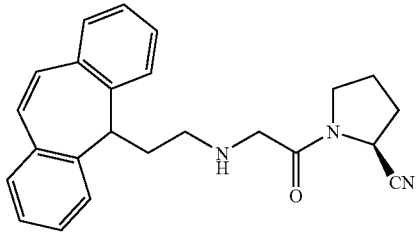
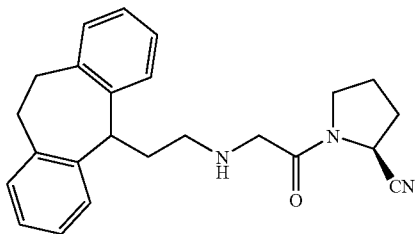
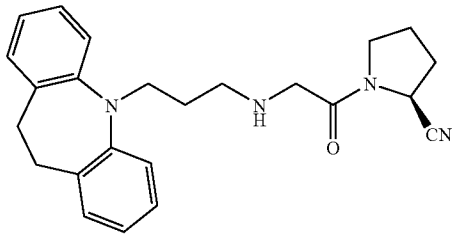
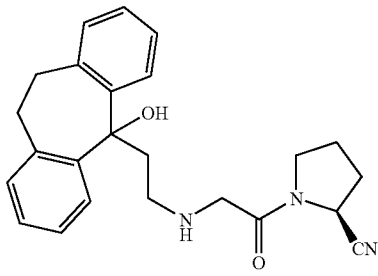
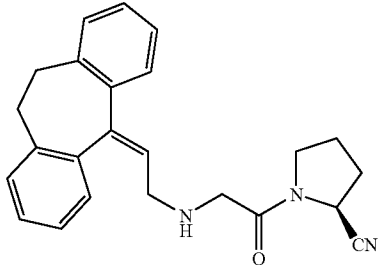
stirred at 0° C. for 2 h and then at rt overnight. The mixture was diluted with 30 ml EtOAc and 10 ml H₂O, the organic phase separated, dried over MgSO₄ and concentrated. The residue was purified by chromatography on silica (CH₂Cl₂/MeOH, 4:1) to afford the title compound (66 mg; 39%; MH⁺=389).

Example 2-14

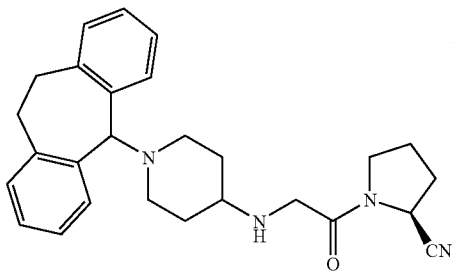
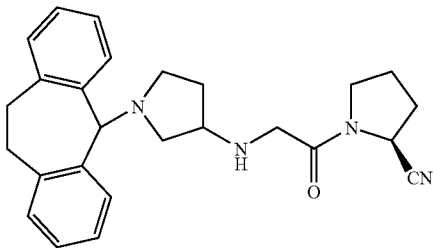
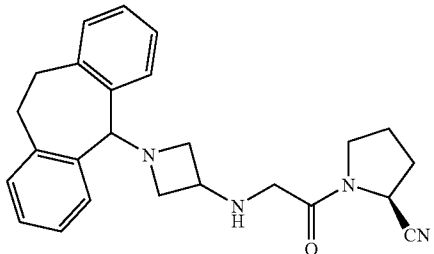
[0831] Following a similar procedure as that described in Example 1, except using the compounds from the Preparative Examples indicated in the Table below, the following compounds were prepared.

Example	Compound Preparative Example	Compound Preparative Example	Product	1. Yield 2. MH ⁺
2	1	6		1. 17% 2. 346
3	1	7		1. 8% 2. 417
4	1	13		1. 19% 2. 360
5	1	14 Step B		1. 18% 2. 389
6	1	14		1. 15% 2. 375

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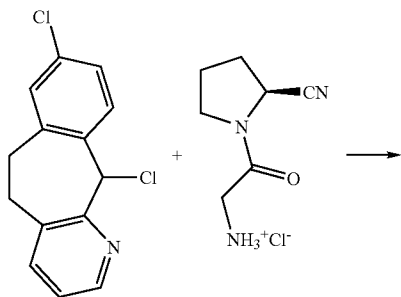
Example	Compound Preparative Example	Compound Preparative Example	Product	1. Yield 2. MH^+
7	1	15 Step C		1. 8% 2. 372
8	1	15		1. 8% 2. 374
9	1	16		1. 16% 2. 389
10	1	17 Step D		1. 7% 2. 390
11	1	17		1. 8% 2. 372

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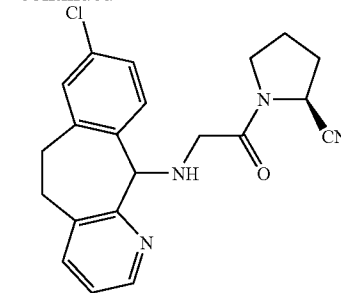
Example	Compound Preparative Example	Compound Preparative Example	Product	1. Yield 2. MH ⁺
12	1	10		1. 16% 2. 429
13	1	11		1. 19% 2. 415
14	1	12		1. 19% 2. 401

Example 15

[0832]



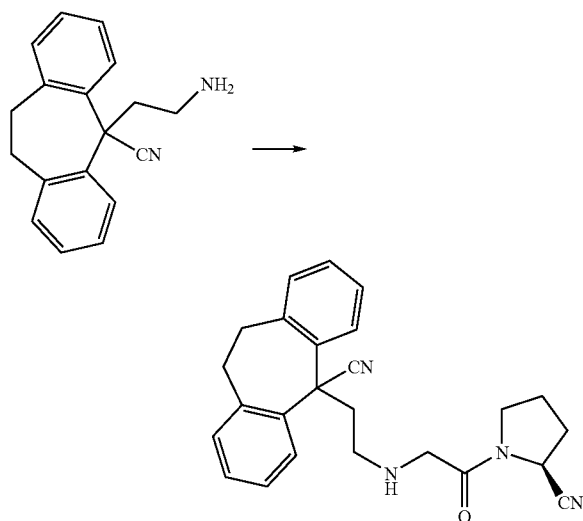
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[0833] An aliquot of the title compound of Preparative Example 3 was taken and the solvent removed. The residue (67 mg) was dissolved in DMF (2 ml) and triethylamine (0.1 ml). The title compound from Preparative Example 90 (71 mg) was added and the mixture was stirred at 60° C. for 2 h. The solvent was removed and the residue was purified by preparative TLC (CHCl₃/MeOH (+0.1% Triethylamine), 4:1) to afford the title compound (12 mg; 13%; MH⁺=381).

Example 16

[0834]



[0835] The title compound from Preparative Example 18 Step B (100 mg) and Preparative Example 2 (68 mg) were dissolved in 2 ml EtOH and 1 ml H₂O. The pH of the solution was adjusted to pH~6 by adding 0.1 M HCl-solution and the mixture was stirred at rt for 10 min. After the addition of NaCNBH₃ (24 mg) the pH was maintained at pH~6 by the addition of 0.1 M HCl and the mixture was stirred at rt

overnight. The mixture was diluted with 30 ml EtOAc and 15 ml sat. NaHCO₃/brine (1:1), the organic phase separated, dried over MgSO₄ and concentrated. The residue was purified by Prep TLC(CH₂Cl₂/MeOH, 95:5) to afford the title compound (25.9 mg; 17%; MH⁺=399).

Example 17-47

[0836] Following a similar procedure as described in Example 16 by dissolving the amine in a EtOH/H₂O— or MeOH/H₂O-mixture and adjusting the pH to pH~6-8 by either 0.1 M HCl, 3 M NaOAc or 1 M NaOH, except using the compounds from the Preparative Examples indicated in the Table below, the following compounds were prepared. In case the reaction was not completed after 24 h as judged by HPLC, additional aldehyde from Preparative Example 2 or 89 and NaCNBH₃ were added, and the reaction was continued for another 1-3 days.

[0837] For the products obtained, the following purification methods were employed:

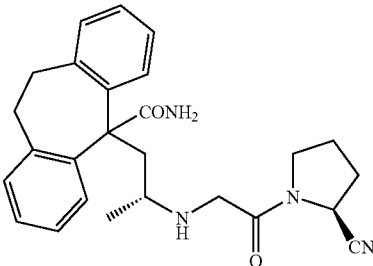
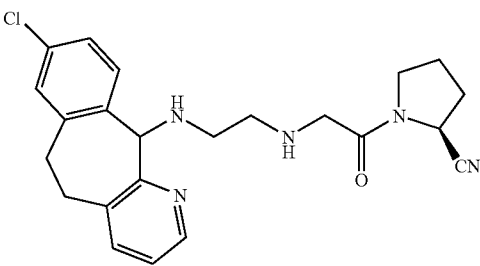
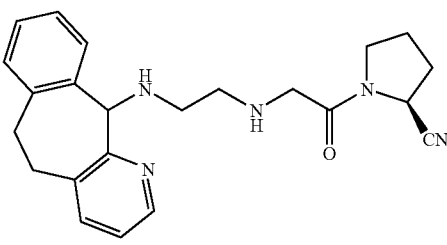
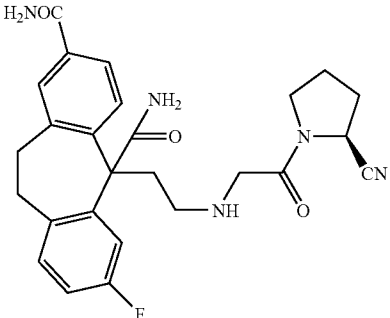
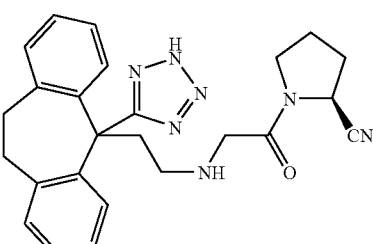
[0838] Method A: chromatography on silica using CH₂Cl₂/MeOH-mixtures; or

[0839] Method B: product was precipitated from the reaction mixture by adding 1 M HCl to pH 1-3 and the precipitate washed with MeOH; or

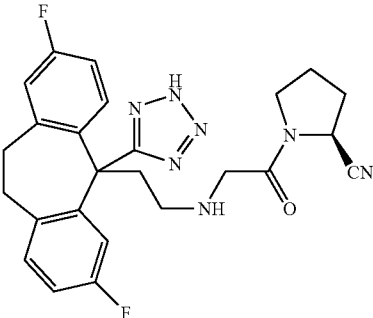
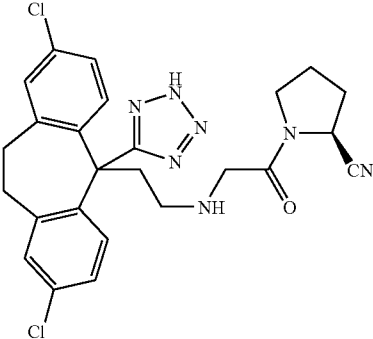
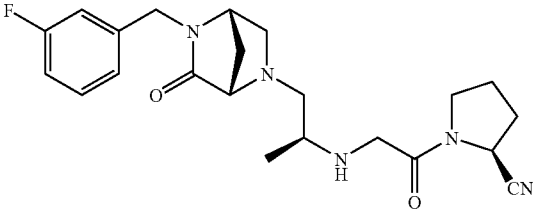
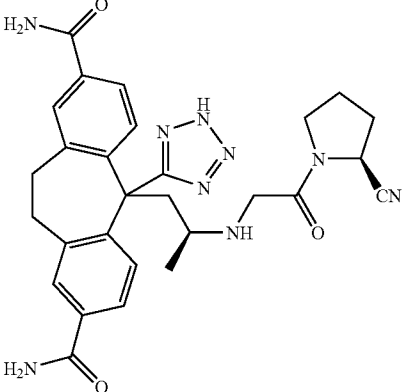
[0840] Method C: reaction mixture was concentrated to half its volume and the crude product purified by reverse phase HPLC (21.5×250 mm, Phenomenex, Luna C-18 (2), 5 μM; flow=15 ml/min or 10×250 mm, Phenomenex, Luna C-18 (2), 5 μM; flow=3 ml/min) using acetonitrile (solvent B; 0.1% formic acid) and H₂O (solvent A; 0.1% formic acid) as eluents and a suitable gradient, ramping solvent B from 0% to 100% over a period of 18 min.

Example	Compound Preparative Example	Compound Preparative Example	Purification Method	Product	1. Yield 2. MH ⁺
17	2	18	A		1. 17% 2. 417
18	2	47	A		1. 41% 2. 431

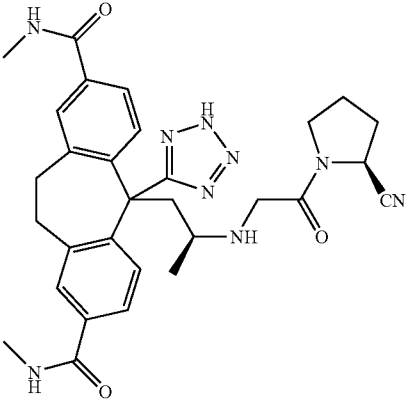
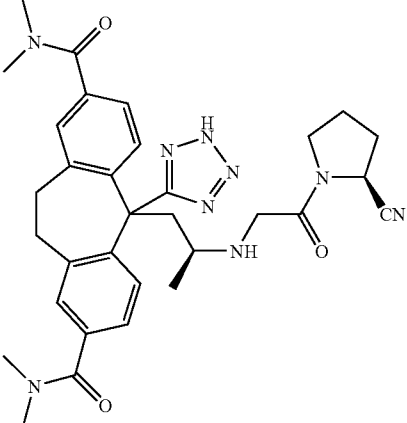
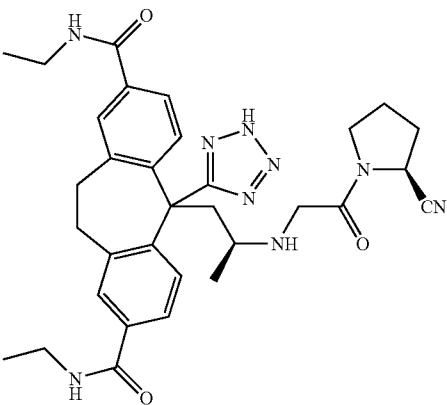
-continued

Example	Compound Preparative Example	Compound Preparative Example	Purification Method	Product	1. Yield 2. MH ⁺
19	2	48	A		1. 18% 2. 431
20	2	8	A		1. 25% 2. 424
21	2	9	A		1. 18% 2. 390
22	2	49	A		1. 21% 2. 478
23	2	50	B		1. 30% 2. 442

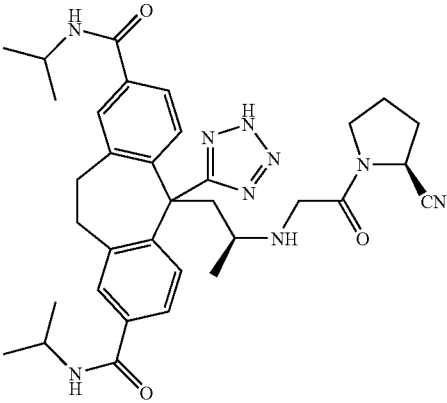
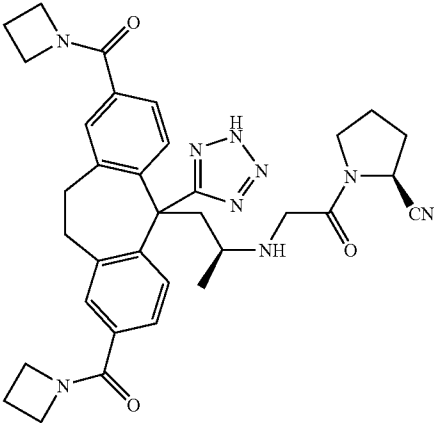
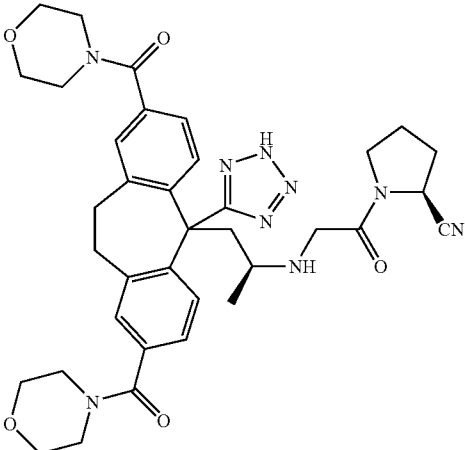
-continued

Example	Compound Preparative Example	Compound Preparative Example	Purification Method	Product	1. Yield 2. MH ⁺
24	2	51	B		1. 5% 2. 478
25	2	87	B		1. 46% 2. 510
26	2	110	A		1. 15% 2. 414
27	2	70	C		1. 36% 2. 542

-continued

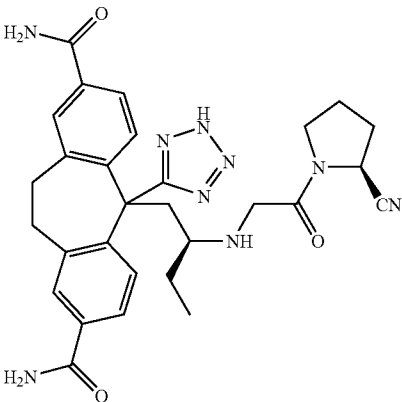
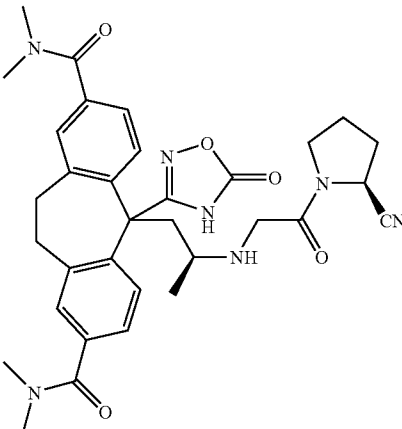
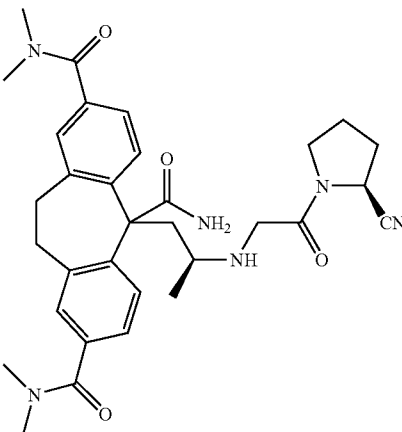
Example	Compound Preparative Example	Compound Preparative Example	Purification Method	Product	1. Yield 2. MH ⁺
28	2	72	C		1. 14% 2. 570
29	2	71	C		1. 38% 2. 598
30	2	73	C		1. 21% 2. 598

-continued

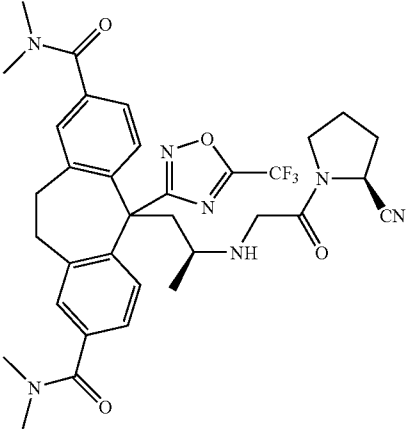
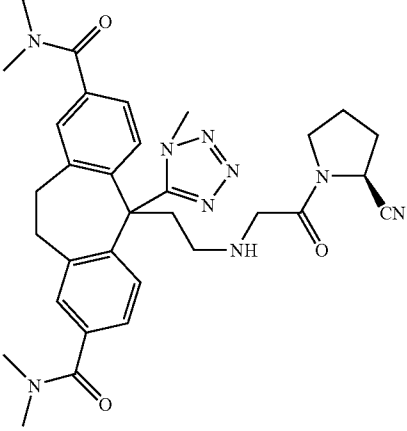
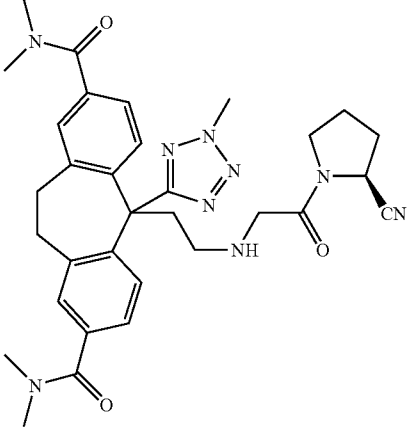
Example	Compound Preparative Example	Compound Preparative Example	Purification Method	Product	1. Yield 2. MH ⁺
31	2	74	C		1. 8% 2. 626
32	2	75	C		1. 58% 2. 622
33	2	76	C		1. 9% 2. 682

CN(C)C(=O)c1ccc2c(c1)C3=CC=CC=C3C(C2)C(=N4C=NC=NC4)CCNC(=O)[C@H]5CCCN5C#N

-continued

Example	Compound Preparative Example	Compound Preparative Example	Purification Method	Product	1. Yield 2. MH ⁺
37	2	79	C		1. 12% 2. 556
38	2	80	C		1. 43% 2. 614
39	2	81	C		1. 2% 2. 573

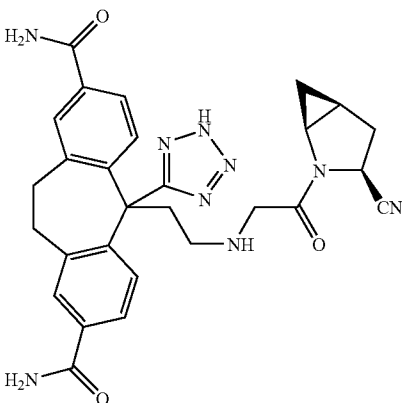
-continued

Example	Compound Preparative Example	Compound Preparative Example	Purification Method	Product	1. Yield 2. MH ⁺
40	2	82	C		1. 26% 2. 666
41	2	83	C		1. 12% 2. 542
42	2	84	C		1. 10% 2. 542

-continued

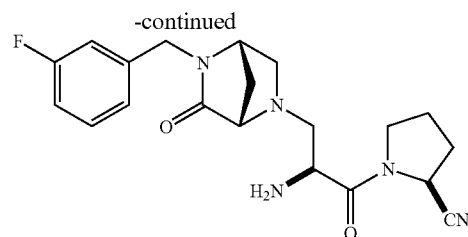
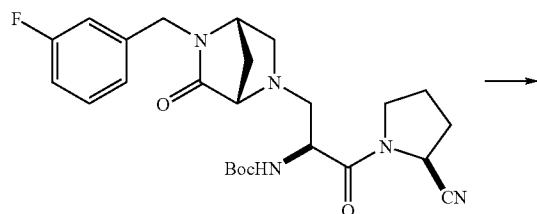
Example	Compound Preparative Example	Compound Preparative Example	Purification Method	Product	1. Yield 2. MH ⁺
43	2	85	C		1. 60% 2. 572
44	2	86	C		1. 28% 2. 544
45	2	52	C		1. 14% 2. 503
46	2	88	C		1. 2% 2. 471

-continued

Example	Compound Preparative Example	Compound Preparative Example	Purification Method	Product	1. Yield 2. MH ⁺
47	89	56	C		1. 9% 2. 540

Example 48

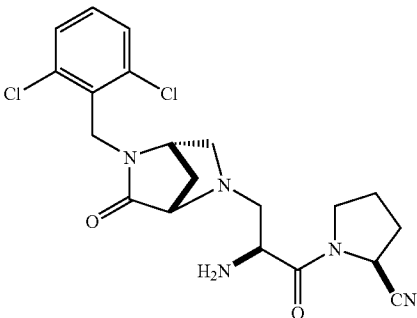
[0841]



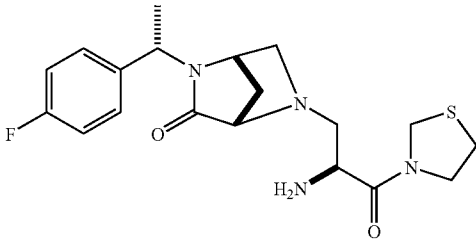
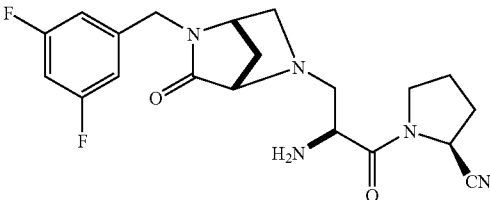
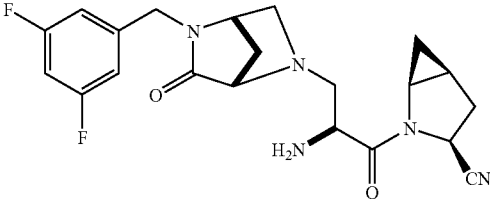
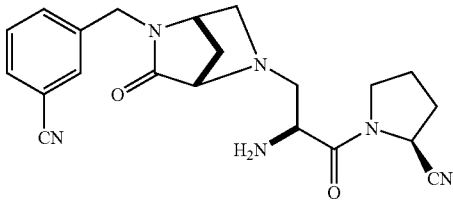
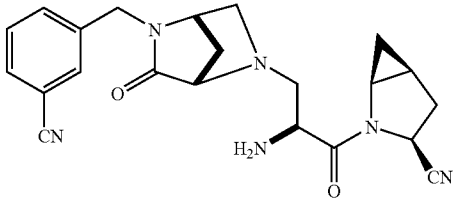
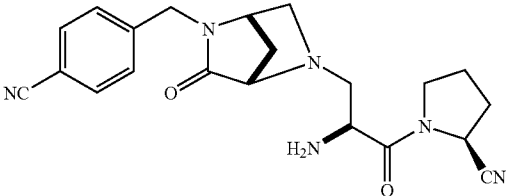
[0842] The title compound from Preparative Example 93 (16 mg) was dissolved in a mixture of H₂O (3 ml) and a solution of 4 M HCl in dioxane (3 ml). After 20 h the reaction mixture was diluted with toluene. The organic layer was evaporated to afford the title compound (14 mg; 99%; MH⁺=386).

Example 49-64

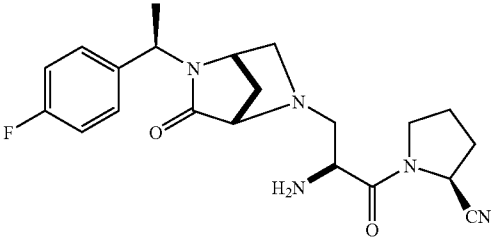
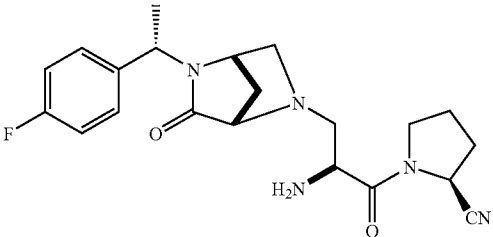
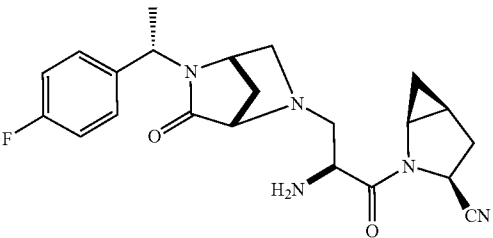
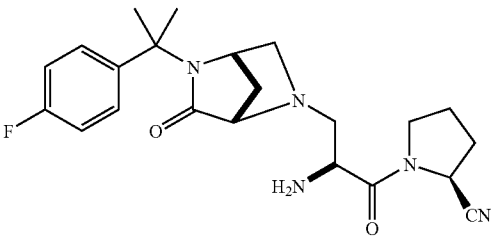
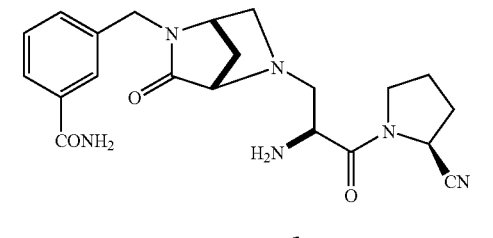
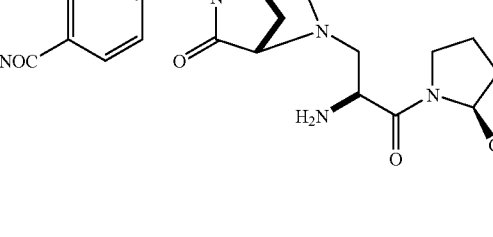
[0843] Following a similar procedure as that described in Example 48, except using the compounds from the Preparative Examples indicated in the Table below, the following compound was prepared.

Example	Compound Preparative Example	Product	1. Yield 2. MH ⁺
49	95		1. 77% 2. 436

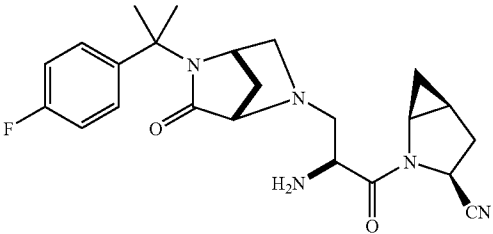
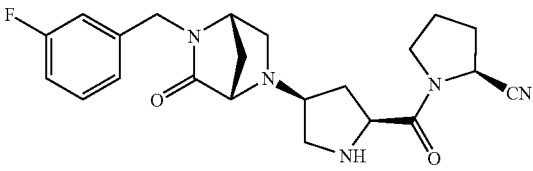
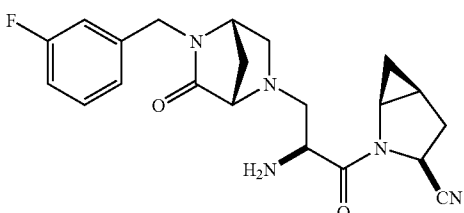
-continued

Example	Compound Preparative Example	Product	1. Yield 2. MH ⁺
50	96		1. 92% 2. 393
51	97		1. 89% 2. 404
52	98		1. 96% 2. 416
53	99		1. 57% 2. 393
54	100		1. 95% 2. 404
55	101		1. 93% 2. 393

-continued

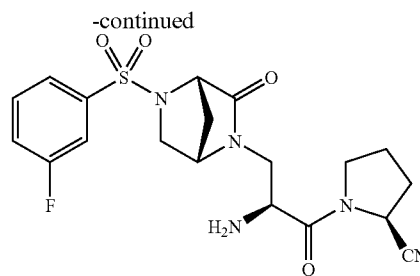
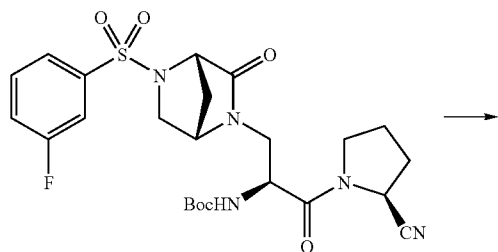
Example	Compound Preparative Example	Product	1. Yield 2. MH ⁺
56	102		1. 98% 2. 400
57	108		1. 96% 2. 400
58	103		1. 95% 2. 412
59	104		1. 95% 2. 414
60	105		1. 92% 2. 411
61	106		1. 95% 2. 411

-continued

Example	Compound Preparative Example	Product	1. Yield 2. MH ⁺
62	107		1. 81% 2. 426
63	109		1. 85% 2. 412
64	94		1. 95% 2. 398

Example 65

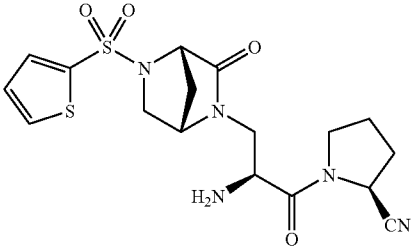
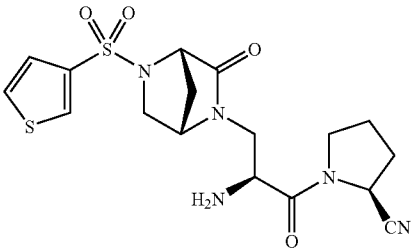
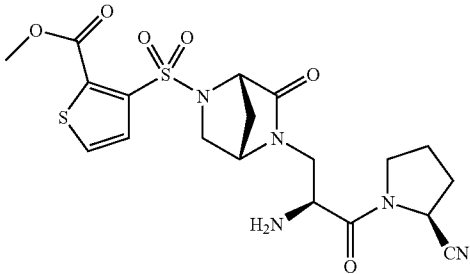
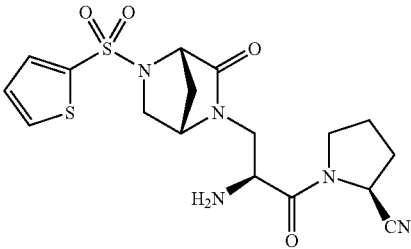
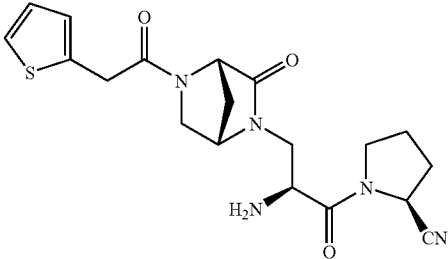
[0844]



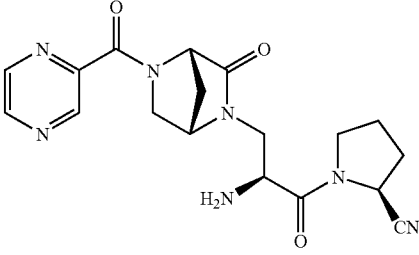
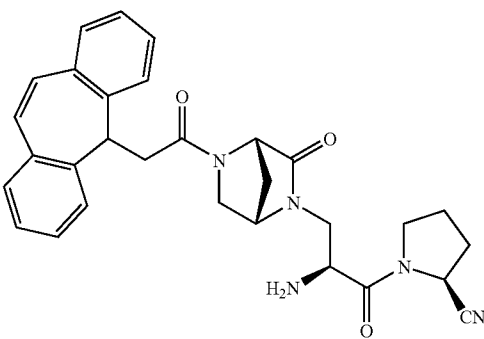
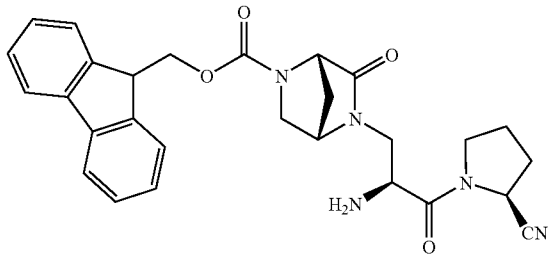
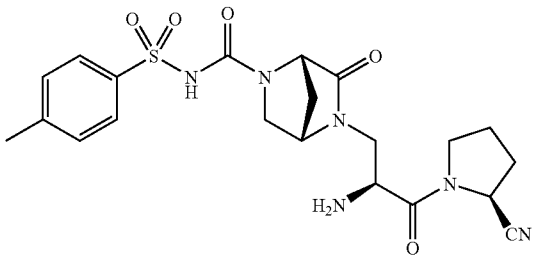
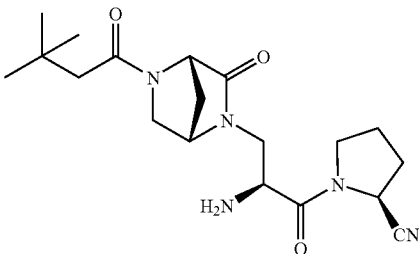
[0845] The title compound from Preparative Example 113 (13 mg) was treated with 4 M HCl in dioxane as described in Example 47 to afford the title compound (11.2 mg, 98%, MH⁺=436).

Example 66-75

[0846] Following a similar procedure as that described in Example 65, except using the compounds from the Preparative Examples indicated in the Table below, the following compounds were prepared.

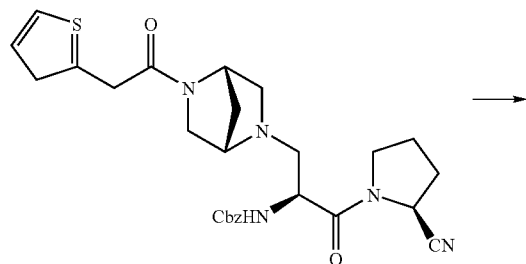
Example	Compound Preparative Example	Product	1. Yield 2. MH ⁺
66	114		1. 100 2. 424
67	115		1. 33 2. 424
68	116		1. 40 2. 482
69	117		1. 85 2. 388
70	118		1. 96 2. 402

-continued

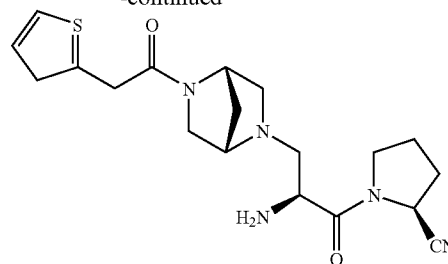
Example	Compound Preparative Example	Product	1. Yield 2. MH ⁺
71	119		1. 84 2. 384
72	122		1. 30 2. 510
73	112 Step D		1. 50 2. 500
74	121		1. 97 2. 475
75	120		1. 100 2. 377

Example 76

[0847]



-continued



[0848] The title compound from Preparative Example 123 (27 mg) was dissolved in dichloromethane (2 ml) and trimethylsilyl iodine (21 mg) was added. The mixture was stirred for 1 h at room temperature. After removal of the solvent the residue was purified by preparative TLC to afford the desired compound ($\text{CHCl}_3/\text{MeOH}$, 4 mg, 20%, $\text{MH}^+=388$).

Examples 77-78


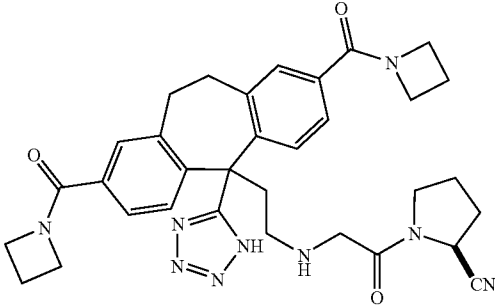
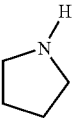
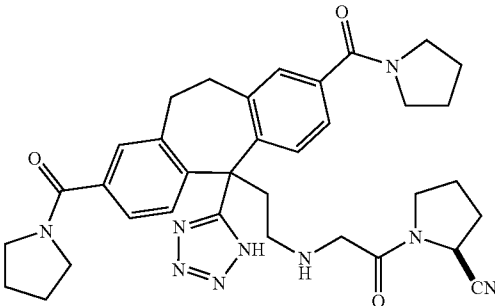
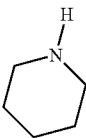
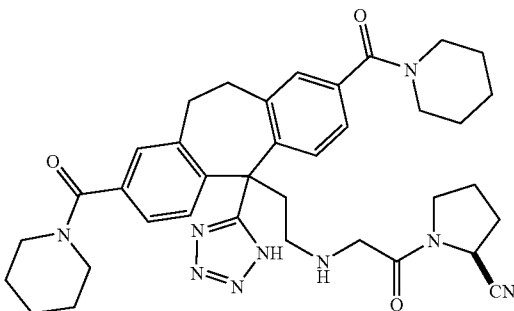
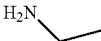
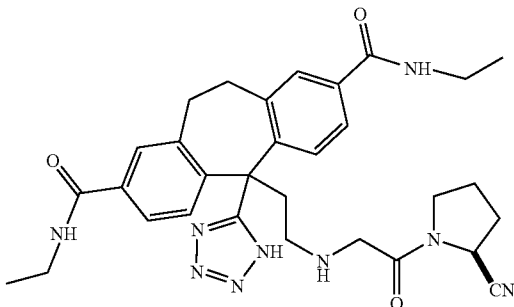
[0849] Following a similar procedure as that described in Example 76, except using the compounds from the Preparative Examples as indicated in the Table below, the following compounds were prepared.

Example	Preparative Example	Product	1. Yield 2. MH^+
77	124		1. 10% 2. 422
78	125		1. 11% 2. 358


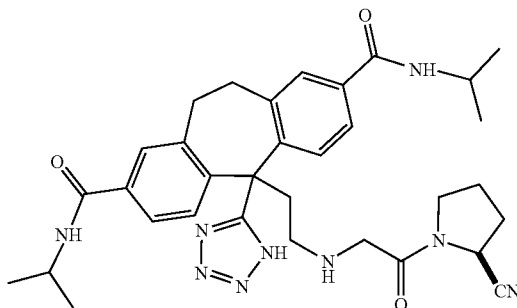

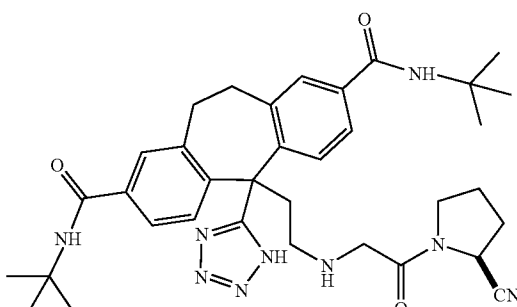
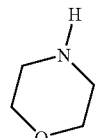
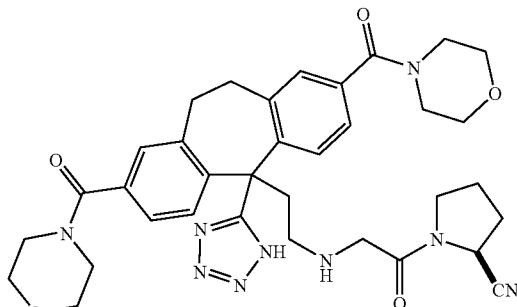
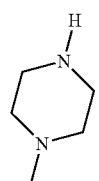
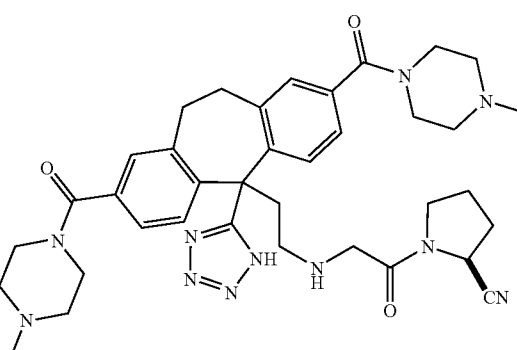
[0850] Examples 79-99 have been intentionally excluded.

Example 100-184

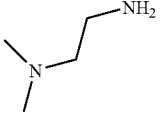
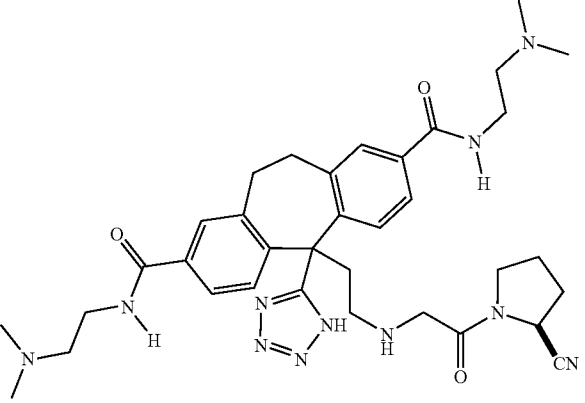
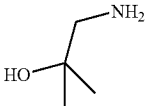
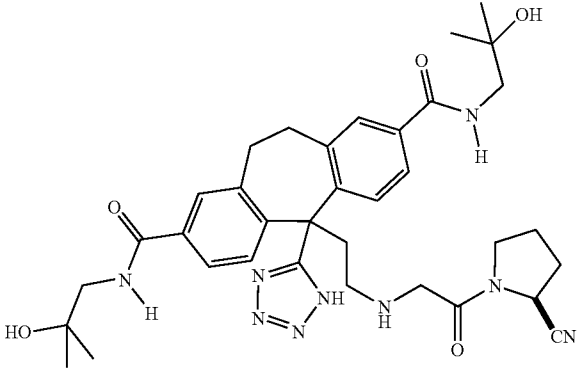
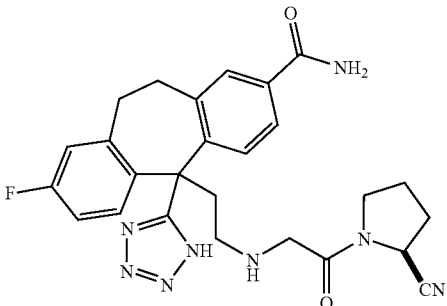
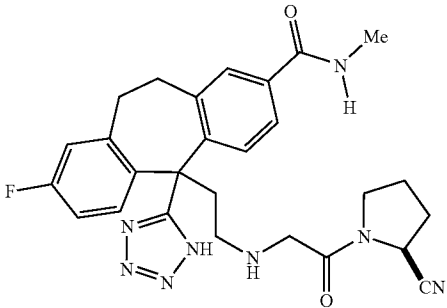
[0851] If one were to follow the procedures outlined in Preparative Example 71 and Examples 28 or 29 but using the amines, carboxylic acids and aldehydes from the Preparative Examples as indicated in the Table below, one would obtain the indicated Product.

Example #	Amine	Carboxylic Acid	Aldehyde	Product
100		Prep Ex 62	Prep Ex 2	
101		Prep Ex 62	Prep Ex 2	
102		Prep Ex 62	Prep Ex 2	
103		Prep Ex 62	Prep Ex 2	

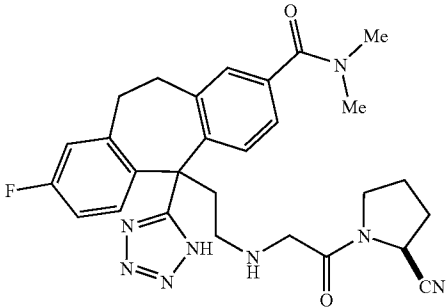
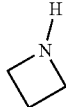
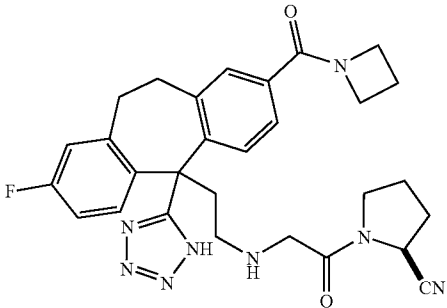
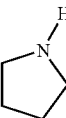
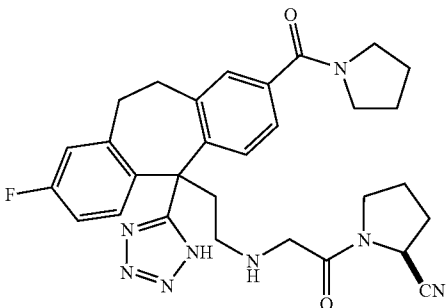
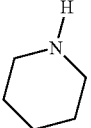
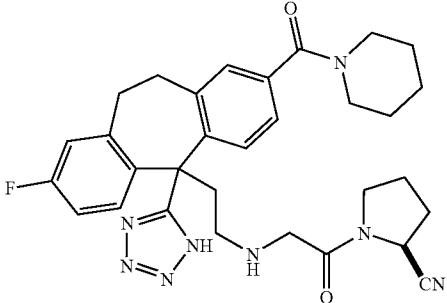
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Example #	Amine	Carboxylic Acid	Aldehyde	Product
104		Prep Ex 62	Prep Ex 2	
105		Prep Ex 62	Prep Ex 2	
106		Prep Ex 62	Prep Ex 2	
107		Prep Ex 62	Prep Ex 2	


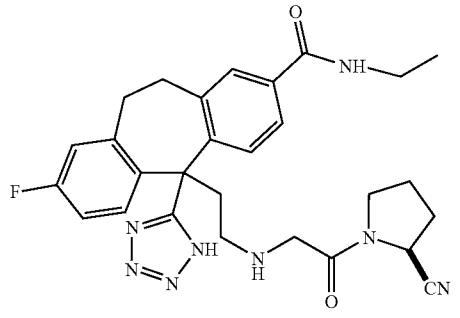

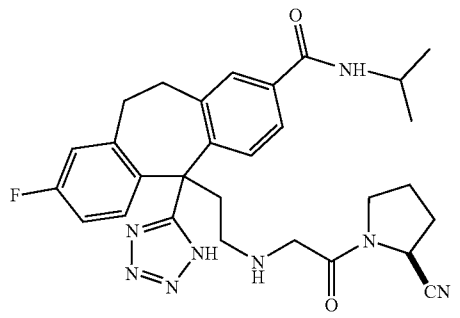

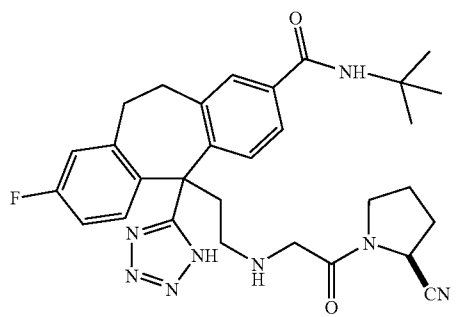
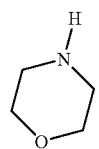
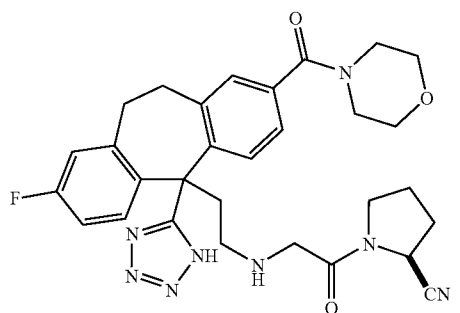
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Example #	Amine	Carboxylic Acid	Aldehyde	Product
108		Prep Ex 62	Prep Ex 2	
109		Prep Ex 62	Prep Ex 2	
110	NH ₃	Prep Ex 55	Prep Ex 2	
111	MeNH ₂	Prep Ex 55	Prep Ex 2	

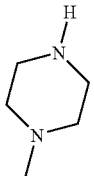
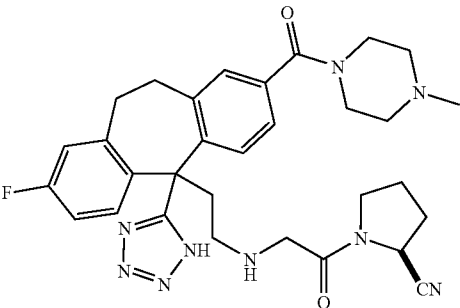
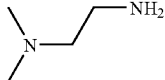
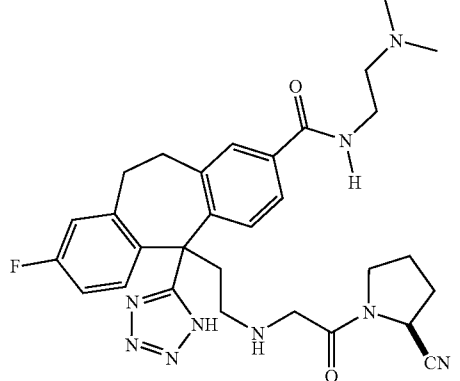
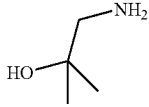
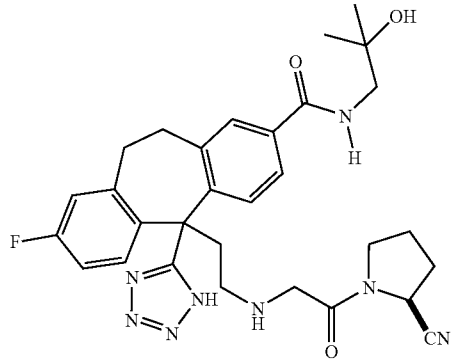
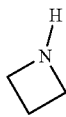
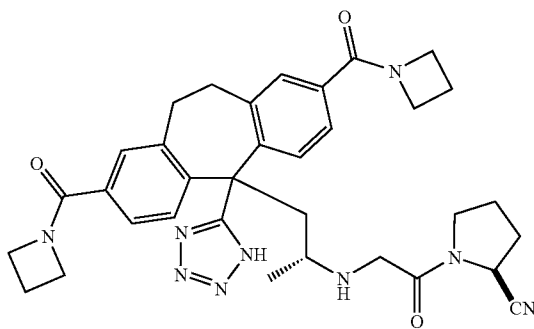
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Example #	Amine	Carboxylic Acid	Aldehyde	Product
112	(Me) ₂ NH	Prep Ex 55	Prep Ex 2	
113		Prep Ex 55	Prep Ex 2	
114		Prep Ex 55	Prep Ex 2	
115		Prep Ex 55	Prep Ex 2	

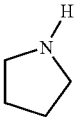
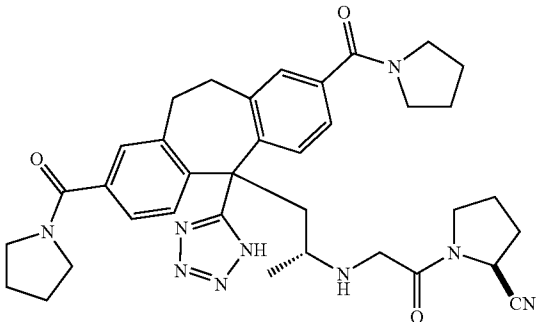
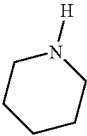
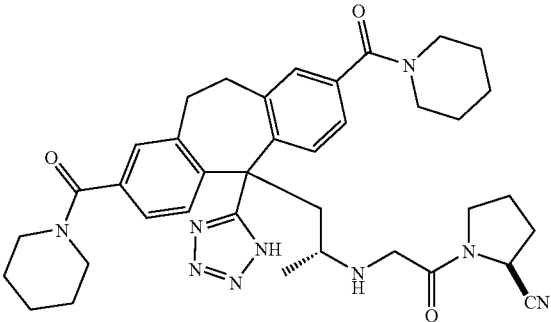
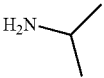
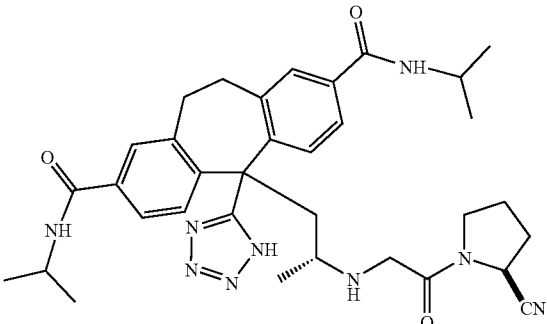
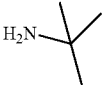
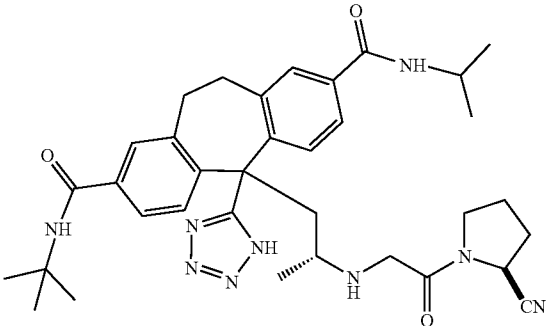
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Example #	Amine	Carboxylic Acid	Aldehyde	Product
116		Prep Ex 55	Prep Ex 2	
117		Prep Ex 55	Prep Ex 2	
118		Prep Ex 55	Prep Ex 2	
119		Prep Ex 55	Prep Ex 2	

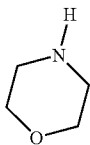
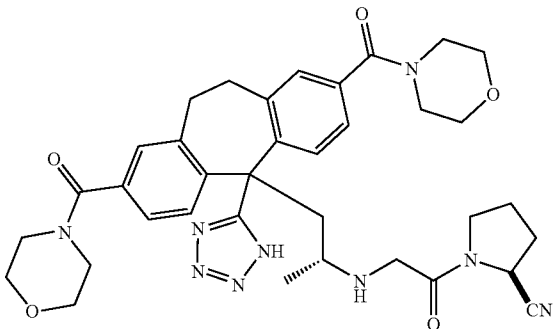
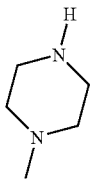
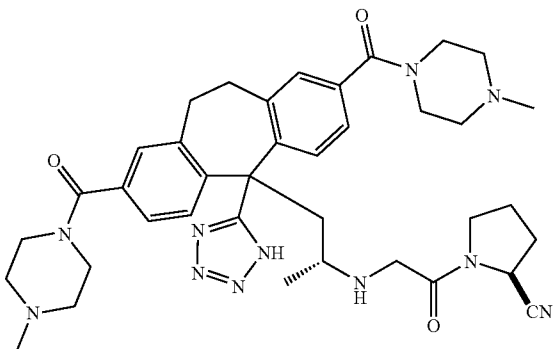
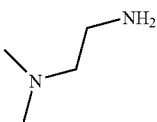
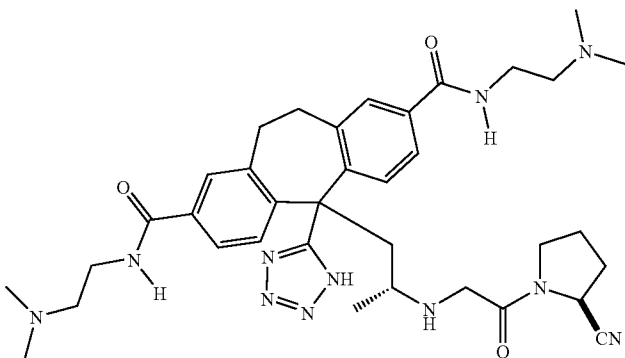
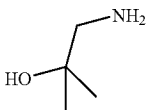
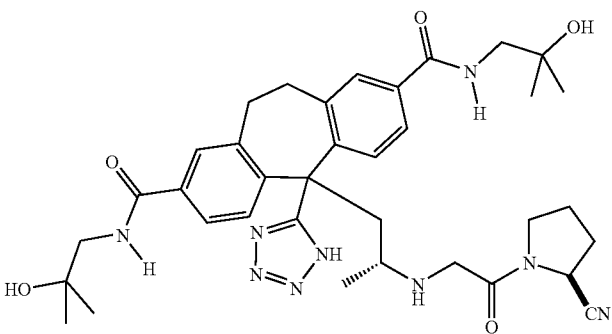
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Example #	Amine	Carboxylic Acid	Aldehyde	Product
120		Prep Ex 55	Prep Ex 2	
121		Prep Ex 55	Prep Ex 2	
122		Prep Ex 55	Prep Ex 2	
123		Prep Ex 65	Prep Ex 2	


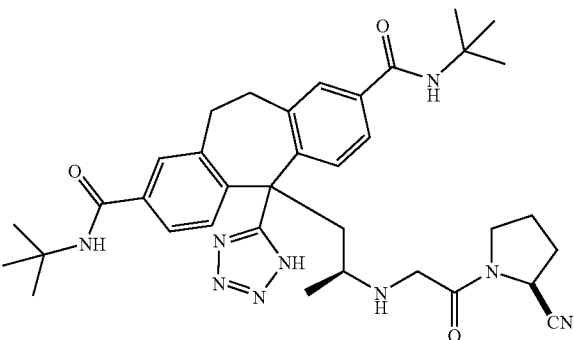
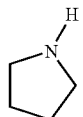
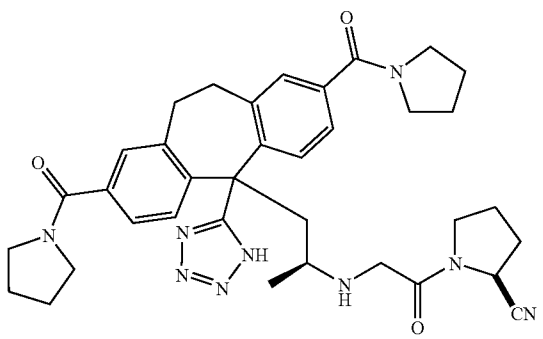
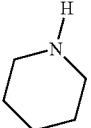
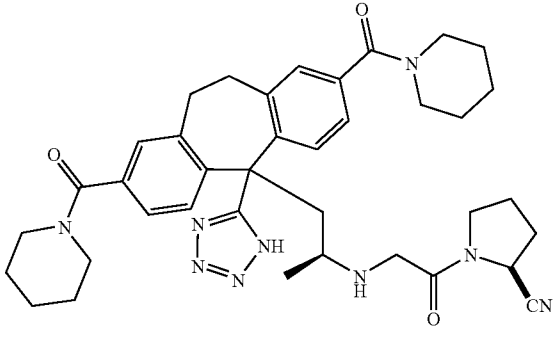
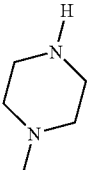
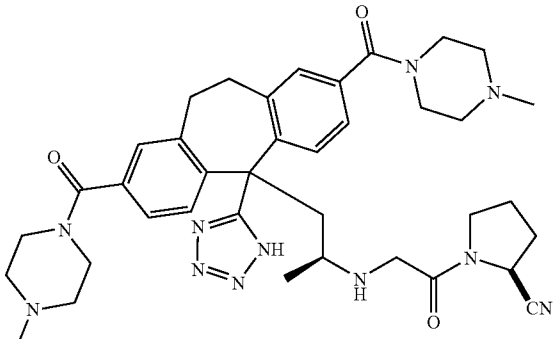
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Example #	Amine	Carboxylic Acid	Aldehyde	Product
124		Prep Ex 65	Prep Ex 2	
125		Prep Ex 65	Prep Ex 2	
126		Prep Ex 65	Prep Ex 2	
127		Prep Ex 65	Prep Ex 2	

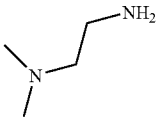
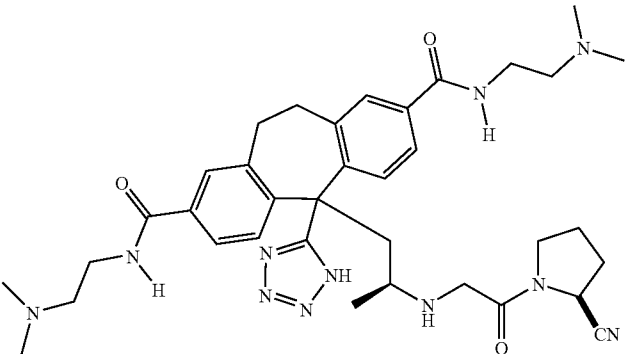
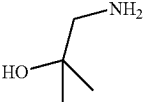
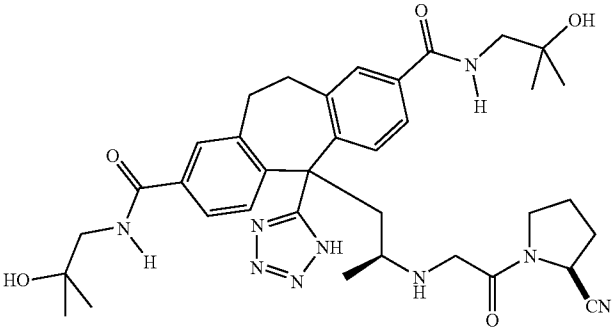
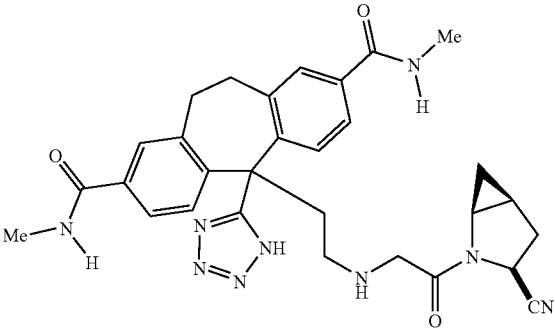
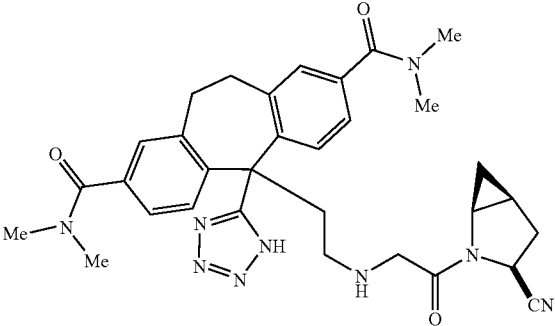
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Example #	Amine	Carboxylic Acid	Aldehyde	Product
128		Prep Ex 65	Prep Ex 2	
129		Prep Ex 65	Prep Ex 2	
130		Prep Ex 65	Prep Ex 2	
131		Prep Ex 65	Prep Ex 2	

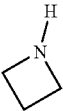
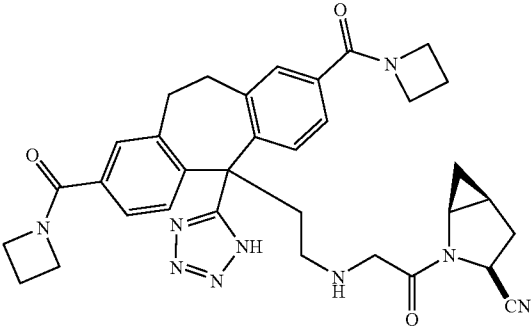
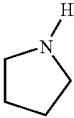
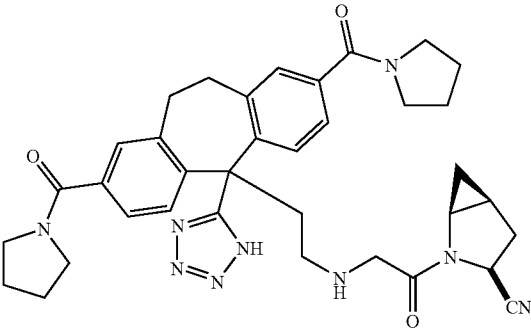
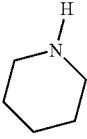
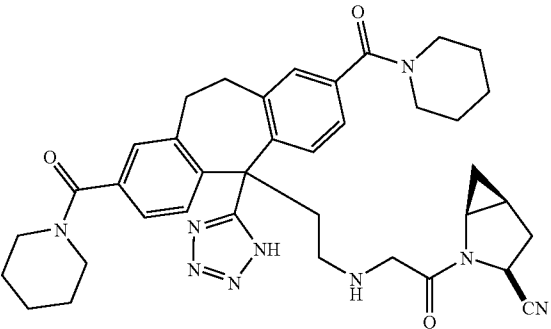
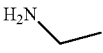
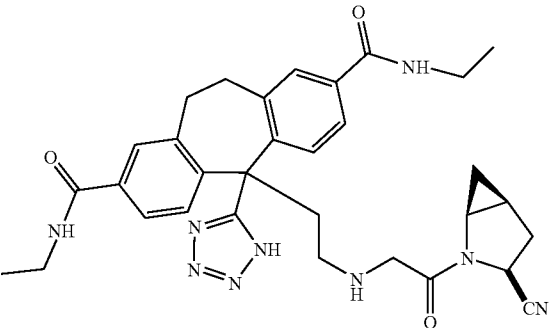
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Example #	Amine	Carboxylic Acid	Aldehyde	Product
132		Prep Ex 61	Prep Ex 2	
133		Prep Ex 61	Prep Ex 2	
134		Prep Ex 61	Prep Ex 2	
135		Prep Ex 61	Prep Ex 2	


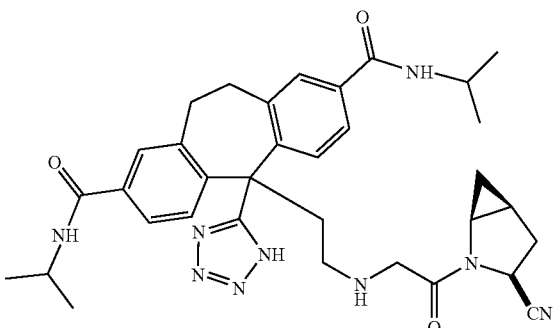

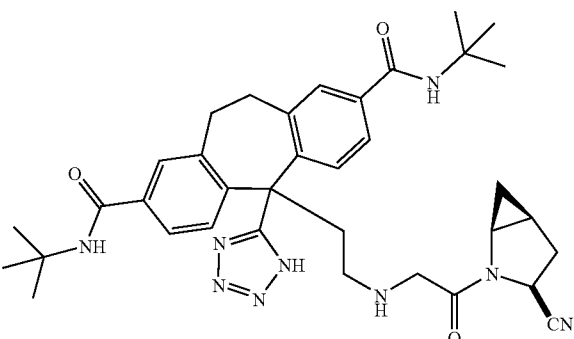
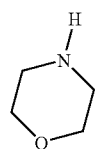
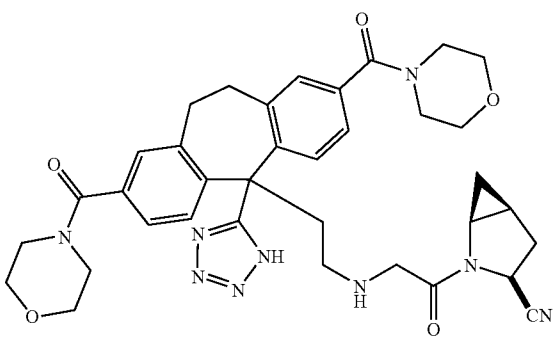
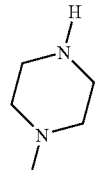
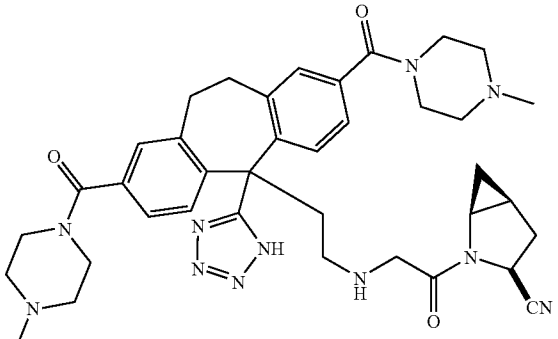
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Example #	Amine	Carboxylic Acid	Aldehyde	Product
136		Prep Ex 61	Prep Ex 2	
137		Prep Ex 61	Prep Ex 2	
138	MeNH ₂	Prep Ex 62	Prep Ex 89	
139	(Me) ₂ NH	Prep Ex 62	Prep Ex 89	

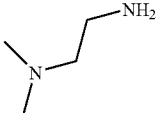
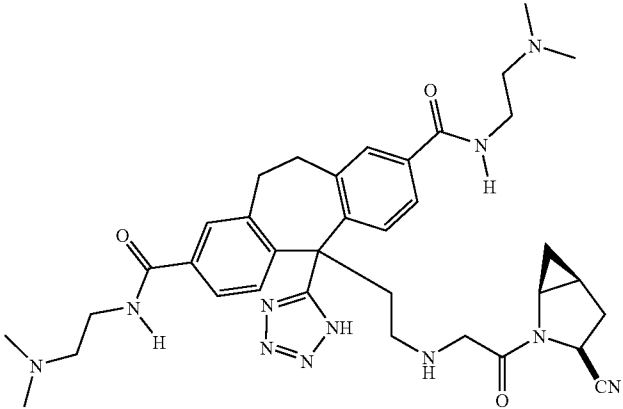
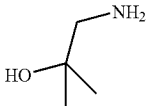
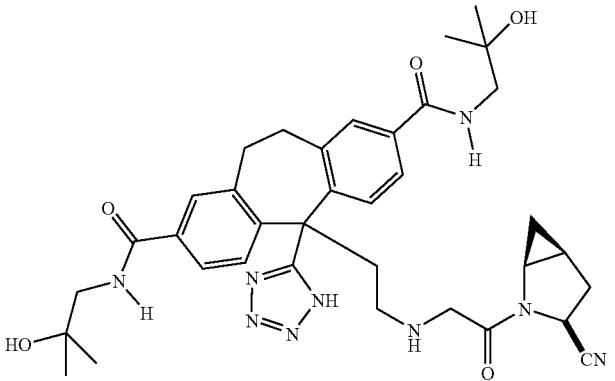
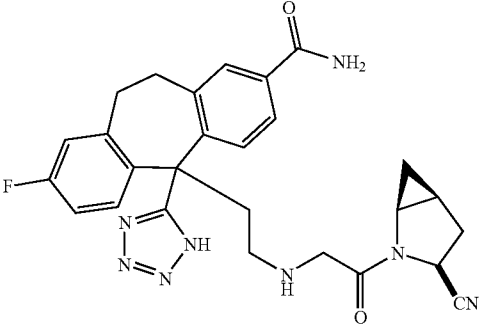
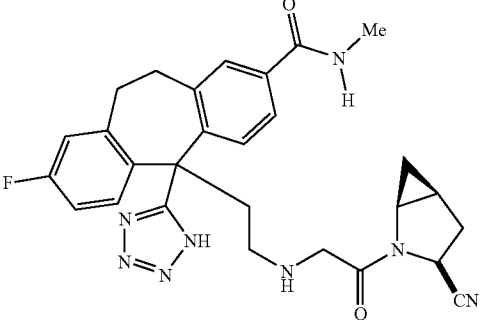
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Example #	Amine	Carboxylic Acid	Aldehyde	Product
140		Prep Ex 62	Prep Ex 89	
141		Prep Ex 62	Prep Ex 89	
142		Prep Ex 62	Prep Ex 89	
143		Prep Ex 62	Prep Ex 89	

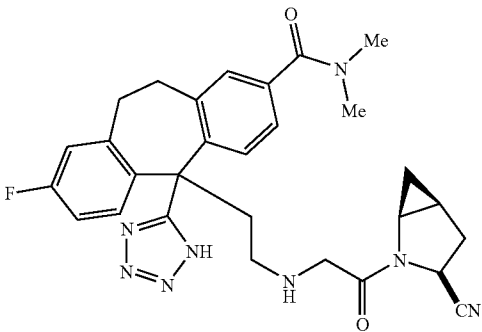
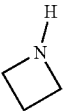
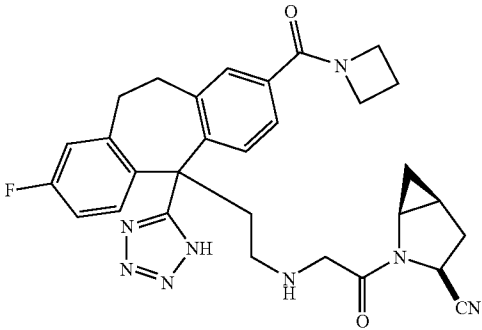
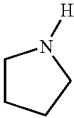
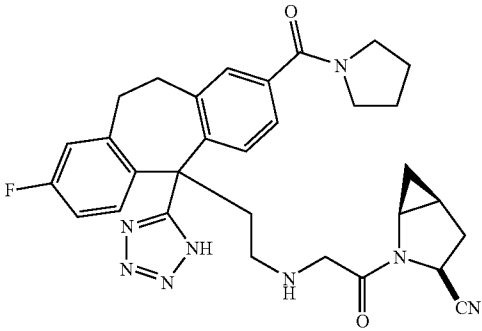
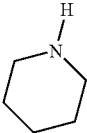
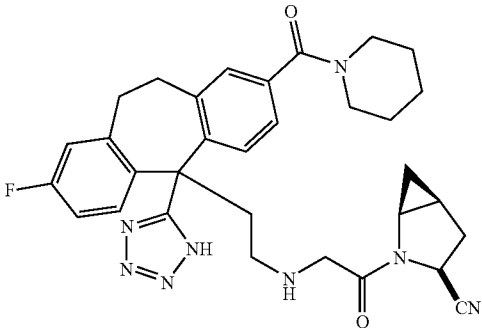
-continued

Example #	Amine	Carboxylic Acid	Aldehyde	Product
144		Prep Ex 62	Prep Ex 89	
145		Prep Ex 62	Prep Ex 89	
146		Prep Ex 62	Prep Ex 89	
147		Prep Ex 62	Prep Ex 89	


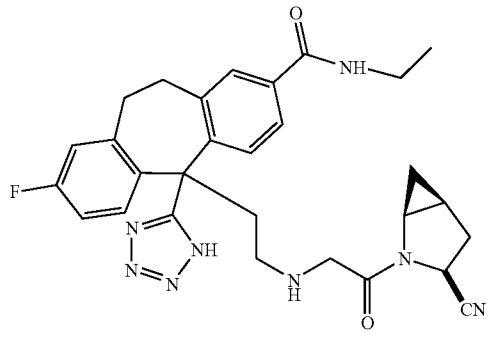

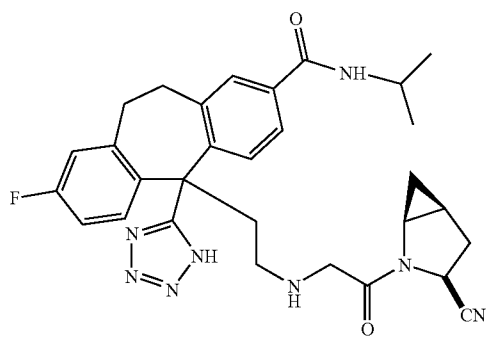
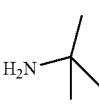
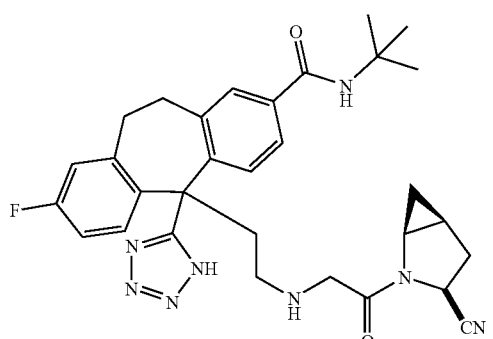
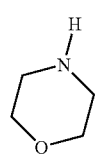
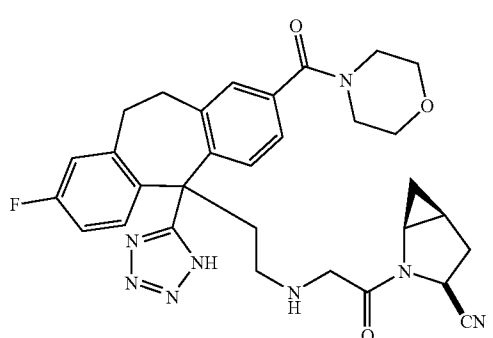
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Example #	Amine	Carboxylic Acid	Aldehyde	Product
148		Prep Ex 62	Prep Ex 89	
149		Prep Ex 62	Prep Ex 89	
150	NH ₃	Prep Ex 55	Prep Ex 89	
151	MeNH ₂	Prep Ex 55	Prep Ex 89	

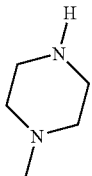
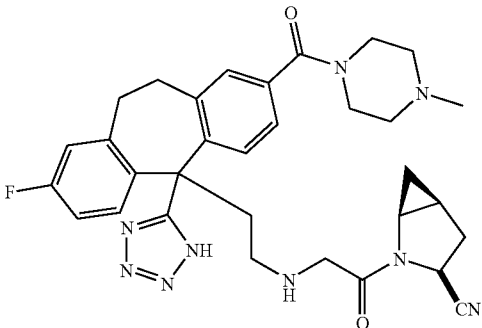
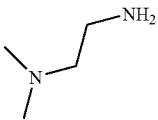
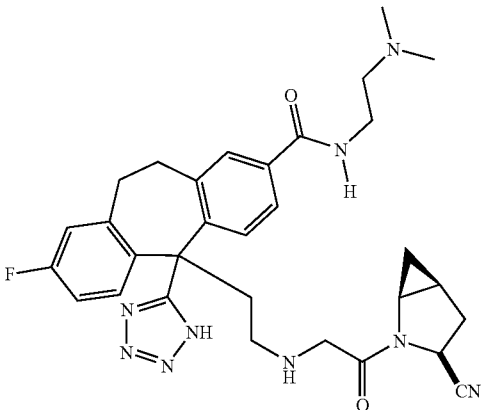
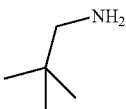
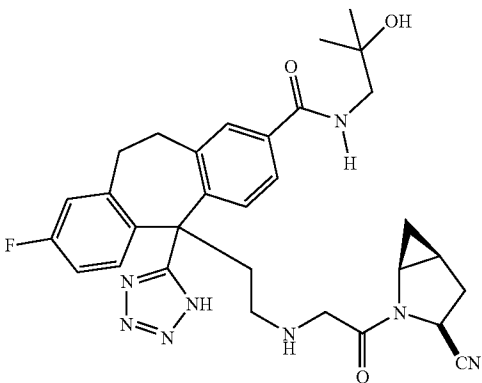
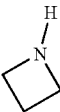
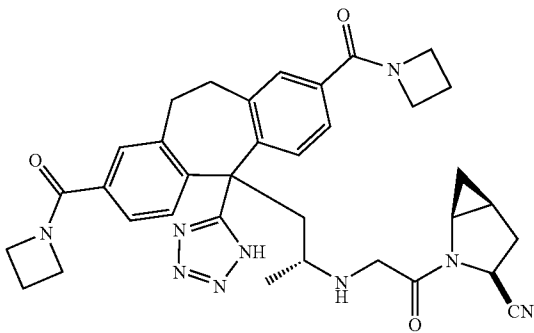
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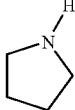
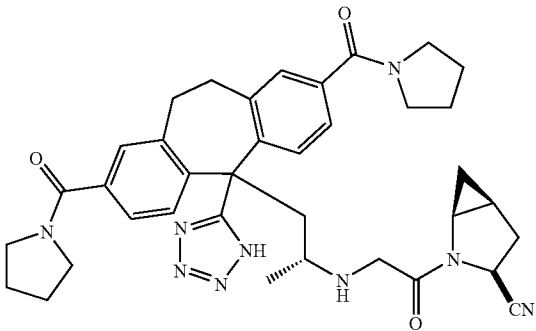
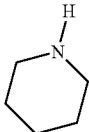
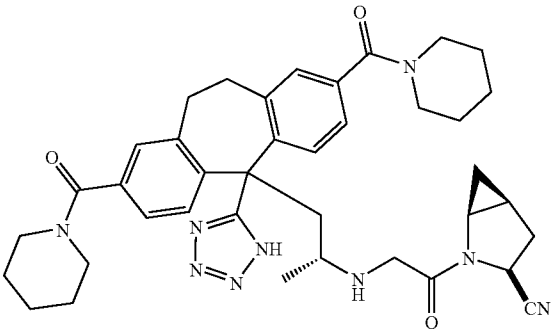
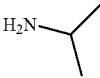
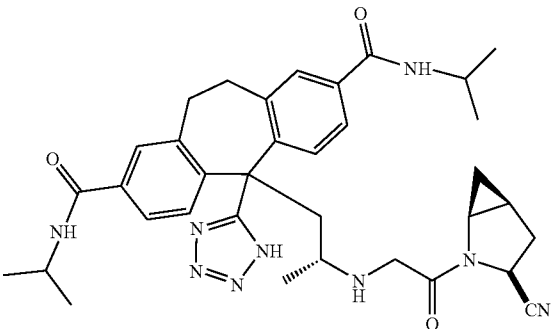
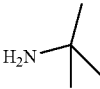
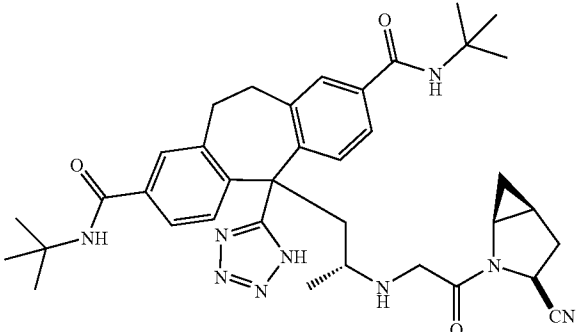
Example #	Amine	Carboxylic Acid	Aldehyde	Product
152	(Me) ₂ NH	Prep Ex 55	Prep Ex 89	
153		Prep Ex 55	Prep Ex 89	
154		Prep Ex 55	Prep Ex 89	
155		Prep Ex 55	Prep Ex 89	

-continued

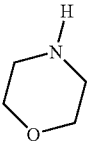
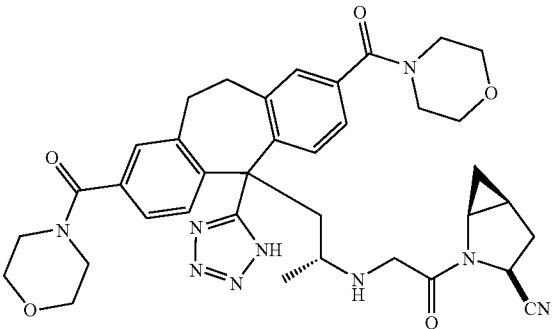
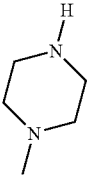
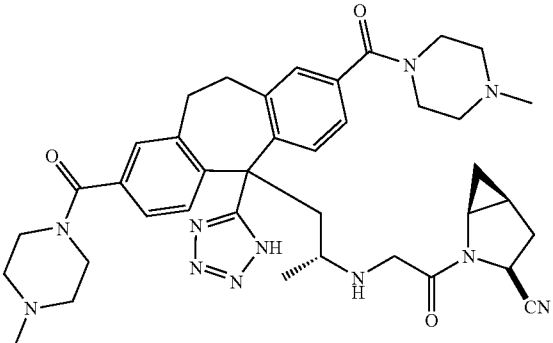
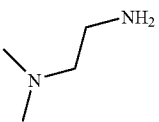
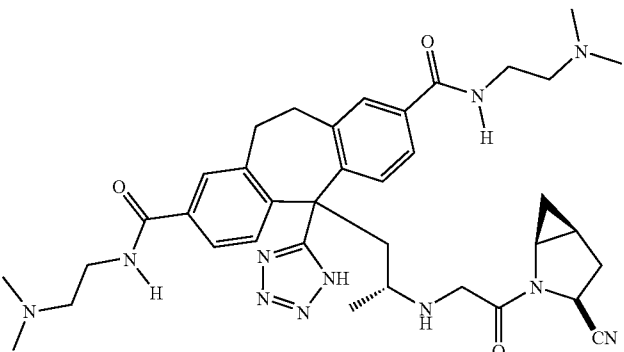
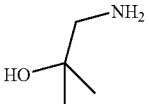
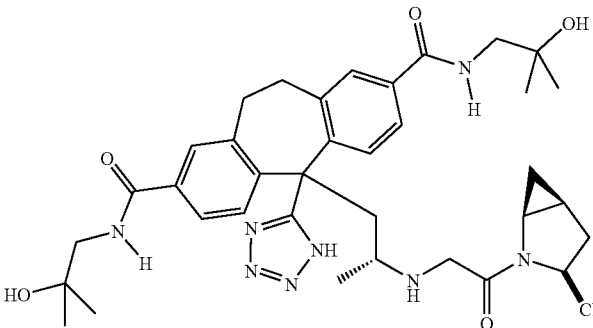
Example #	Amine	Carboxylic Acid	Aldehyde	Product
156		Prep Ex 55	Prep Ex 89	
157		Prep Ex 55	Prep Ex 89	
158		Prep Ex 55	Prep Ex 89	
159		Prep Ex 55	Prep Ex 89	

-continued

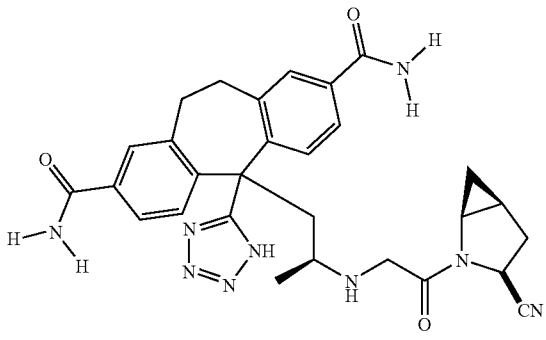
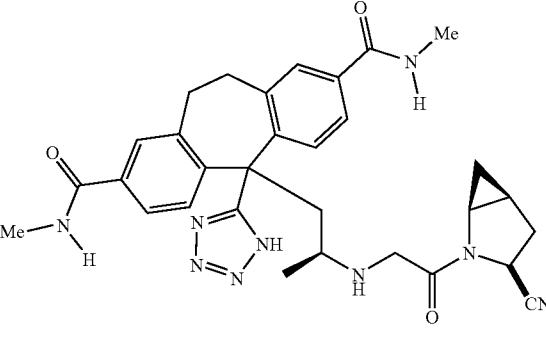
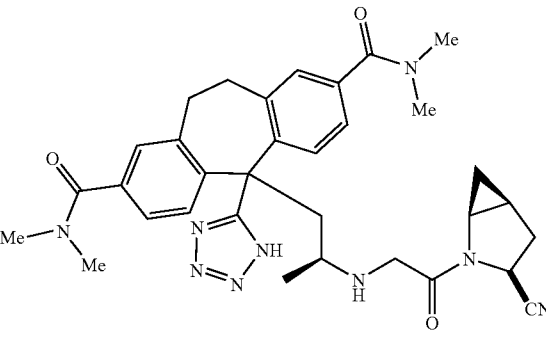
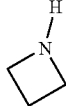
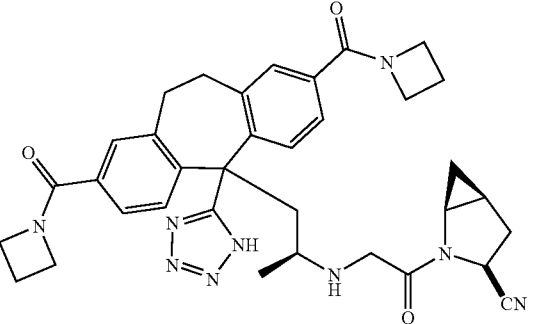
Example #	Amine	Carboxylic Acid	Aldehyde	Product
160		Prep Ex 55	Prep Ex 89	
161		Prep Ex 55	Prep Ex 89	
162		Prep Ex 55	Prep Ex 89	
163		Prep Ex 65	Prep Ex 89	

Example #	Amine	Carboxylic Acid	Aldehyde	Product
164		Prep Ex 65	Prep Ex 89	
165		Prep Ex 65	Prep Ex 89	
166		Prep Ex 65	Prep Ex 89	
167		Prep Ex 65	Prep Ex 89	

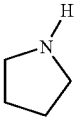
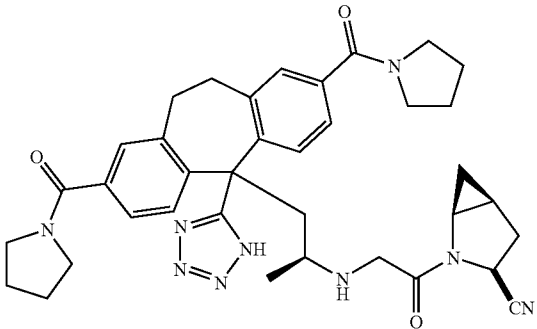
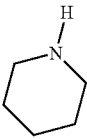
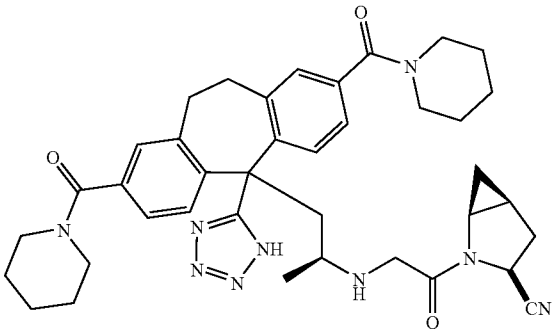
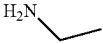
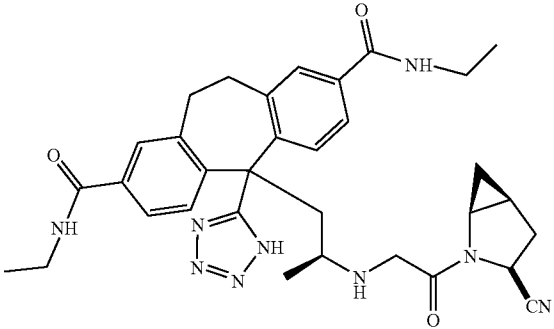
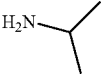
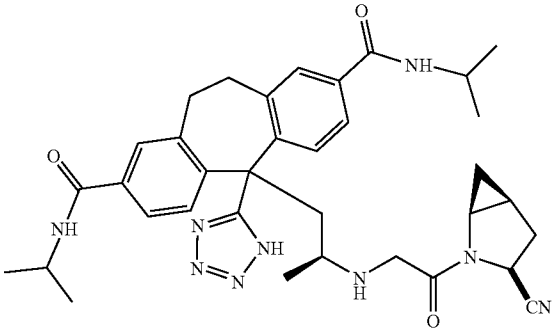
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Example #	Amine	Carboxylic Acid	Aldehyde	Product
168		Prep Ex 65	Prep Ex 89	
169		Prep Ex 65	Prep Ex 89	
170		Prep Ex 65	Prep Ex 89	
171		Prep Ex 65	Prep Ex 89	


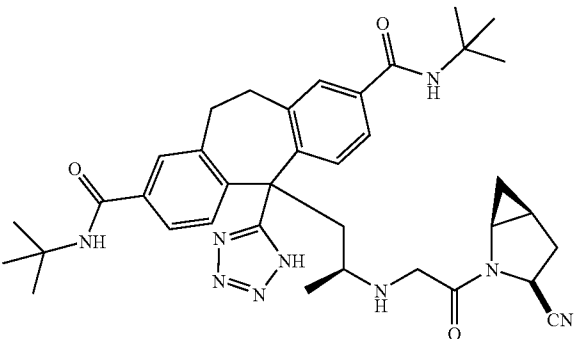
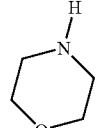
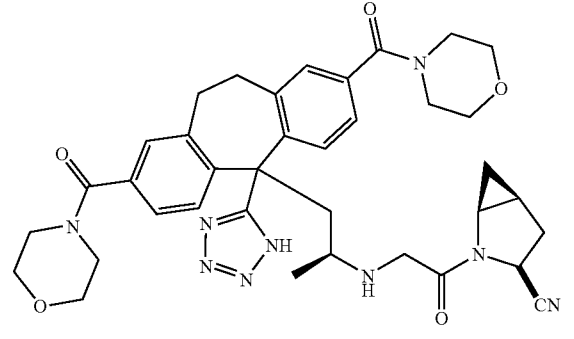
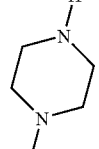
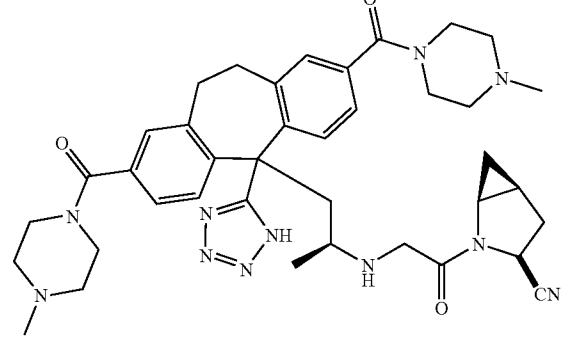
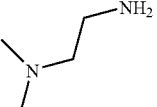
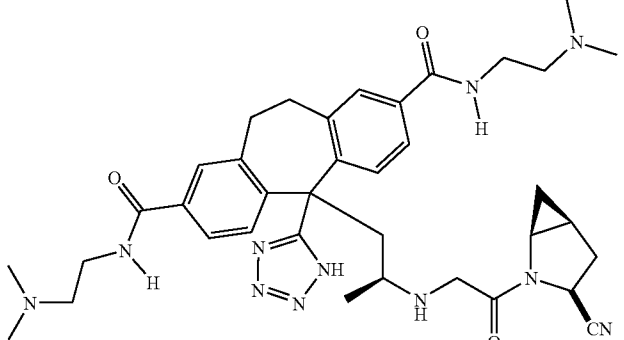
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Example #	Amine	Carboxylic Acid	Aldehyde	Product
172	NH ₃	Prep Ex 61	Prep Ex 89	
173	MeNH ₂	Prep Ex 61	Prep Ex 89	
174	(Me) ₂ NH	Prep Ex 61	Prep Ex 89	
175		Prep Ex 61	Prep Ex 89	

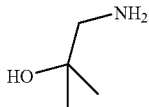
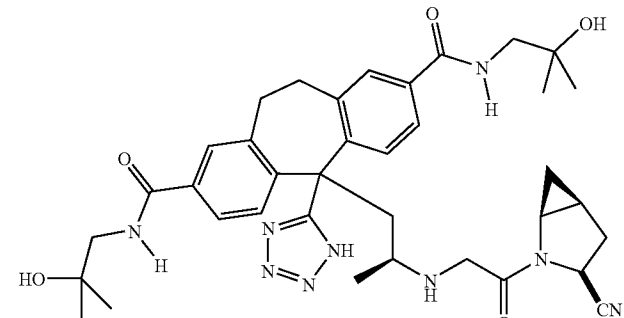
-continued

Example #	Amine	Carboxylic Acid	Aldehyde	Product
176		Prep Ex 61	Prep Ex 89	
177		Prep Ex 61	Prep Ex 89	
178		Prep Ex 61	Prep Ex 89	
179		Prep Ex 61	Prep Ex 89	

-continued

Example #	Amine	Carboxylic Acid	Aldehyde	Product
180		Prep Ex 61	Prep Ex 89	
181		Prep Ex 61	Prep Ex 89	
182		Prep Ex 61	Prep Ex 89	
183		Prep Ex 61	Prep Ex 89	

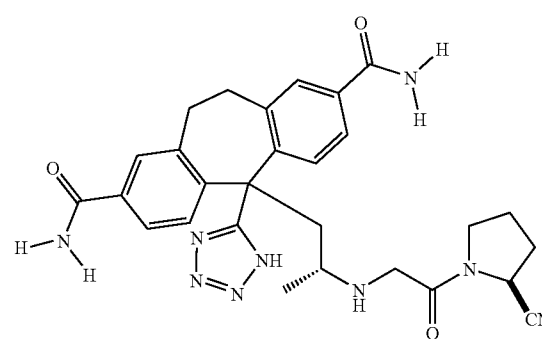
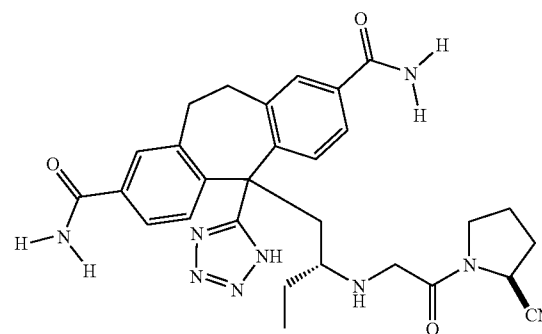
-continued

Example #	Amine	Carboxylic Acid	Aldehyde	Product
184		Prep Ex 61	Prep Ex 89	

[0852] Examples 185-199 have been intentionally excluded.

Example 200-389

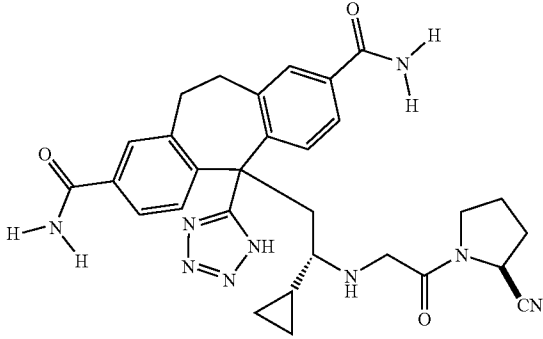
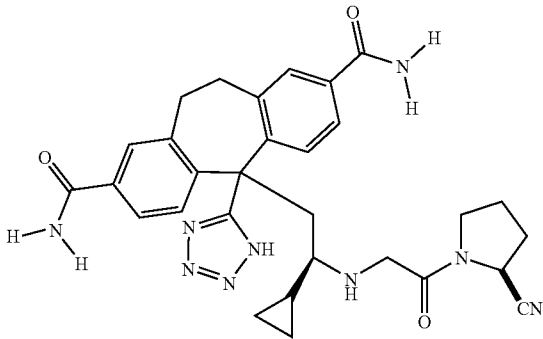
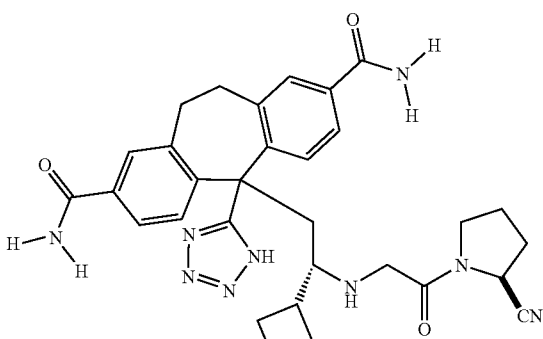
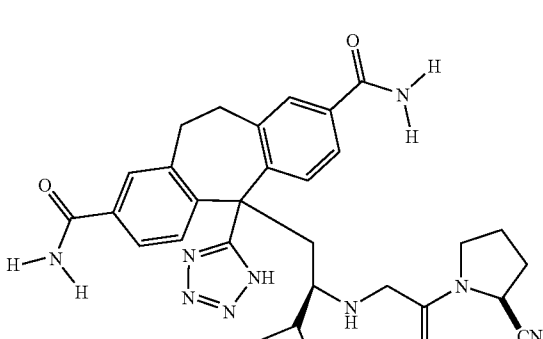
[0853] If one were to follow the procedures outlined in Examples 28 or 29 except using the compounds from the Preparative Examples as indicated in the Table below, one would obtain the indicated Product.

Example	Preparative Example	Preparative Example	Product
200	200	2	
201	201	2	

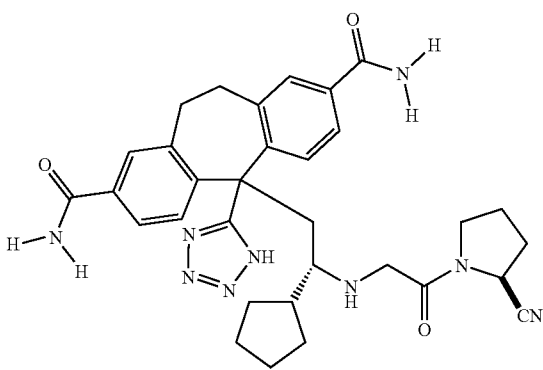
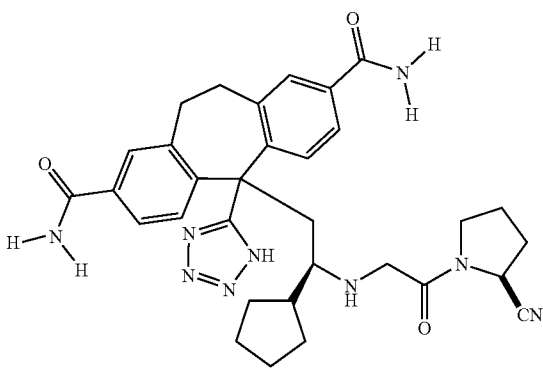
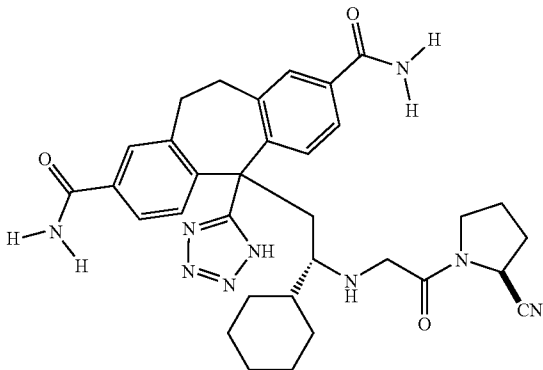
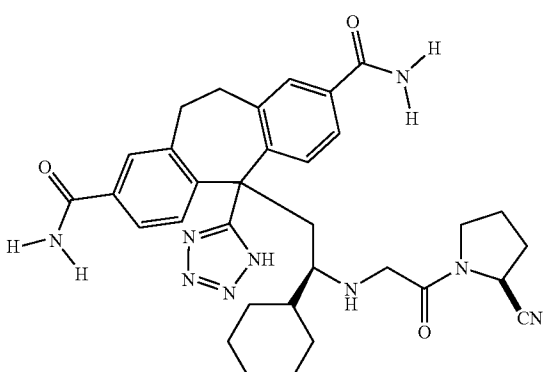
-continued

Example	Preparative Example	Preparative Example	Product
202	202	2	
203	203	2	
204	204	2	
205	205	2	

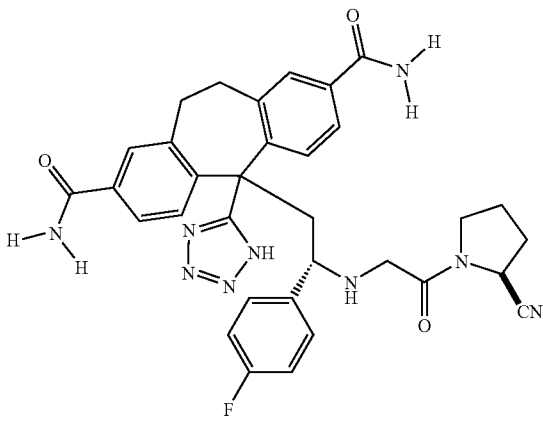
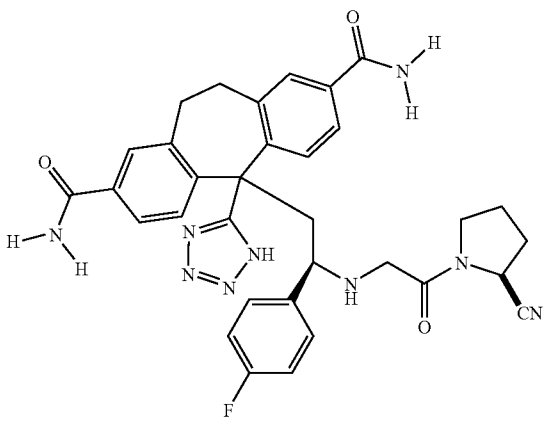
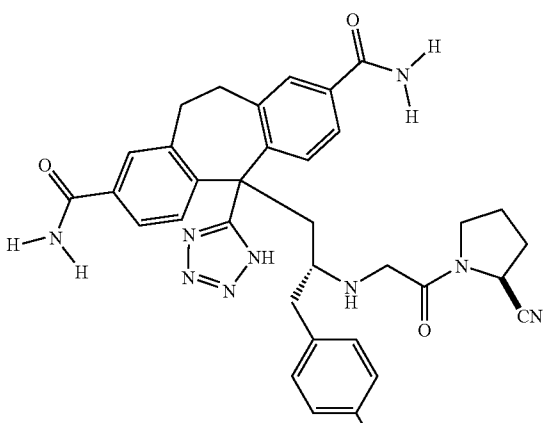
-continued

Example	Preparative Example	Preparative Example	Product
206	206	2	
207	207	2	
208	208	2	
209	209	2	

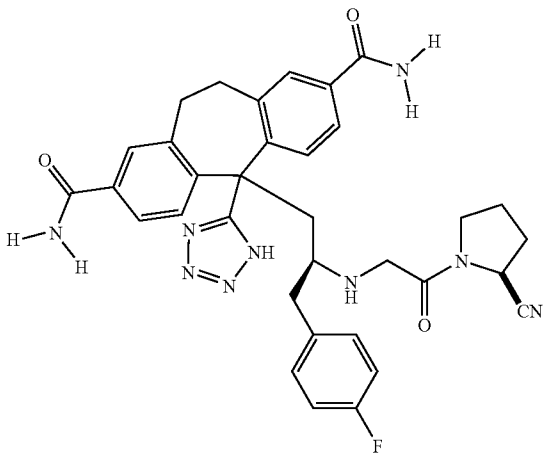
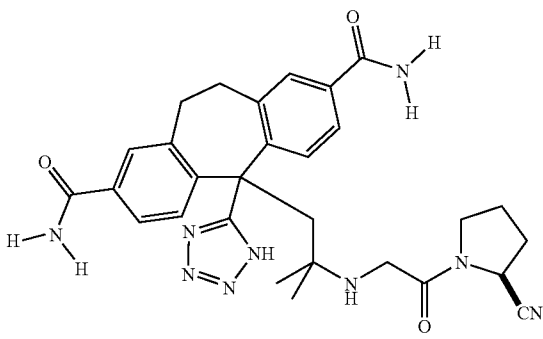
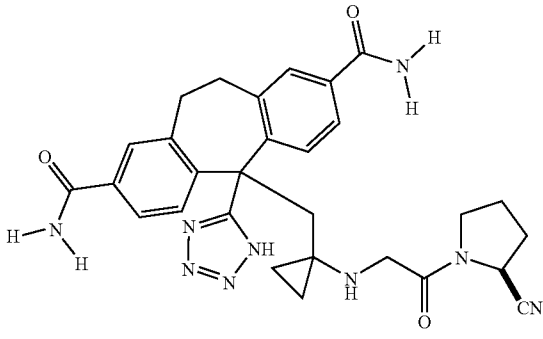
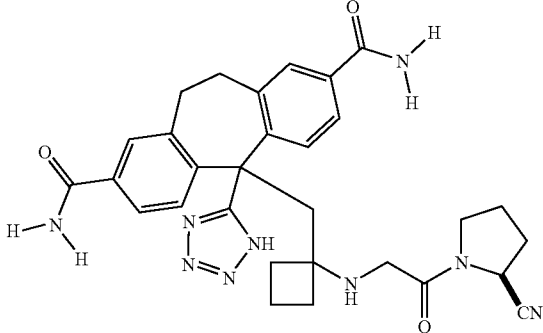
-continued

Example	Preparative Example	Preparative Example	Product
210	210	2	
211	211	2	
212	212	2	
213	213	2	

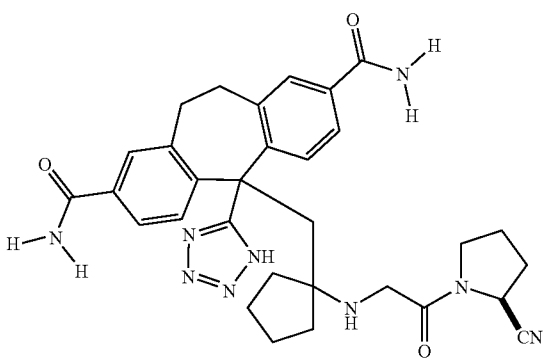
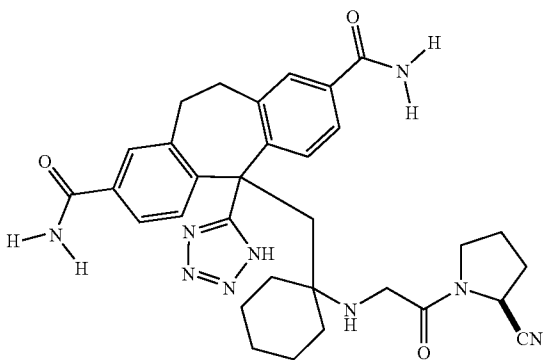
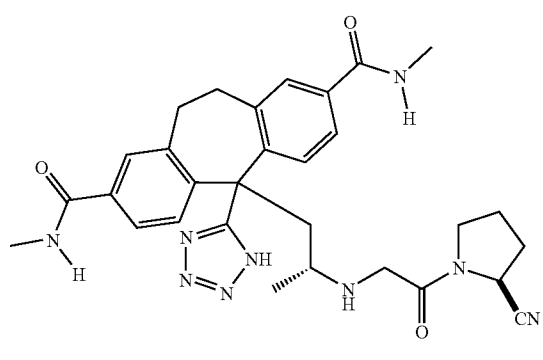
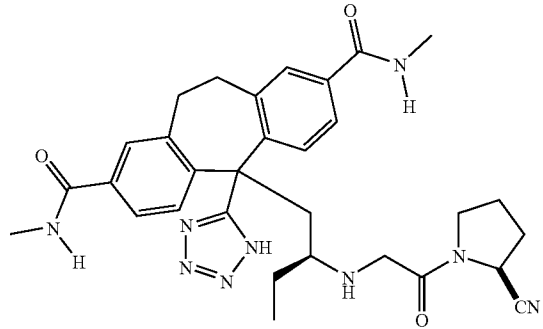
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Example	Preparative Example	Preparative Example	Product
214	214	2	
215	215	2	
216	216	2	

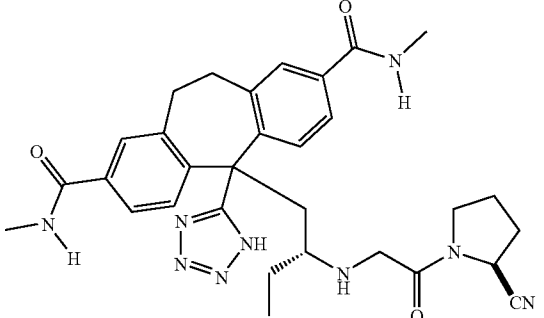
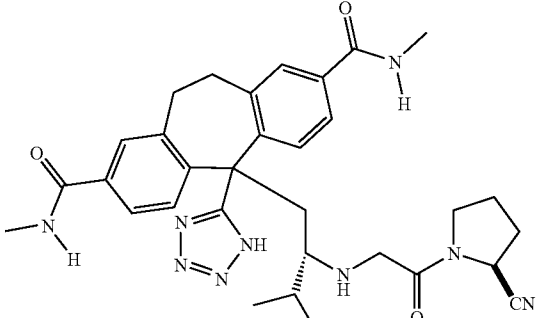
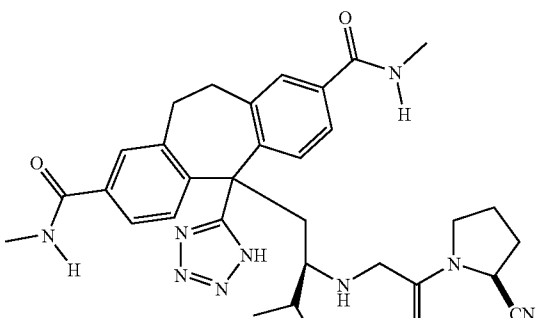
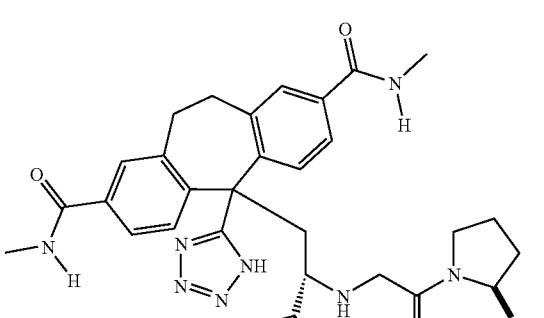
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Example	Preparative Example	Preparative Example	Product
217	217	2	
218	218	2	
219	219	2	
220	220	2	

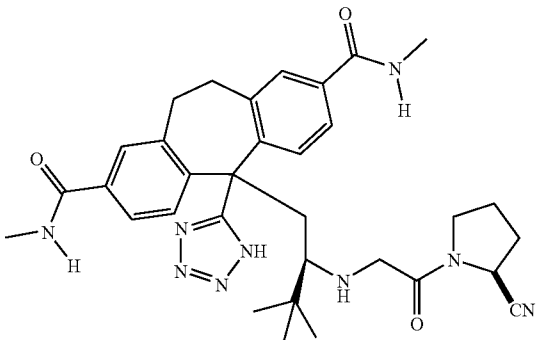
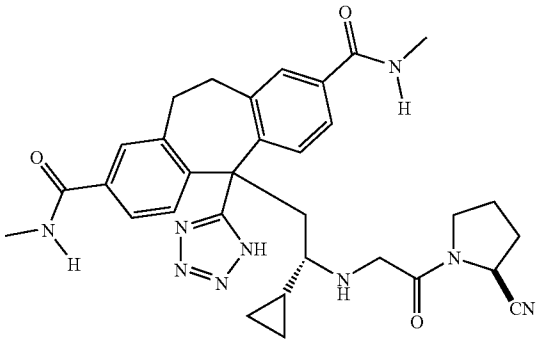
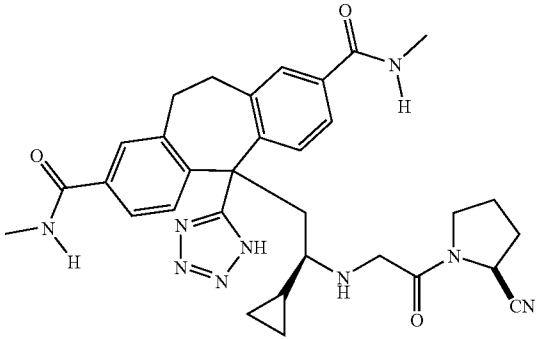
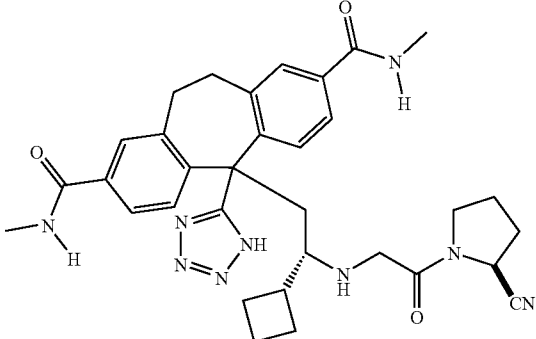
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Example	Preparative Example	Preparative Example	Product
221	221	2	
222	222	2	
223	223	2	
224	224	2	

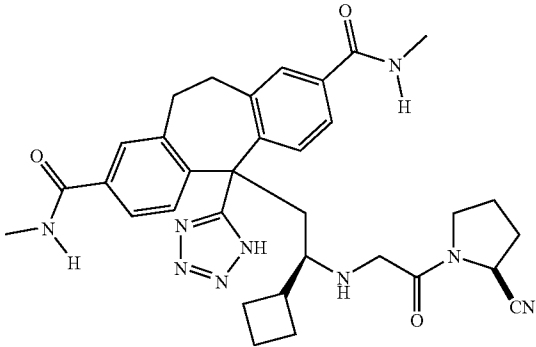
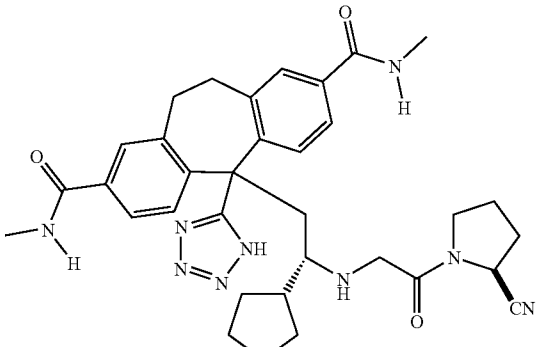
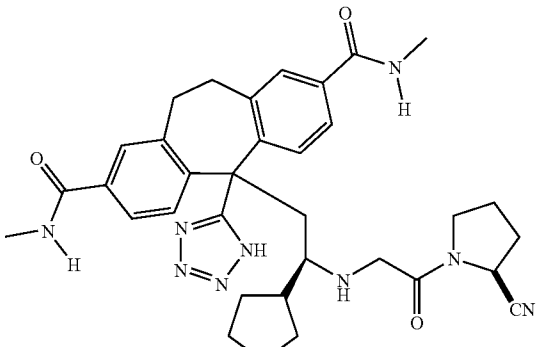
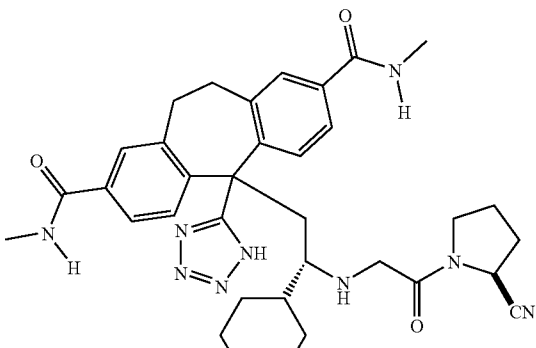
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Example	Preparative Example	Preparative Example	Product
225	225	2	
226	226	2	
227	227	2	
228	228	2	

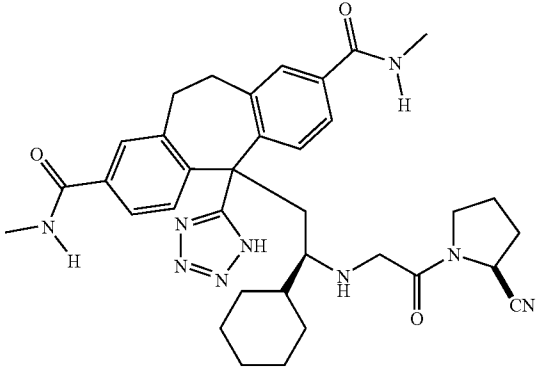
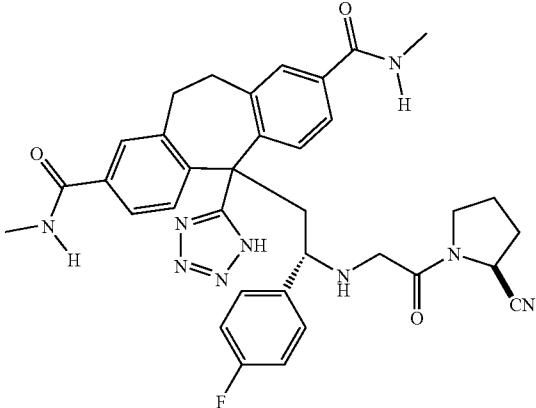
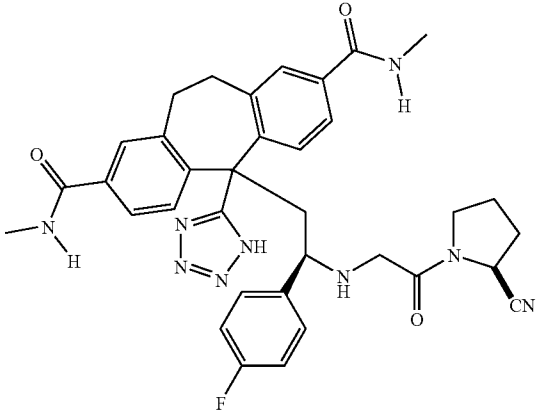
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Example	Preparative Example	Preparative Example	Product
229	229	2	
230	230	2	
231	231	2	
232	232	2	

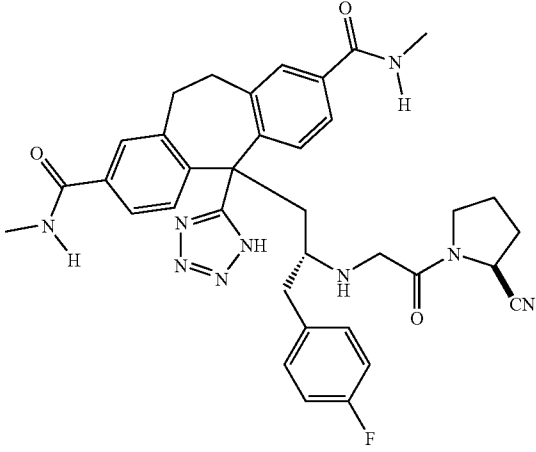
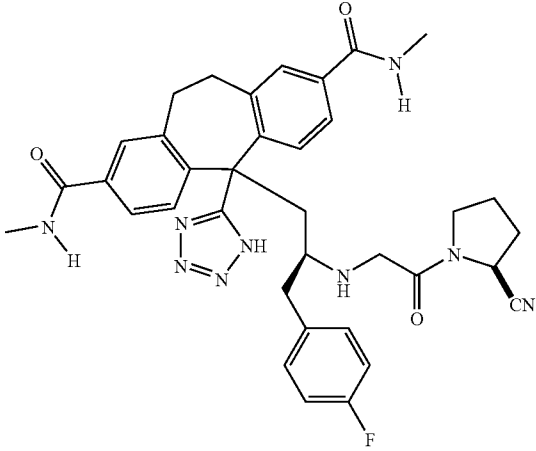
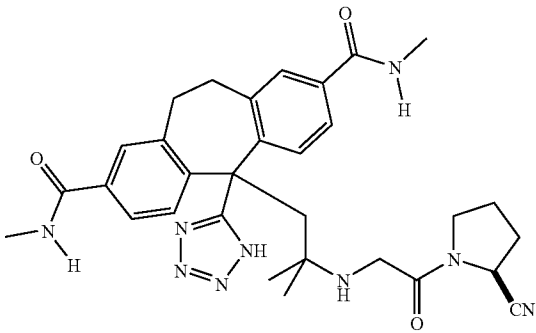
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Example	Preparative Example	Preparative Example	Product
233	233	2	
234	234	2	
235	235	2	
236	236	2	

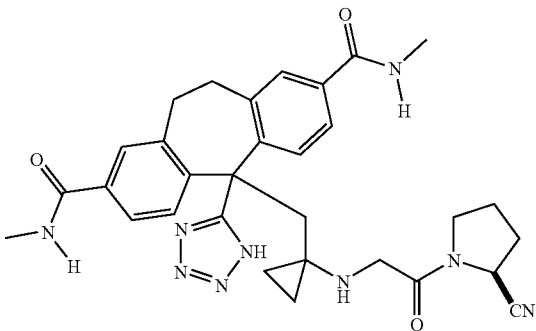
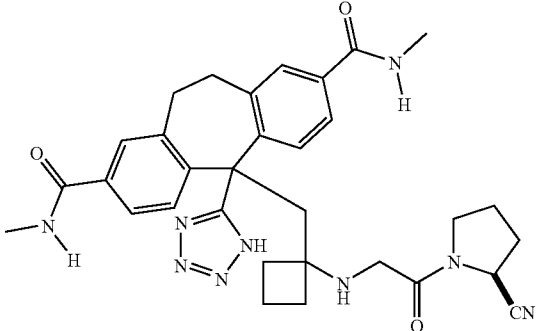
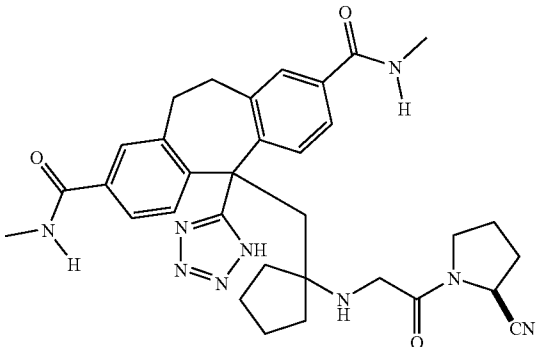
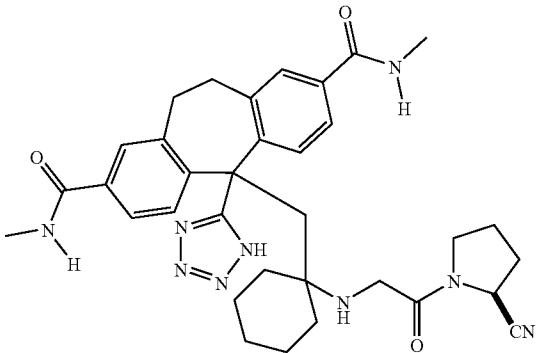
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Example	Preparative Example	Preparative Example	Product
237	237	2	
238	238	2	
239	239	2	

-continued

Example	Preparative Example	Preparative Example	Product
240	240	2	
241	241	2	
242	242	2	

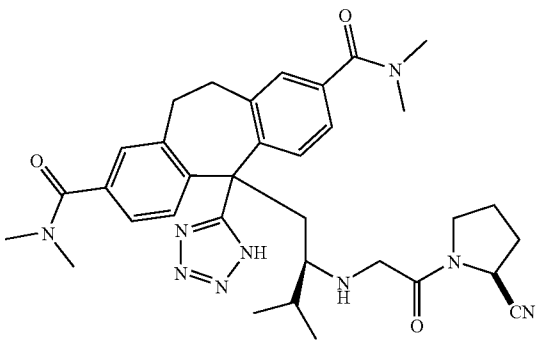
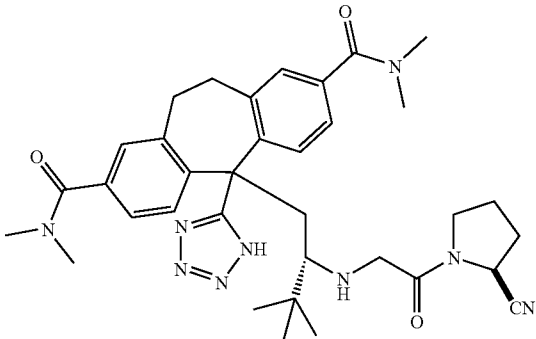
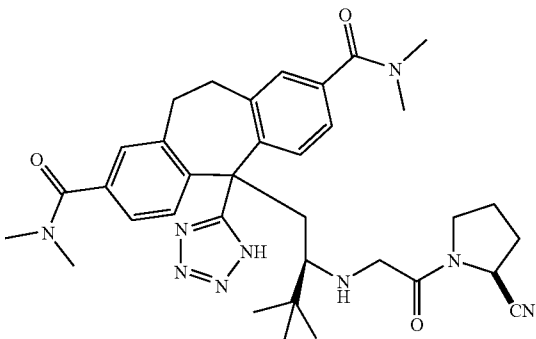
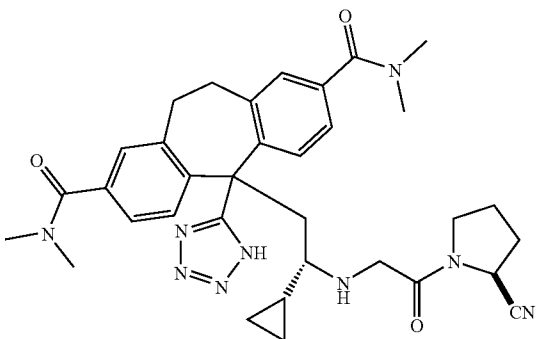
-continued

Example	Preparative Example	Preparative Example	Product
243	243	2	
244	244	2	
245	245	2	
246	246	2	

-continued

Example	Preparative Example	Preparative Example	Product
247	247	2	
248	248	2	
249	249	2	
250	250	2	

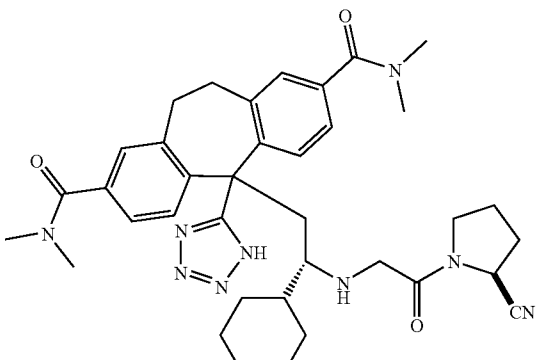
-continued

Example	Preparative Example	Preparative Example	Product
251	251	2	
252	252	2	
253	253	2	
254	254	2	

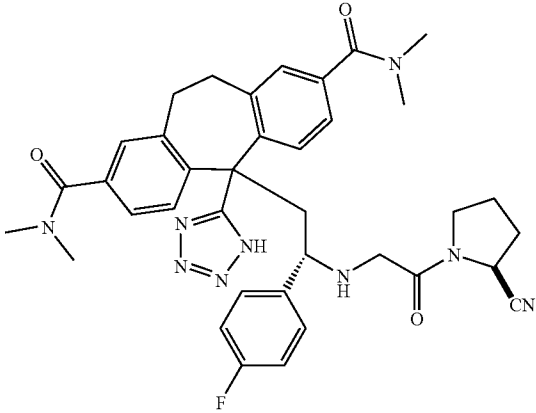
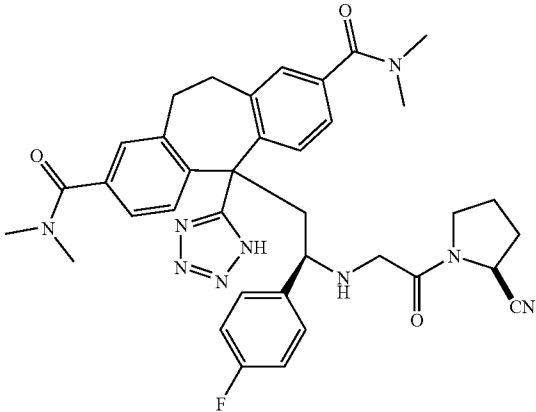
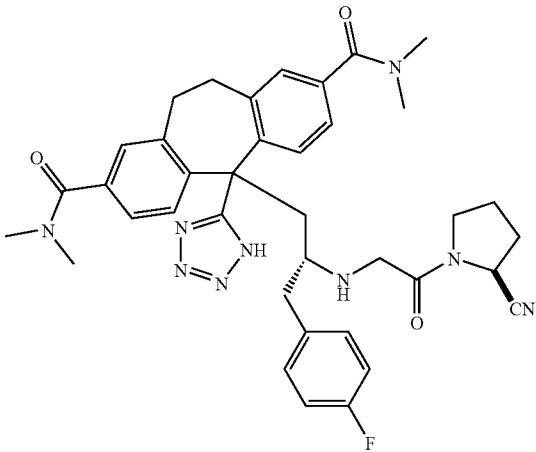
-continued

Example	Preparative Example	Preparative Example	Product
255	255	2	
256	256	2	
257	257	2	
258	258	2	

-continued

Example	Preparative Example	Preparative Example	Product
259	259	2	
260	260	2	
261	261	2	

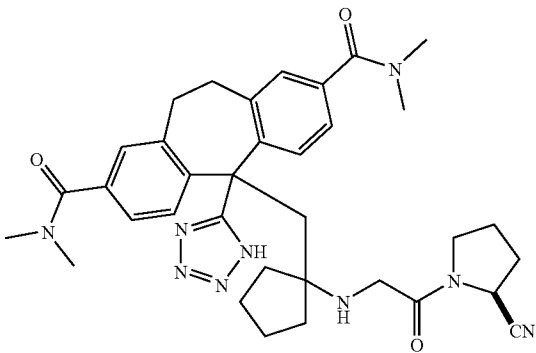
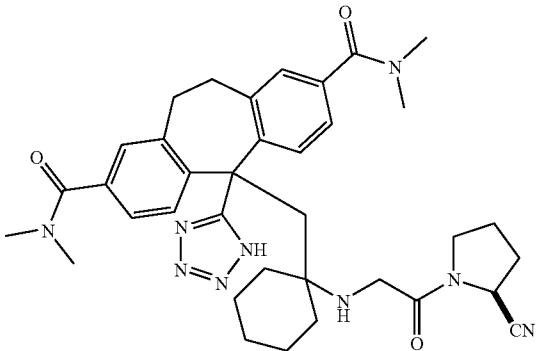
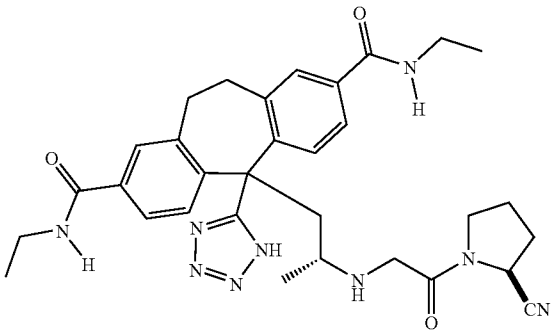
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Example	Preparative Example	Preparative Example	Product
262	262	2	 <p>Chemical structure of compound 262: A complex molecule featuring a central benzotriazole core. The benzotriazole ring is substituted with a dimethylamino group (-N(CH₃)₂) at the 2-position and a 4-fluorophenyl group at the 4-position. The benzotriazole ring is also connected to a 4-(dimethylamino)phenyl group at the 5-position. The 4-fluorophenyl group is further substituted with a dimethylamino group (-N(CH₃)₂) at the 2-position. The 4-(dimethylamino)phenyl group is connected to a 4-fluorophenyl group at the 5-position. The 4-fluorophenyl group is further substituted with a dimethylamino group (-N(CH₃)₂) at the 2-position. The 4-(dimethylamino)phenyl group is connected to a 4-fluorophenyl group at the 5-position. The 4-fluorophenyl group is further substituted with a dimethylamino group (-N(CH₃)₂) at the 2-position.</p>
263	263	2	 <p>Chemical structure of compound 263: A complex molecule featuring a central benzotriazole core. The benzotriazole ring is substituted with a dimethylamino group (-N(CH₃)₂) at the 2-position and a 4-fluorophenyl group at the 4-position. The benzotriazole ring is also connected to a 4-(dimethylamino)phenyl group at the 5-position. The 4-fluorophenyl group is further substituted with a dimethylamino group (-N(CH₃)₂) at the 2-position. The 4-(dimethylamino)phenyl group is connected to a 4-fluorophenyl group at the 5-position. The 4-fluorophenyl group is further substituted with a dimethylamino group (-N(CH₃)₂) at the 2-position. The 4-(dimethylamino)phenyl group is connected to a 4-fluorophenyl group at the 5-position. The 4-fluorophenyl group is further substituted with a dimethylamino group (-N(CH₃)₂) at the 2-position.</p>
264	264	2	 <p>Chemical structure of compound 264: A complex molecule featuring a central benzotriazole core. The benzotriazole ring is substituted with a dimethylamino group (-N(CH₃)₂) at the 2-position and a 4-fluorophenyl group at the 4-position. The benzotriazole ring is also connected to a 4-(dimethylamino)phenyl group at the 5-position. The 4-fluorophenyl group is further substituted with a dimethylamino group (-N(CH₃)₂) at the 2-position. The 4-(dimethylamino)phenyl group is connected to a 4-fluorophenyl group at the 5-position. The 4-fluorophenyl group is further substituted with a dimethylamino group (-N(CH₃)₂) at the 2-position. The 4-(dimethylamino)phenyl group is connected to a 4-fluorophenyl group at the 5-position. The 4-fluorophenyl group is further substituted with a dimethylamino group (-N(CH₃)₂) at the 2-position.</p>

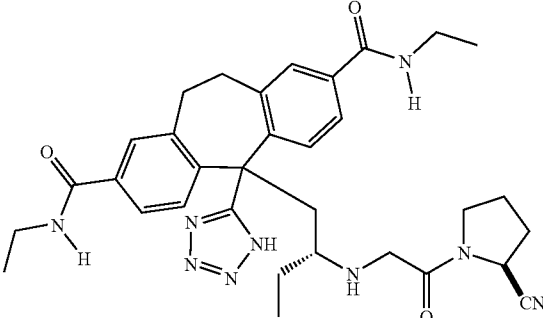
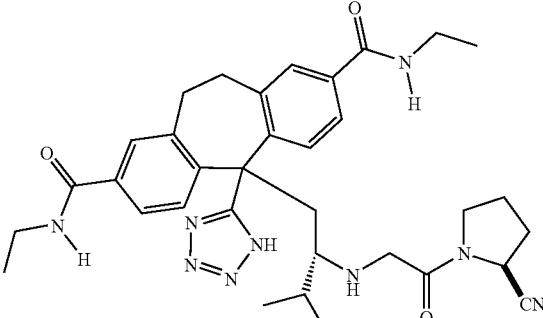
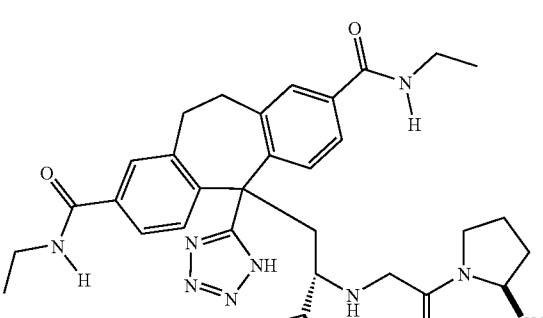
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Example	Preparative Example	Preparative Example	Product
265	265	2	
266	266	2	
267	267	2	
268	268	2	

-continued

Example	Preparative Example	Preparative Example	Product
269	269	2	
270	270	2	
271	271	2	
272	272	2	

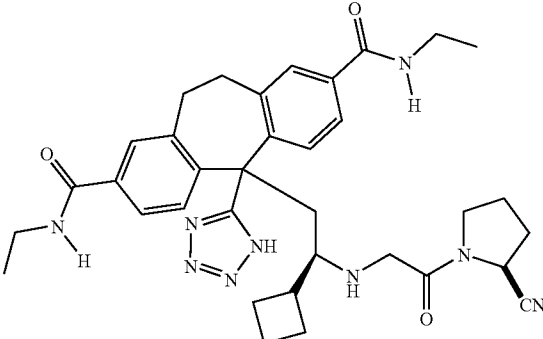
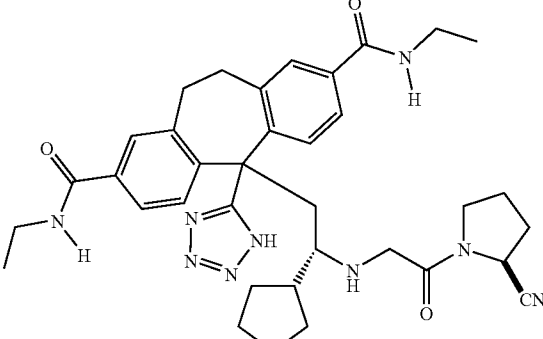
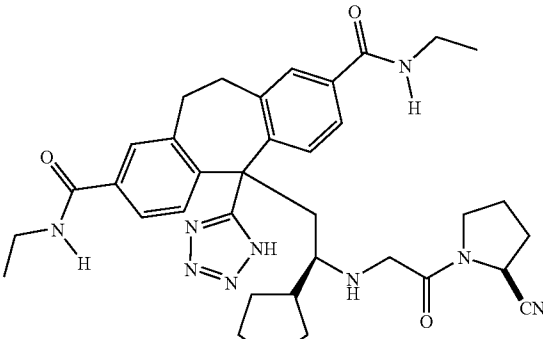
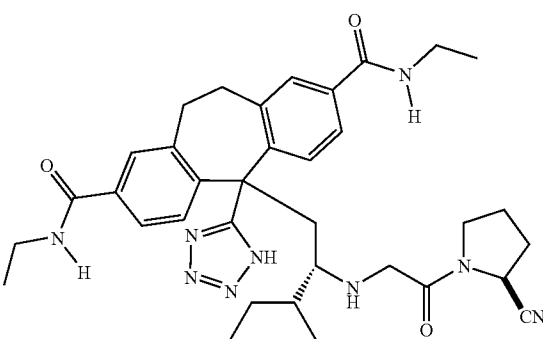
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Example	Preparative Example	Preparative Example	Product
273	273	2	
274	274	2	
275	275	2	
276	276	2	

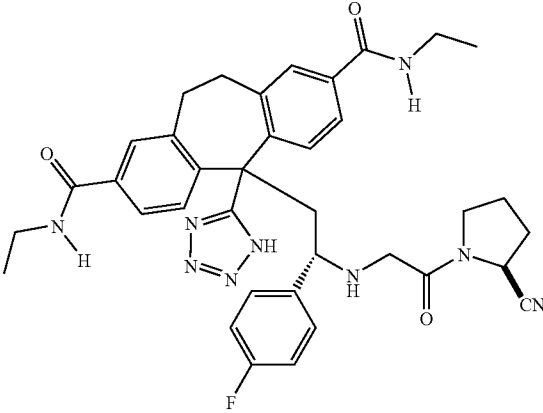
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Example	Preparative Example	Preparative Example	Product
277	277	2	
278	278	2	
279	279	2	
280	280	2	

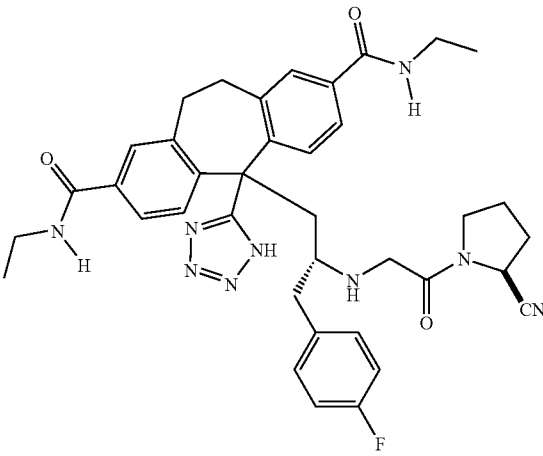
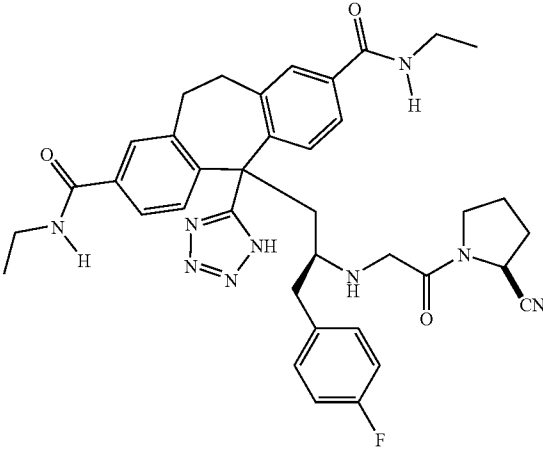
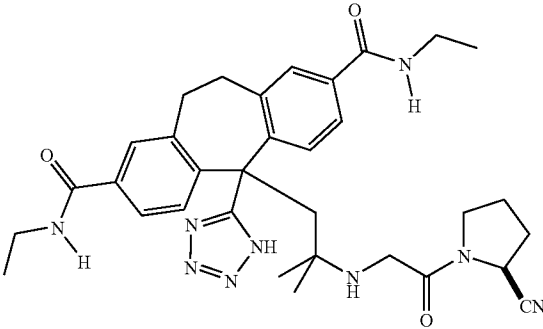
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Example	Preparative Example	Preparative Example	Product
281	281	2	
282	282	2	
283	283	2	
284	284	2	

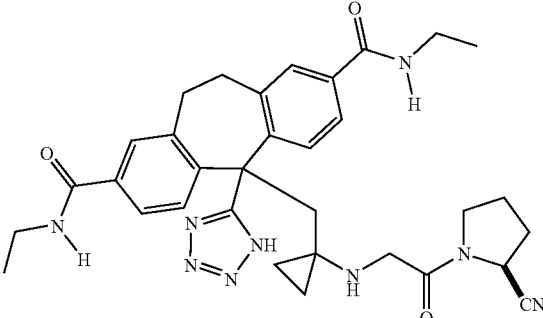
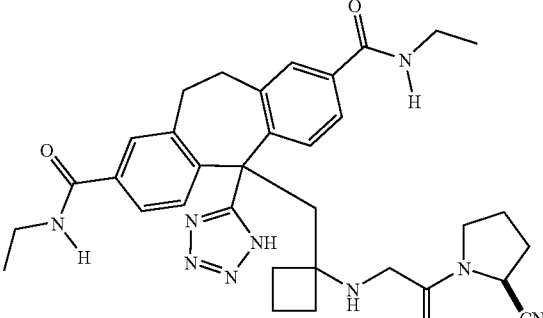
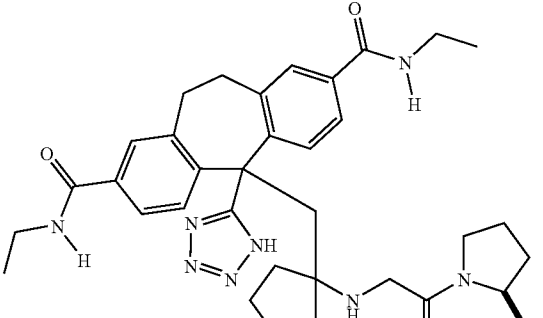
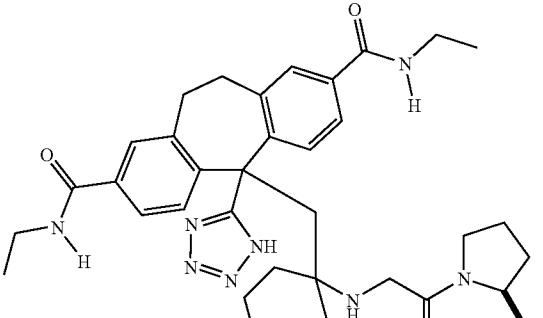
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Example	Preparative Example	Preparative Example	Product
285	285	2	
286	286	2	
287	287	2	

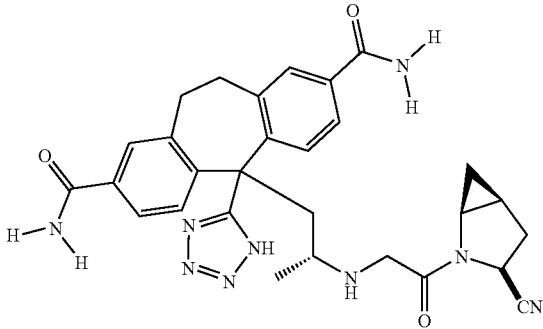
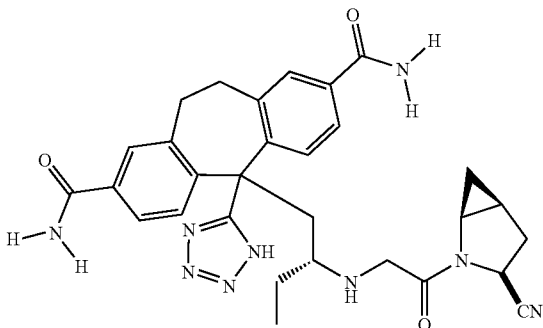
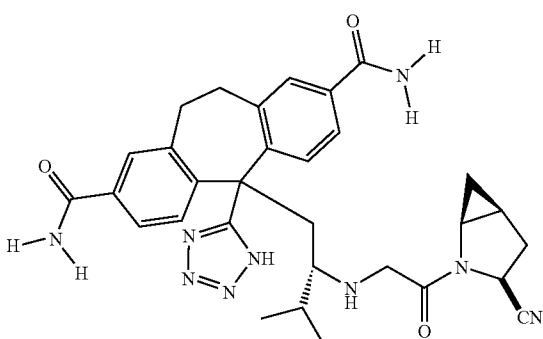
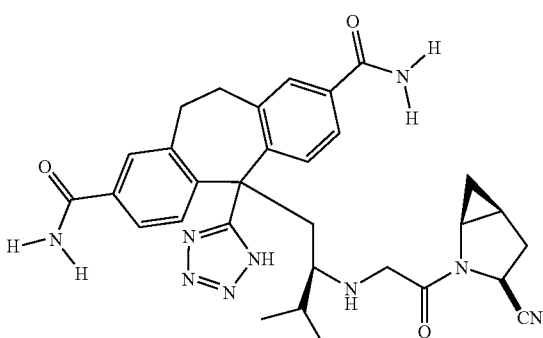
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Example	Preparative Example	Preparative Example	Product
288	288	2	
289	289	2	
290	290	2	

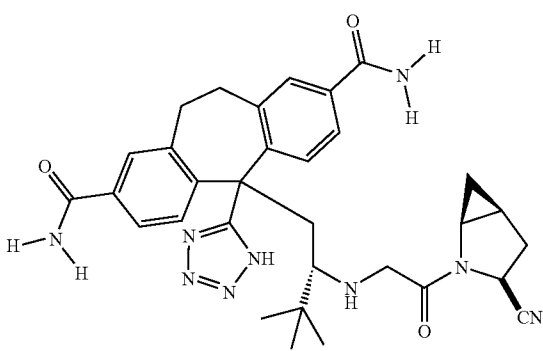
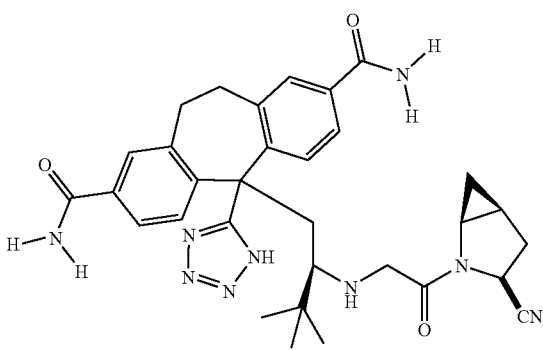
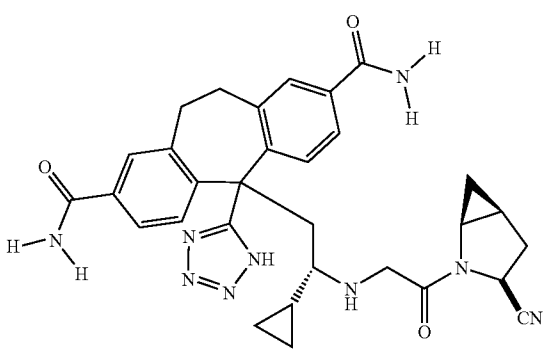
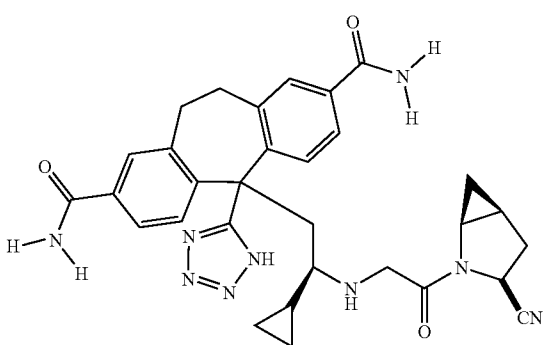
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Example	Preparative Example	Preparative Example	Product
291	291	2	
292	292	2	
293	293	2	
294	294	2	

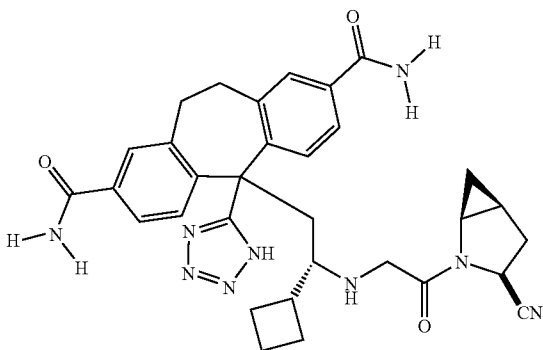
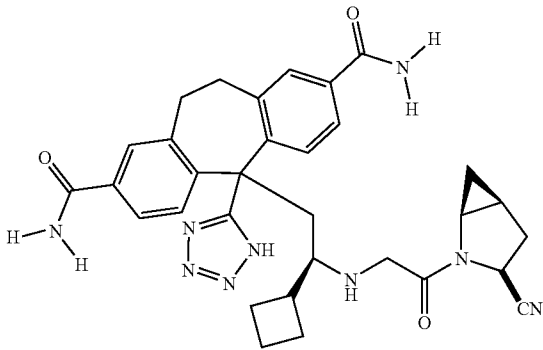
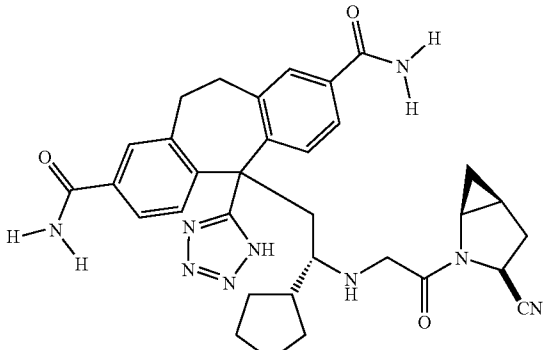
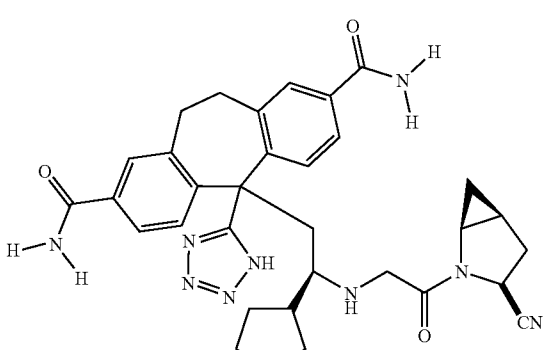
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Example	Preparative Example	Preparative Example	Product
295	200	89	
296	201	89	
297	202	89	
298	203	89	

-continued

Example	Preparative Example	Preparative Example	Product
299	204	89	
300	205	89	
301	206	89	
302	207	89	

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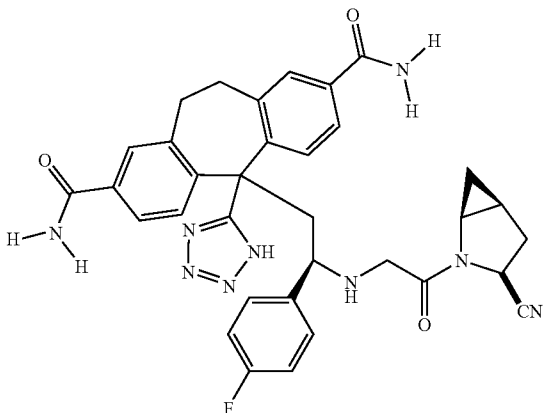
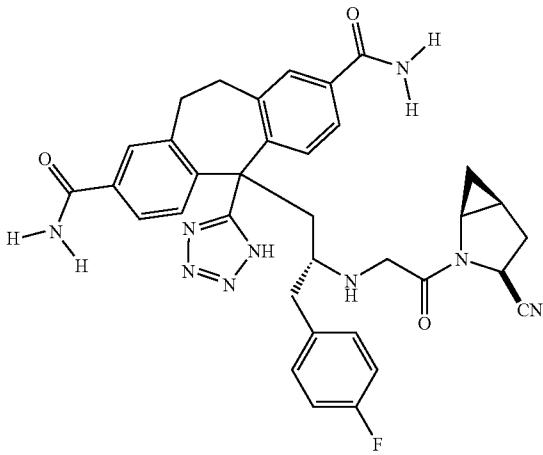
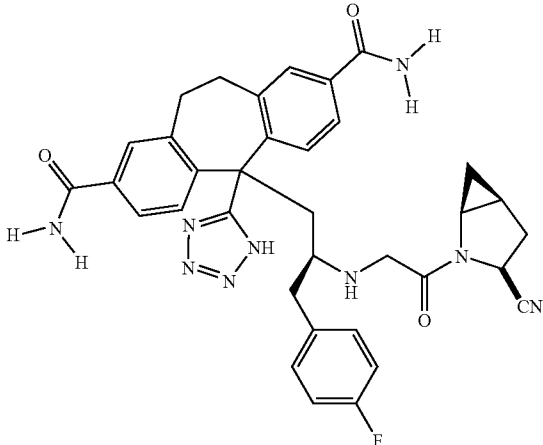
Example	Preparative Example	Preparative Example	Product
303	208	89	
304	209	89	
305	210	89	
306	211	89	

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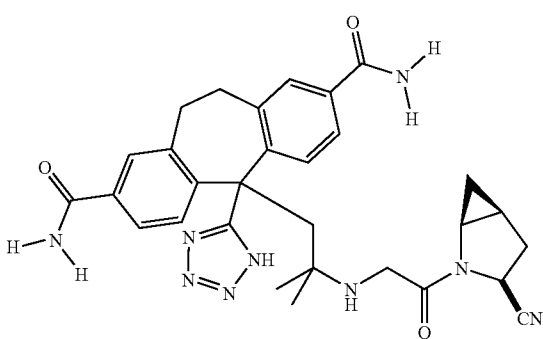
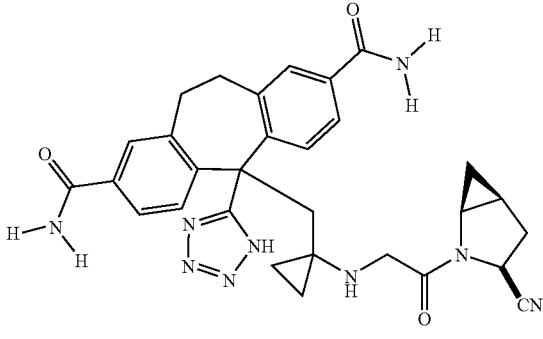
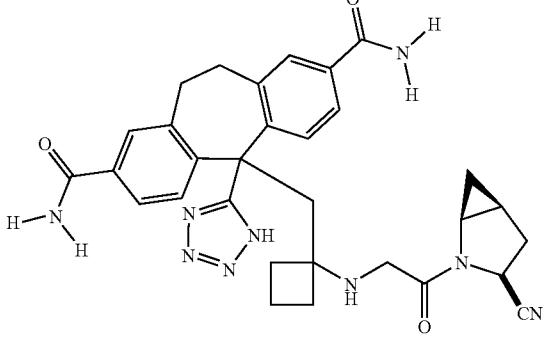
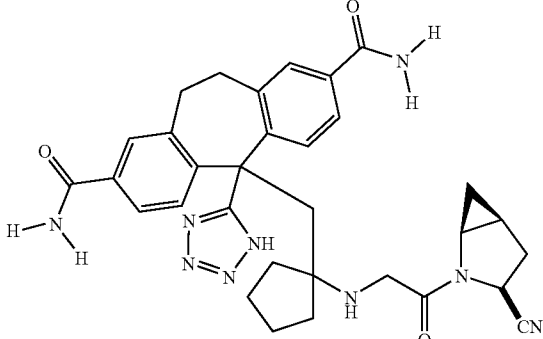
Example	Preparative Example	Preparative Example	Product
307	212	89	
308	213	89	
309	214	89	

Example	Preparative Example	Preparative Example	Product
307	212	89	
308	213	89	
309	214	89	

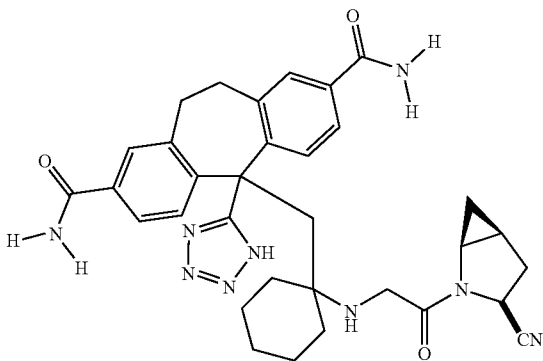
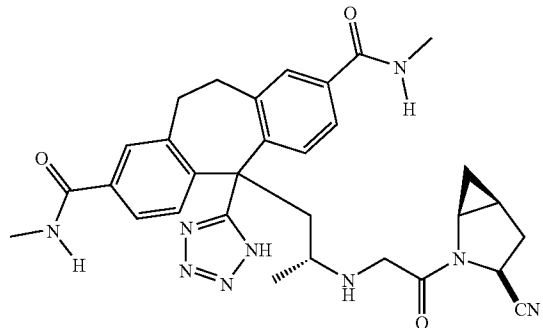
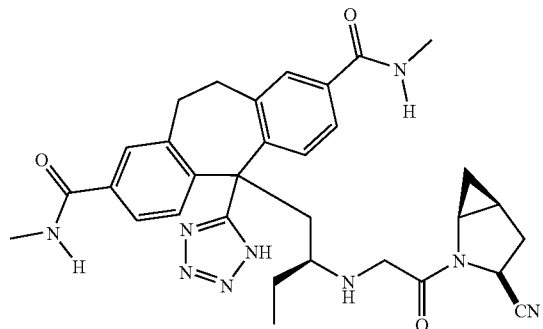
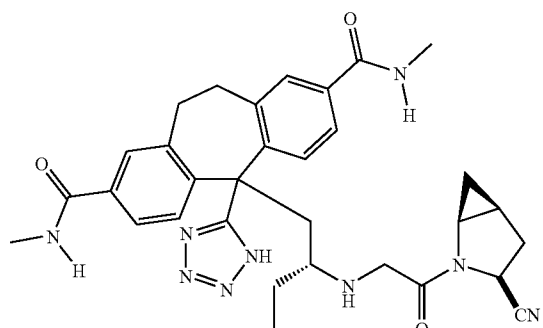
-continued

Example	Preparative Example	Preparative Example	Product
310	215	89	
311	216	89	
312	217	89	

-continued

Example	Preparative Example	Preparative Example	Product
313	218	89	
314	219	89	
315	220	89	
316	221	89	

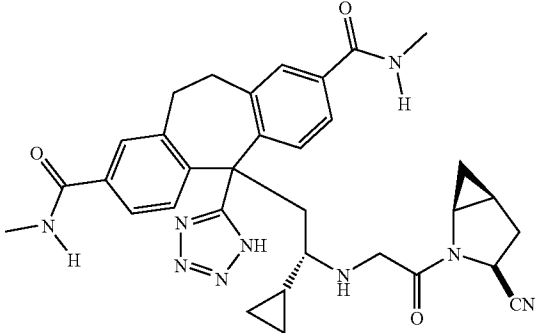
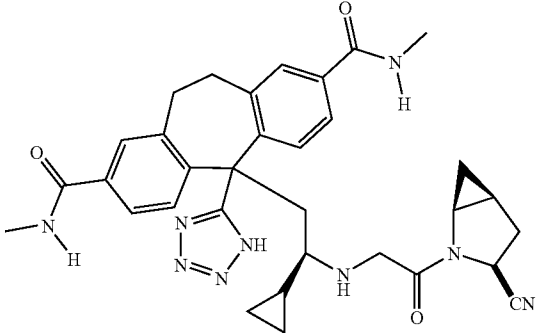
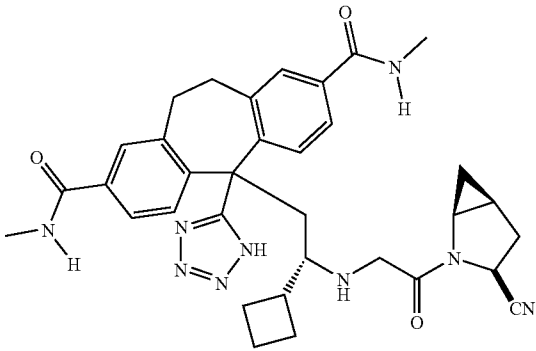
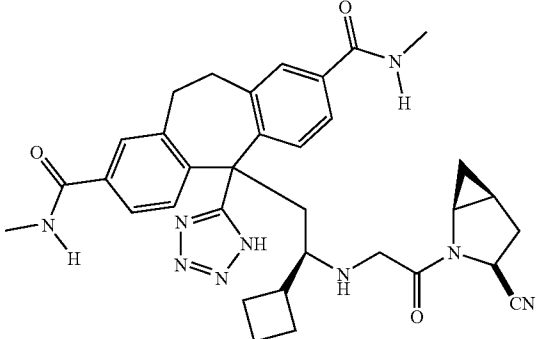
-continued

Example	Preparative Example	Preparative Example	Product
317	222	89	
318	223	89	
319	224	89	
320	225	89	

-continued

Example	Preparative Example	Preparative Example	Product
321	226	89	
322	227	89	
323	228	89	
324	229	89	

-continued

Example	Preparative Example	Preparative Example	Product
325	230	89	
326	231	89	
327	232	89	
328	233	89	

-continued

Example	Preparative Example	Preparative Example	Product
329	234	89	
330	235	89	
331	236	89	
332	237	89	

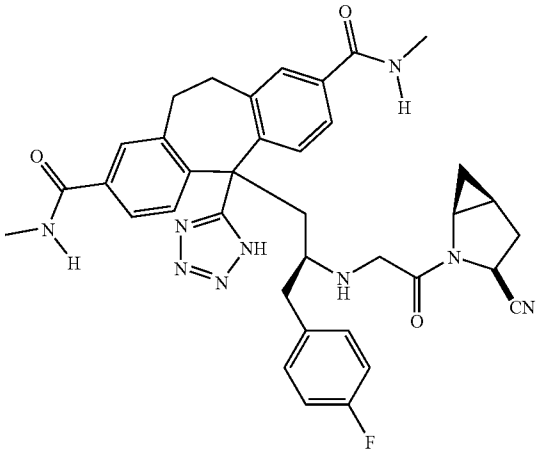
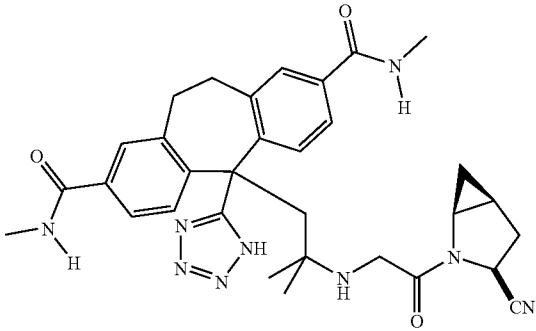
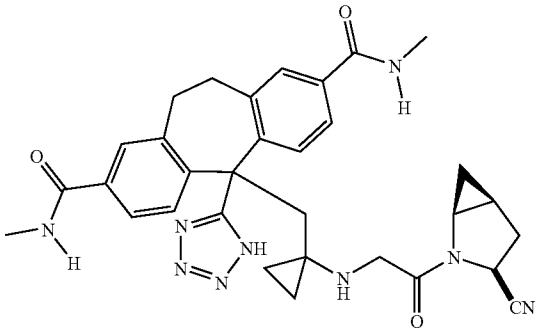
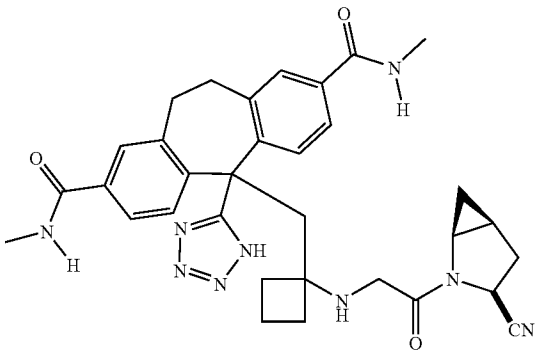
-continued

Example	Preparative Example	Preparative Example	Product
333	238	89	
334	239	89	
335	240	89	

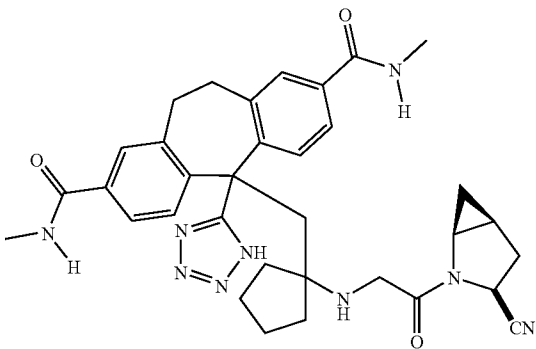
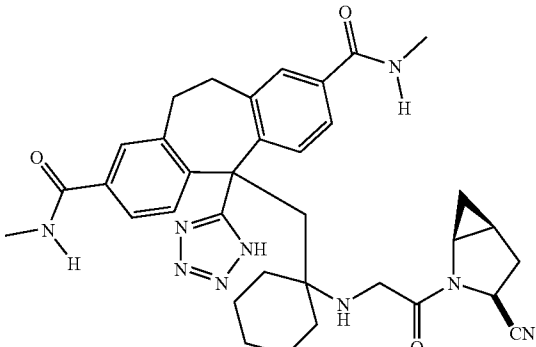
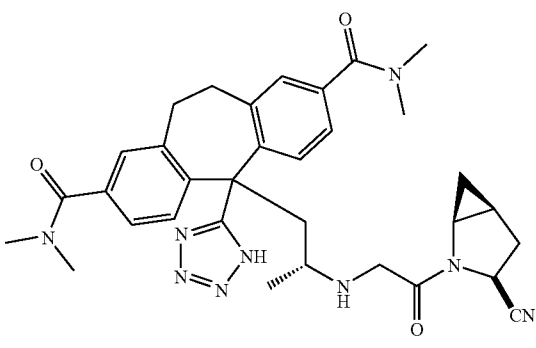
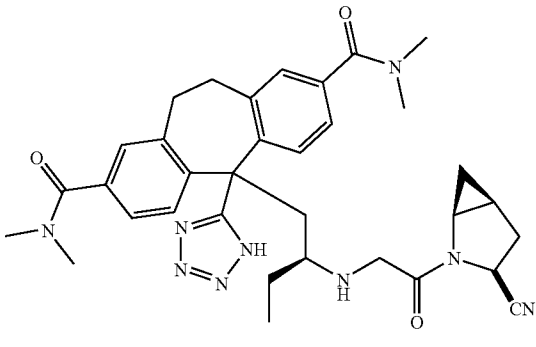
Example	Preparative Example	Preparative Example	Product
333	238	89	
334	239	89	
335	240	89	

Example	Preparative Example	Preparative Example	Product
333	238	89	
334	239	89	
335	240	89	

-continued

Example	Preparative Example	Preparative Example	Product
336	241	89	
337	242	89	
338	243	89	
339	244	89	

-continued

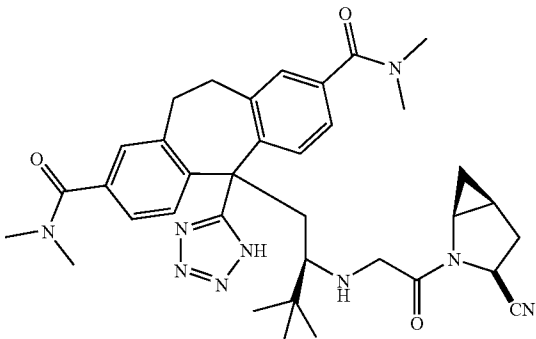
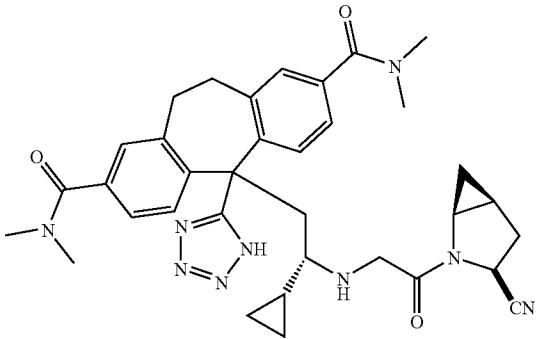
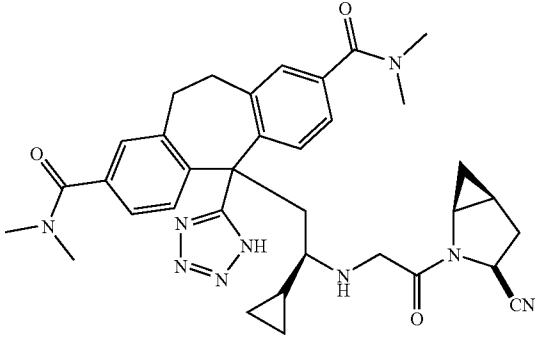
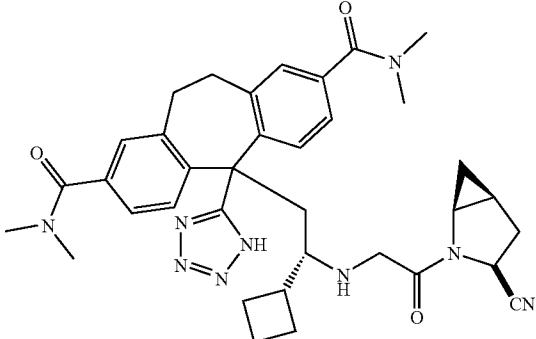
Example	Preparative Example	Preparative Example	Product
340	245	89	
341	246	89	
342	247	89	
343	248	89	

-continued

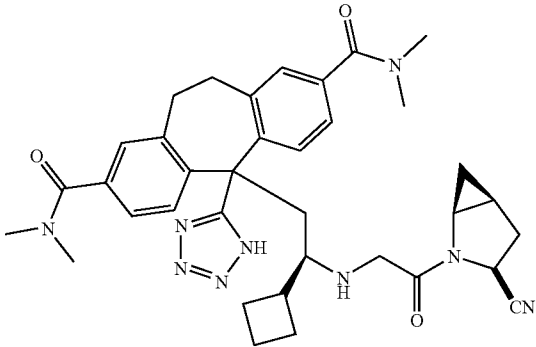
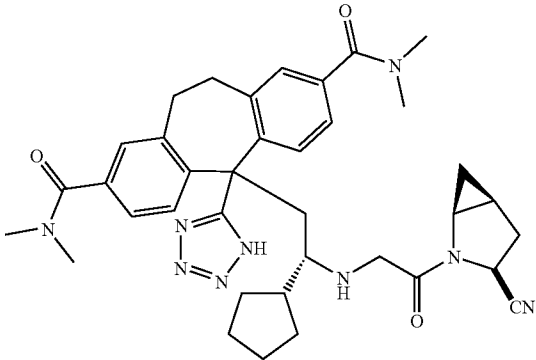
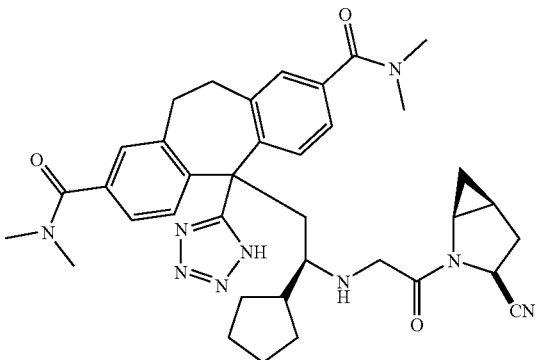
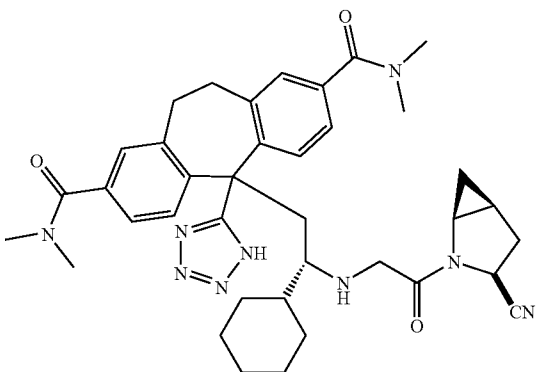
Example	Preparative Example	Preparative Example	Product
344	249	89	
345	250	89	
346	251	89	
347	252	89	

Example	Preparative Example	Preparative Example	Product
344	249	89	
345	250	89	
346	251	89	
347	252	89	

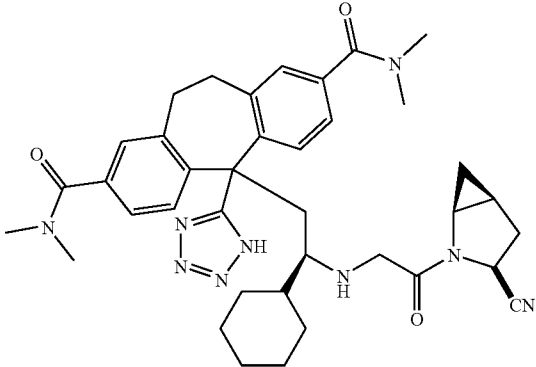
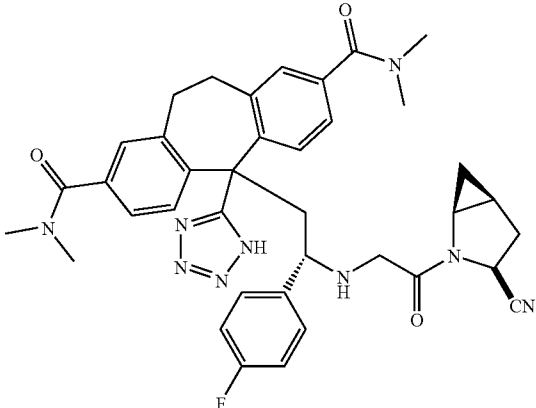
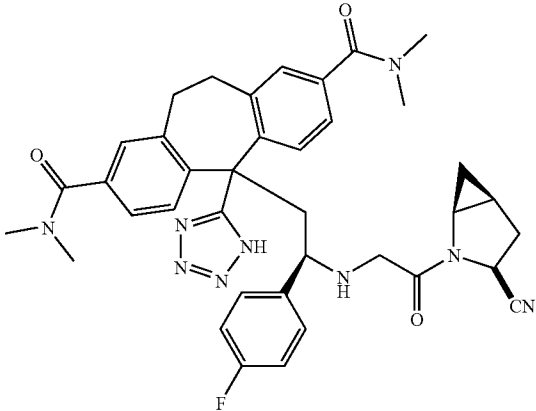
-continued

Example	Preparative Example	Preparative Example	Product
348	253	89	
349	254	89	
350	255	89	
351	256	89	

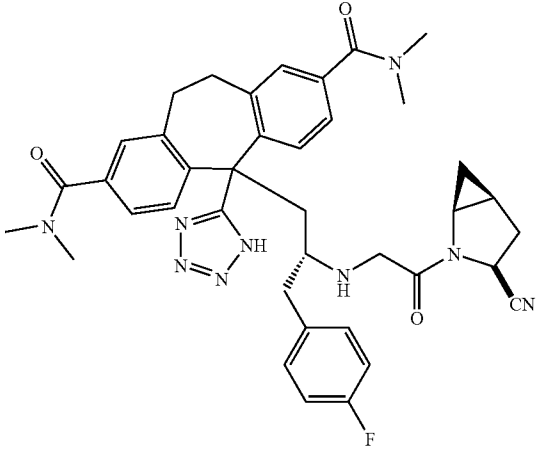
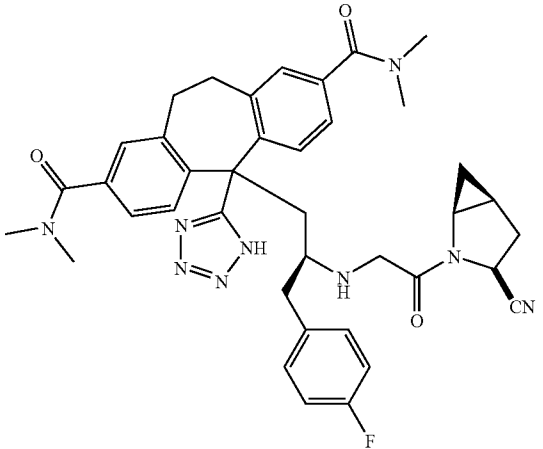
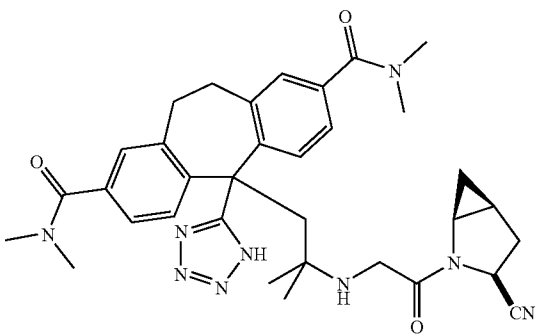
-continued

Example	Preparative Example	Preparative Example	Product
352	257	89	
353	258	89	
354	259	89	
355	260	89	

-continued

Example	Preparative Example	Preparative Example	Product
356	261	89	
357	262	89	
358	263	89	

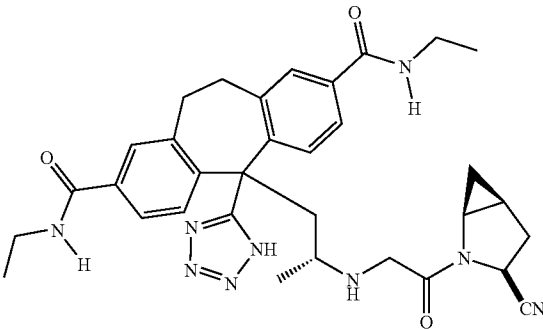
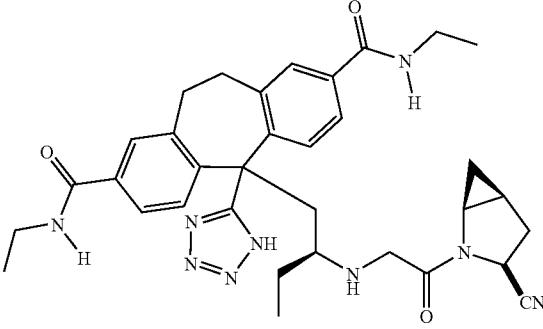
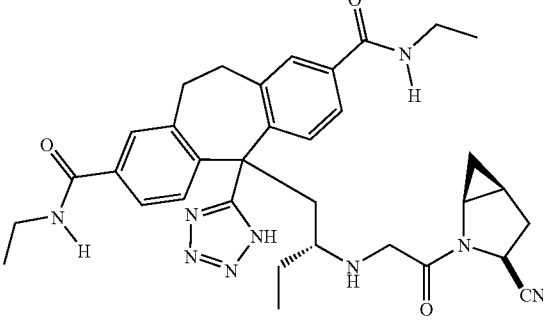
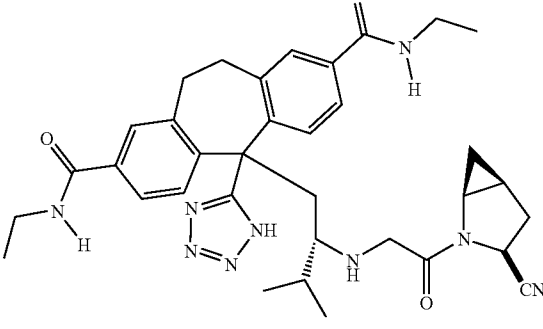
-continued

Example	Preparative Example	Preparative Example	Product
359	264	89	
360	265	89	
361	266	89	

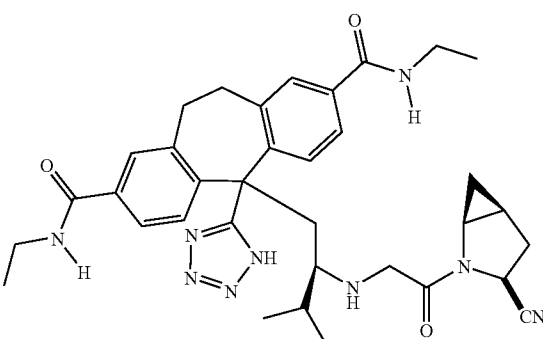
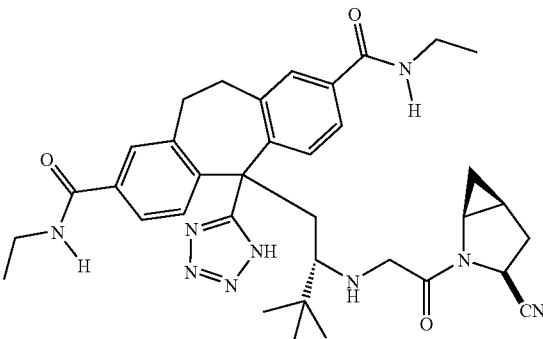
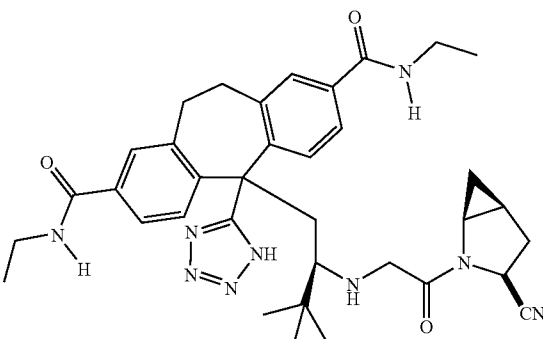
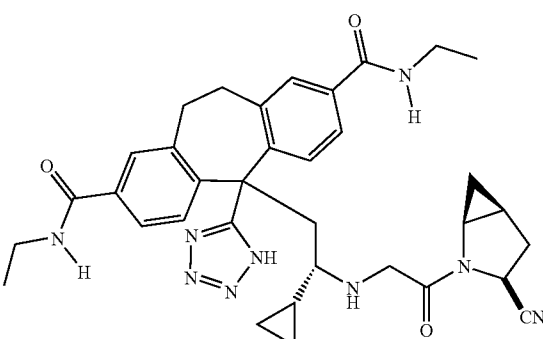
-continued

Example	Preparative Example	Preparative Example	Product
362	267	89	
363	268	89	
364	269	89	
365	270	89	

-continued

Example	Preparative Example	Preparative Example	Product
366	271	89	
367	272	89	
368	273	89	
369	274	89	

-continued

Example	Preparative Example	Preparative Example	Product
370	275	89	
371	276	89	
372	277	89	
373	278	89	

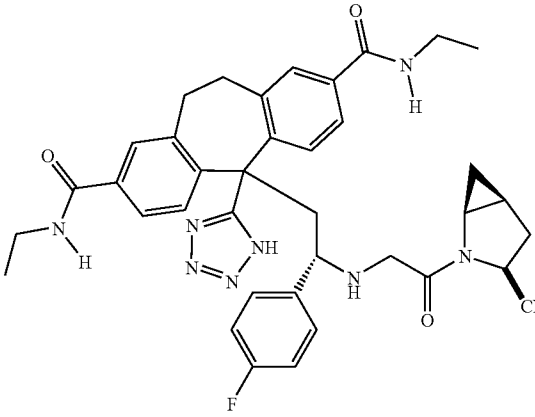
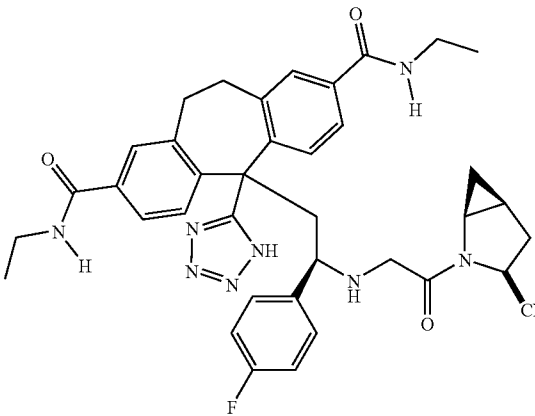
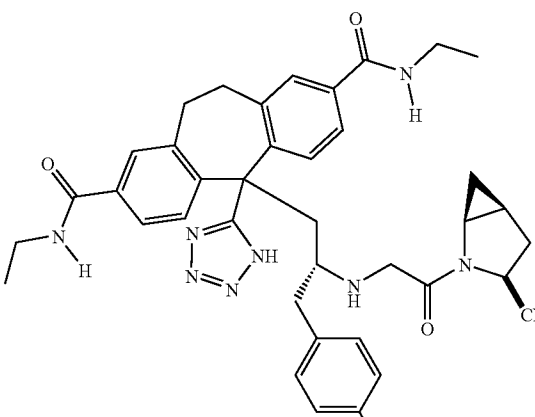
-continued

Example	Preparative Example	Preparative Example	Product
374	279	89	
375	280	89	
376	281	89	
377	282	89	

-continued

Example	Preparative Example	Preparative Example	Product
378	283	89	
379	284	89	
380	285	89	

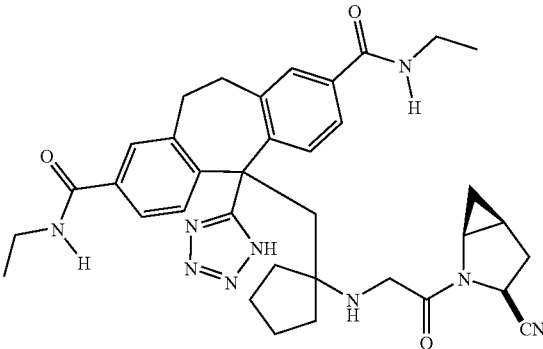
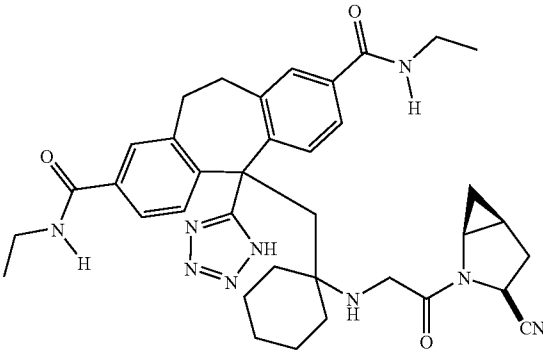
-continued

Example	Preparative Example	Preparative Example	Product
381	286	89	
382	287	89	
383	288	89	

-continued

Example	Preparative Example	Preparative Example	Product
384	289	89	
385	290	89	
386	291	89	
387	292	89	

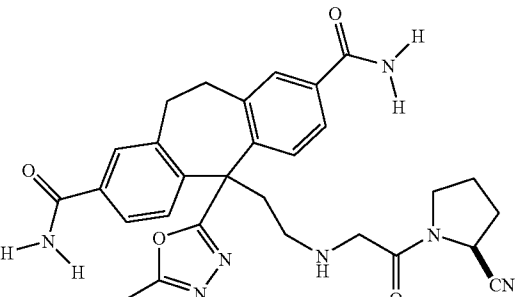
-continued

Example	Preparative Example	Preparative Example	Product
388	293	89	
389	294	89	

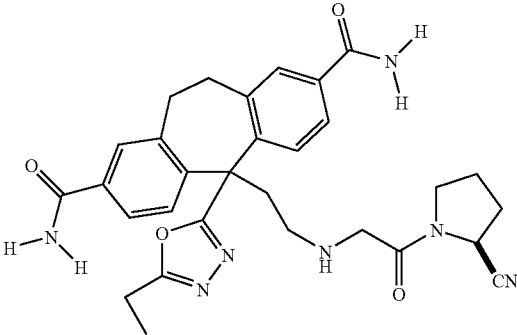
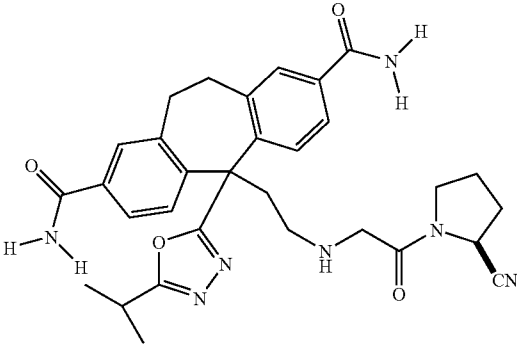
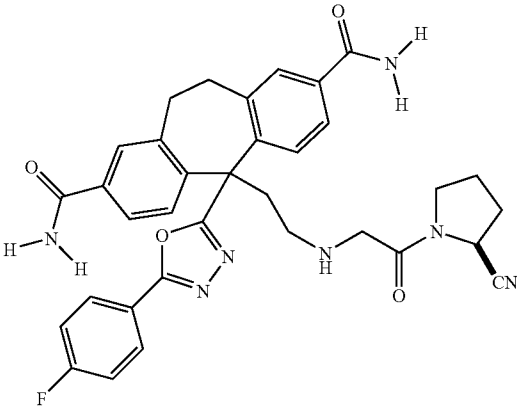
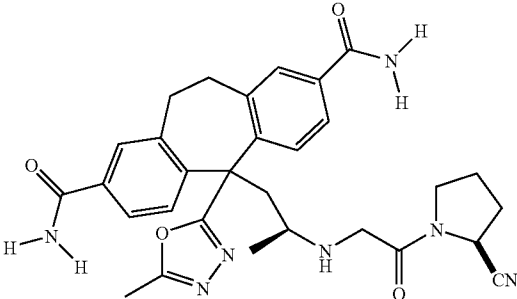
[0854] Examples 390-399 have been intentionally excluded.

Example 400-595

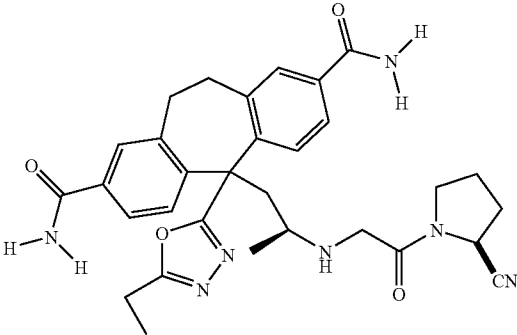
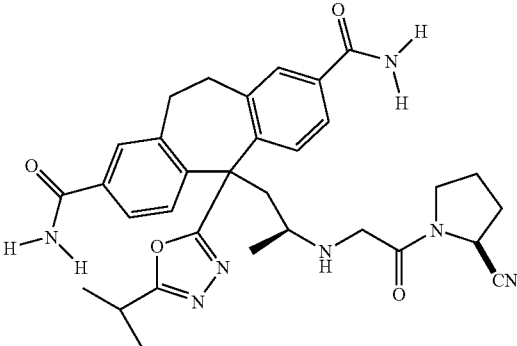
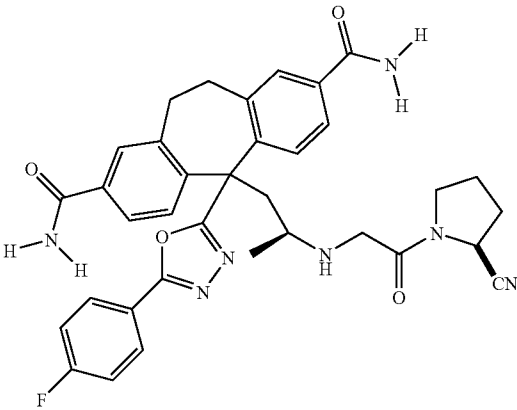
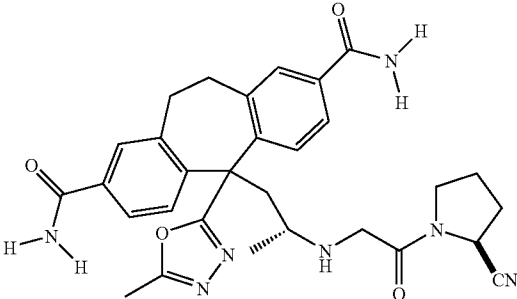
[0855] If one were to follow the procedures outlined in Examples 28 or 29 except using the compounds from the Preparative Examples as indicated in the Table below, one would obtain the indicated Product.

Example	Preparative Example	Preparative Example	Product
400	300	2	

-continued

Example	Preparative Example	Preparative Example	Product
401	301	2	
402	302	2	
403	303	2	
404	304	2	

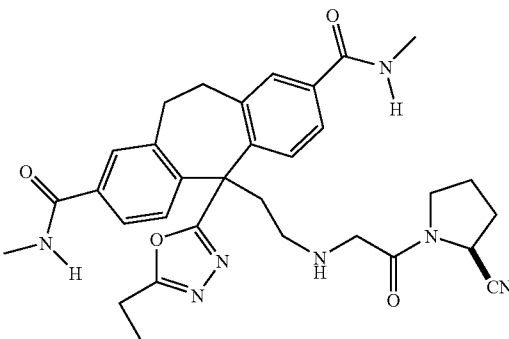
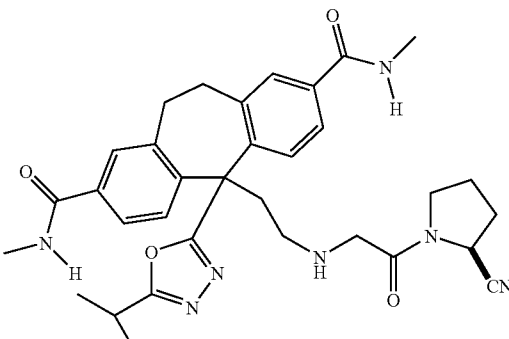
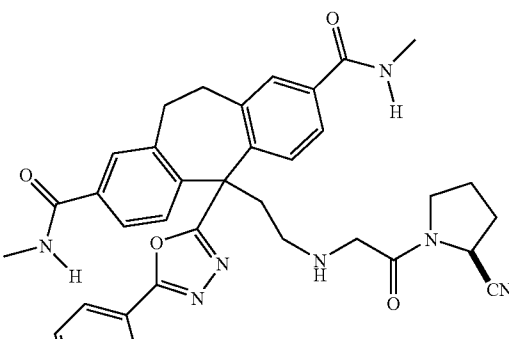
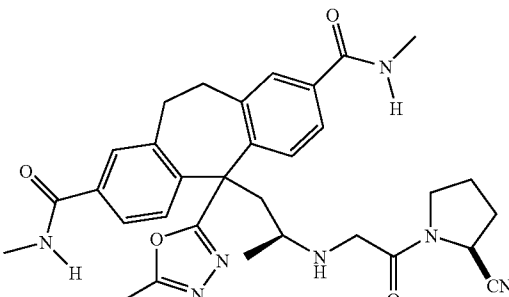
-continued

Example	Preparative Example	Preparative Example	Product
405	305	2	
406	306	2	
407	307	2	
408	308	2	

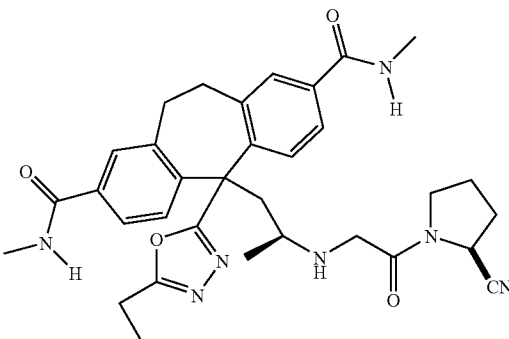
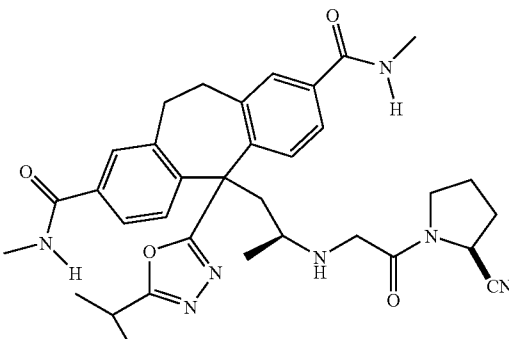
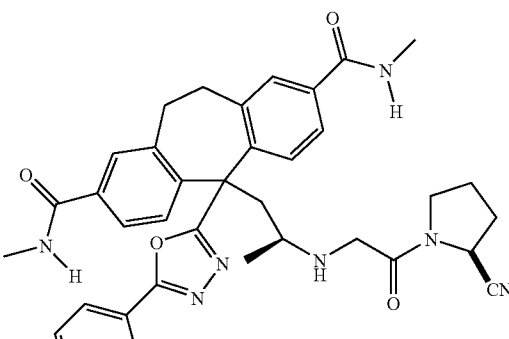
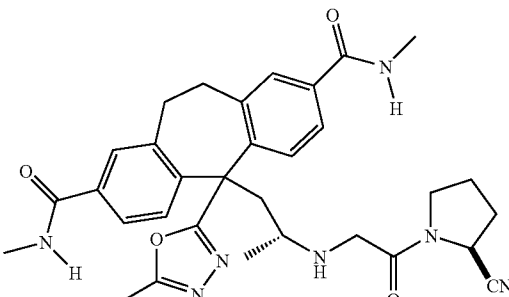
-continued

Example	Preparative Example	Preparative Example	Product
409	309	2	
410	310	2	
411	311	2	
412	312	2	

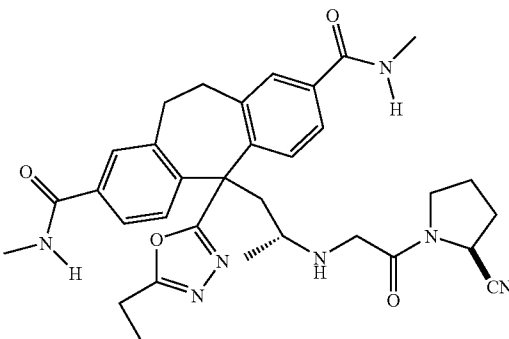
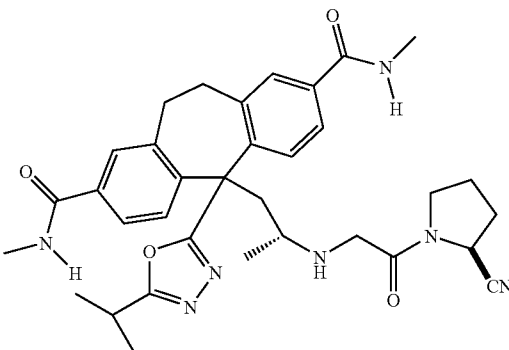
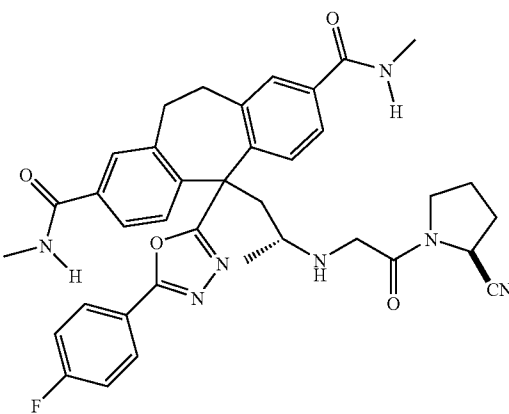
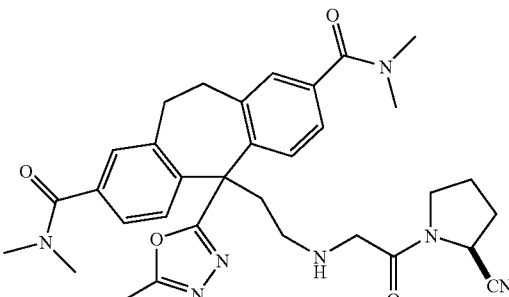
-continued

Example	Preparative Example	Preparative Example	Product
413	313	2	
414	314	2	
415	315	2	
416	316	2	

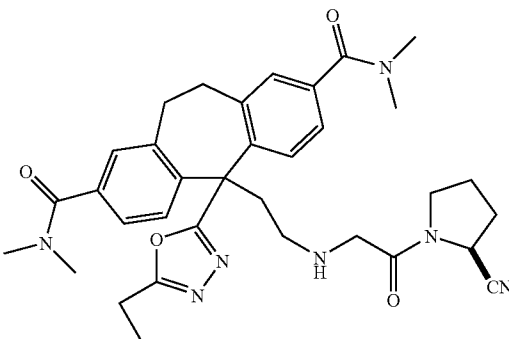
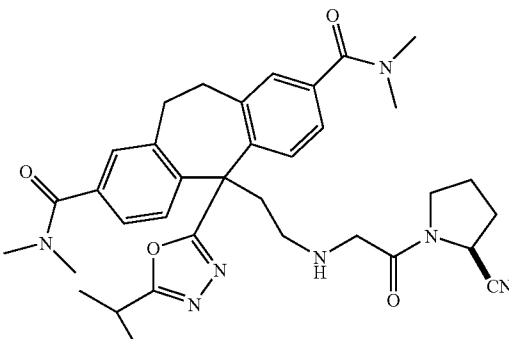
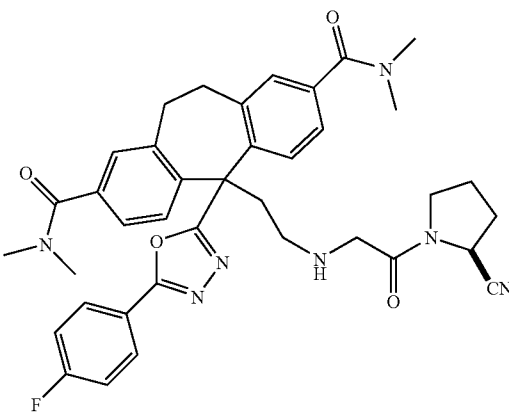
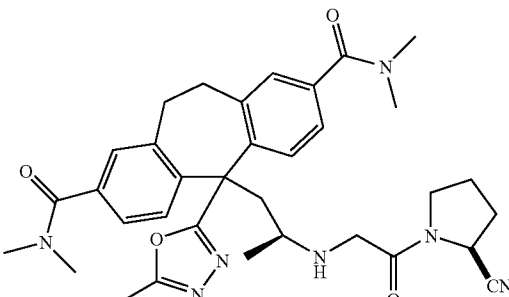
-continued

Example	Preparative Example	Preparative Example	Product
417	317	2	
418	318	2	
419	319	2	
420	320	2	

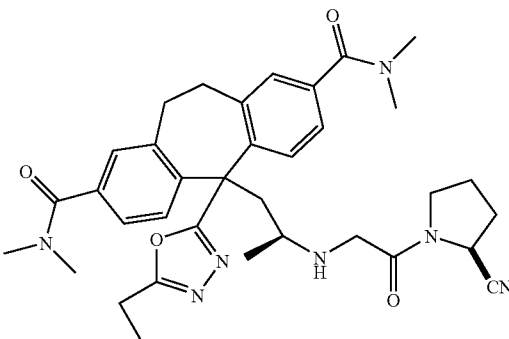
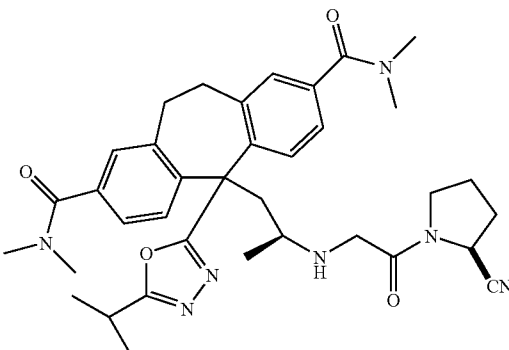
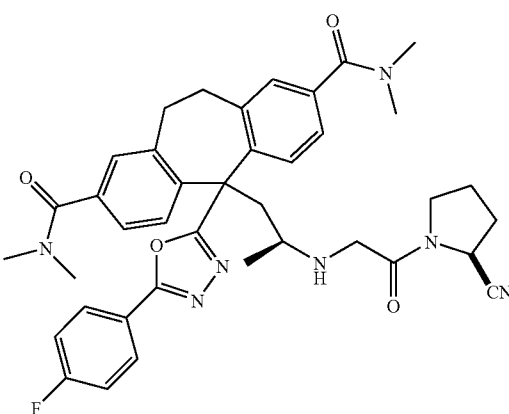
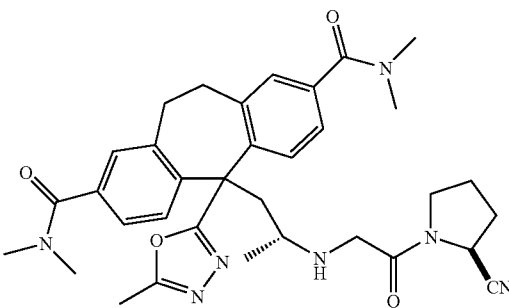
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Example	Preparative Example	Preparative Example	Product
421	321	2	
422	322	2	
423	323	2	
424	324	2	

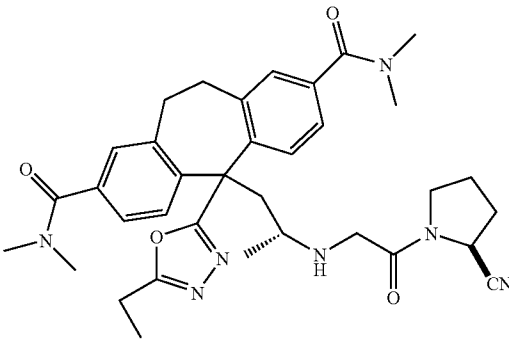
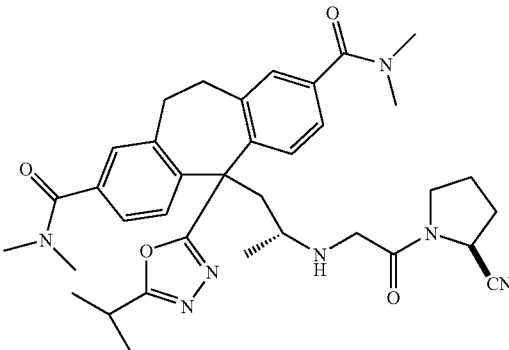
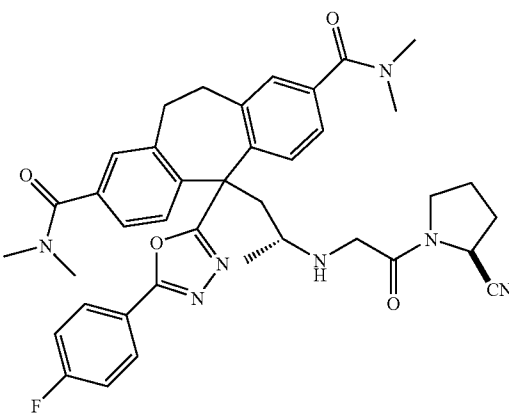
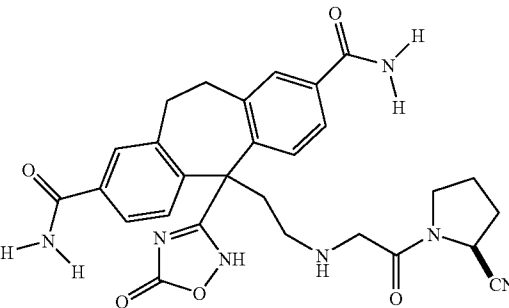
-continued

Example	Preparative Example	Preparative Example	Product
425	325	2	
426	326	2	
427	327	2	
428	328	2	

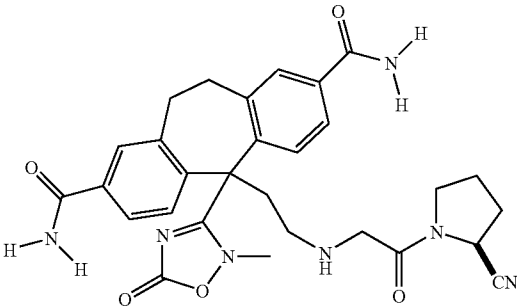
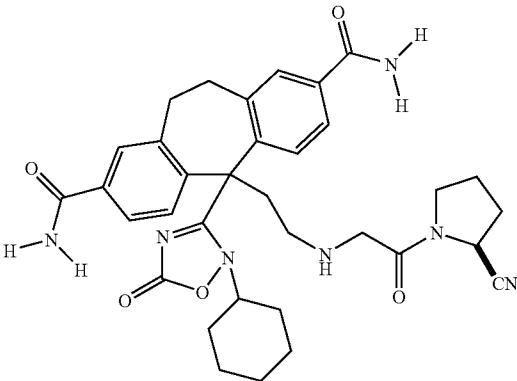
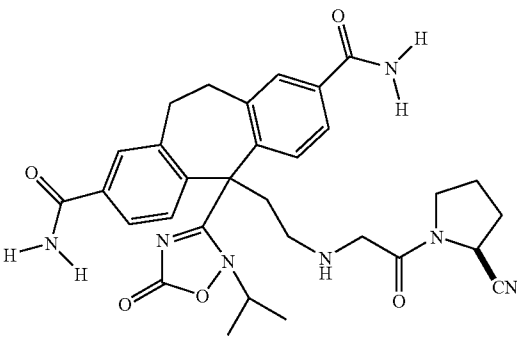
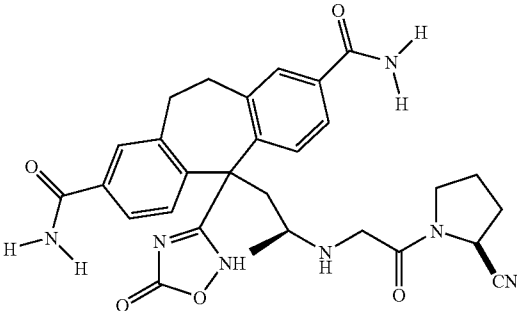
-continued

Example	Preparative Example	Preparative Example	Product
429	329	2	
430	330	2	
431	331	2	
432	332	2	

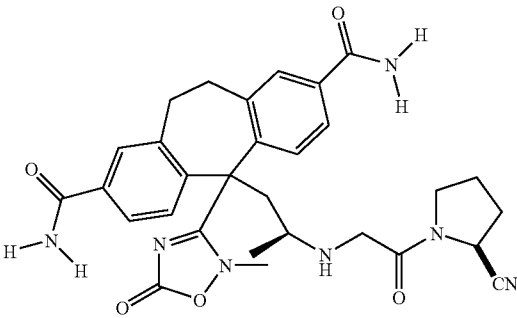
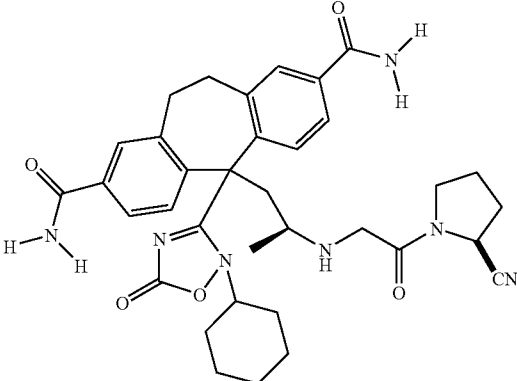
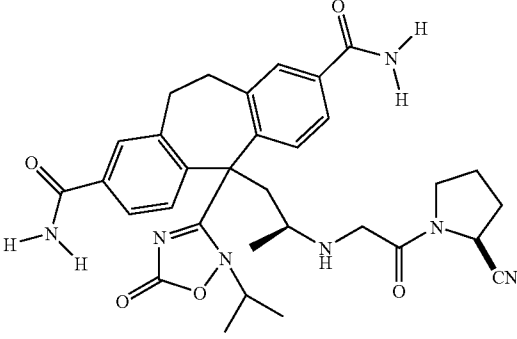
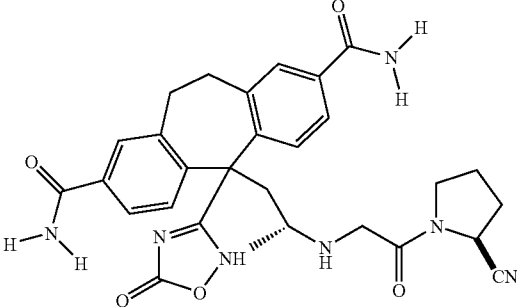
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Example	Preparative Example	Preparative Example	Product
433	333	2	
434	334	2	
435	335	2	
436	400	2	

-continued

Example	Preparative Example	Preparative Example	Product
437	401	2	
438	402	2	
439	403	2	
440	404	2	

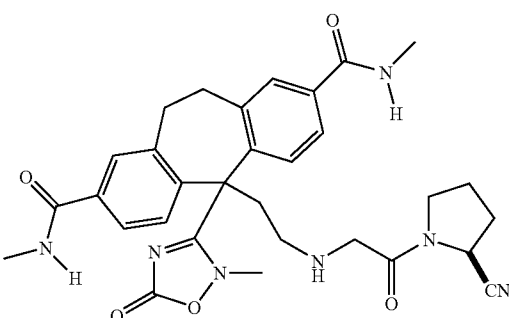
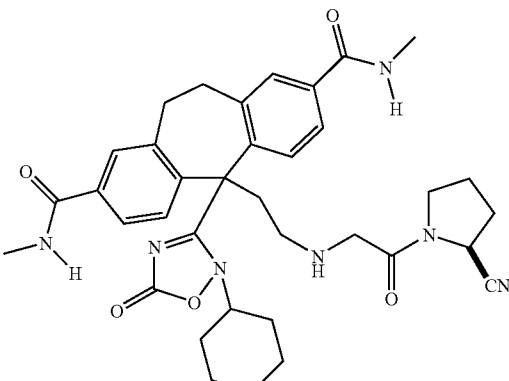
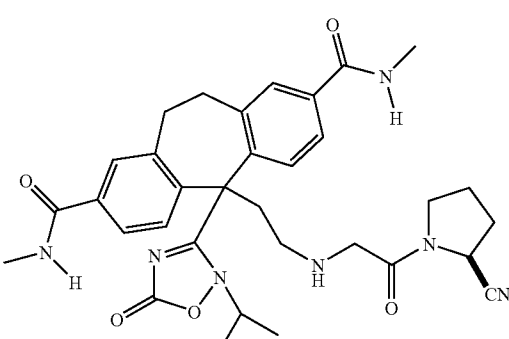
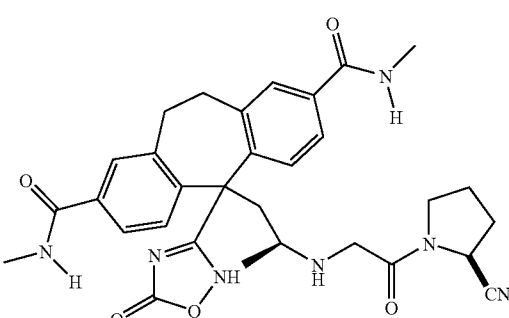
-continued

Example	Preparative Example	Preparative Example	Product
441	405	2	
442	406	2	
443	407	2	
444	408	2	

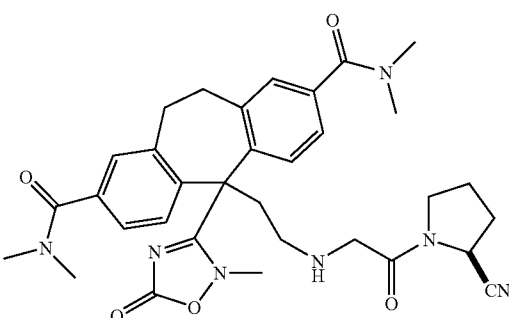
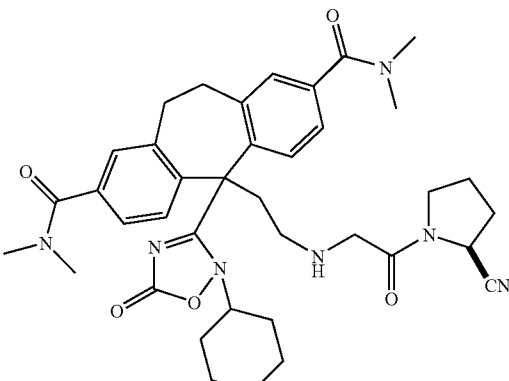
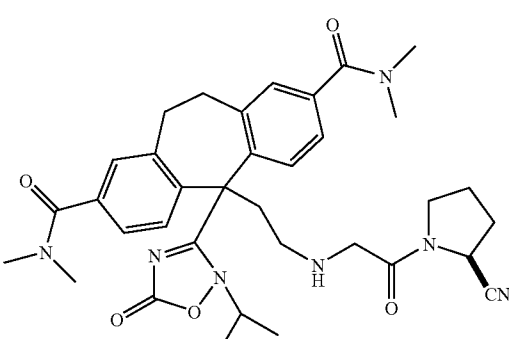
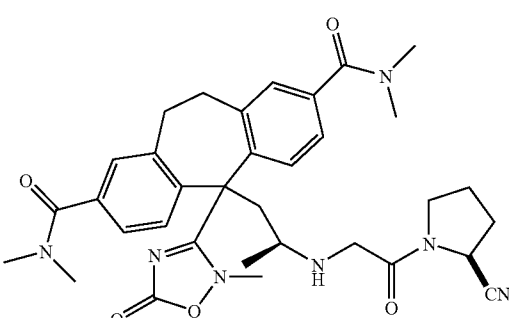
-continued

Example	Preparative Example	Preparative Example	Product
445	409	2	
446	410	2	
447	411	2	
448	412	2	

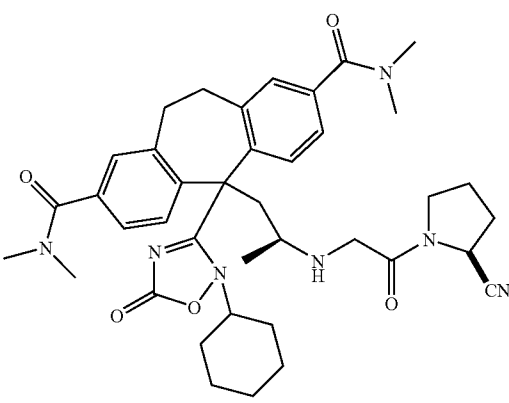
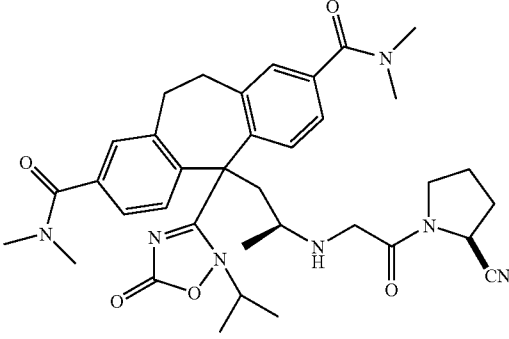
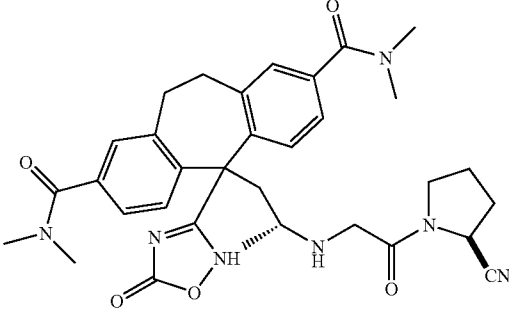
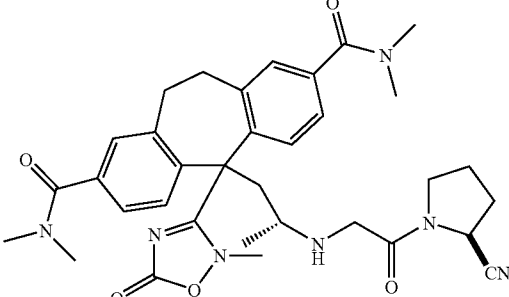
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Example	Preparative Example	Preparative Example	Product
449	413	2	
450	414	2	
451	415	2	
452	416	2	

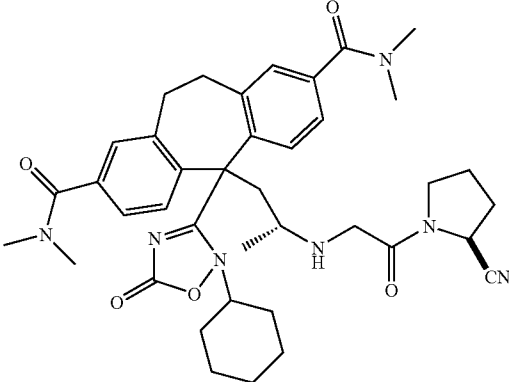
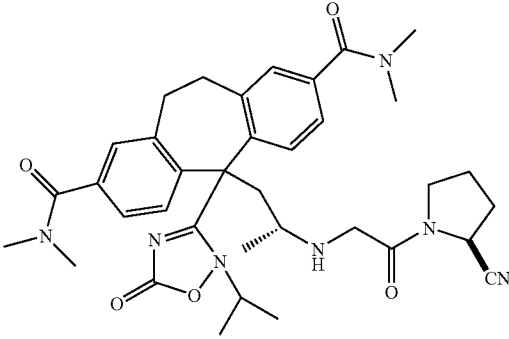
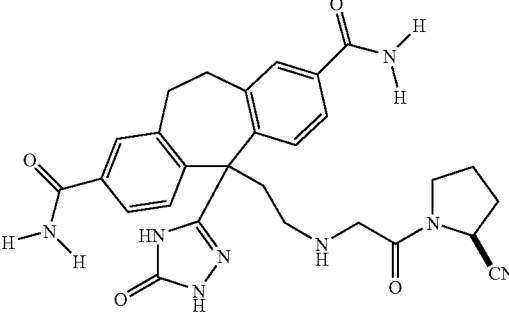
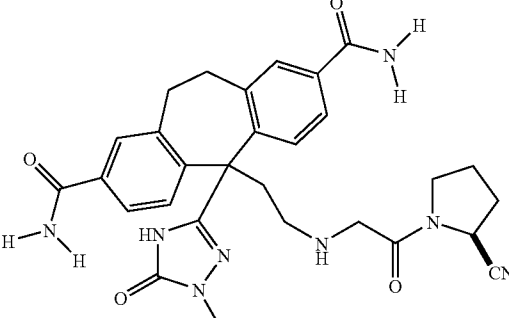
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Example	Preparative Example	Preparative Example	Product
461	425	2	
462	426	2	
463	427	2	
464	428	2	

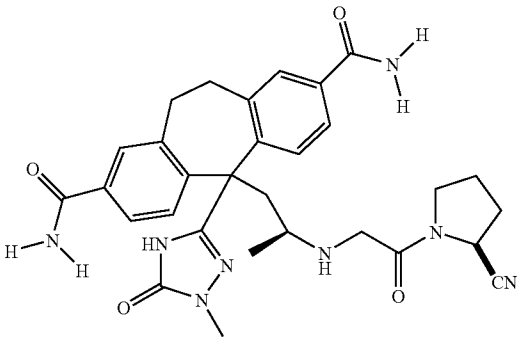
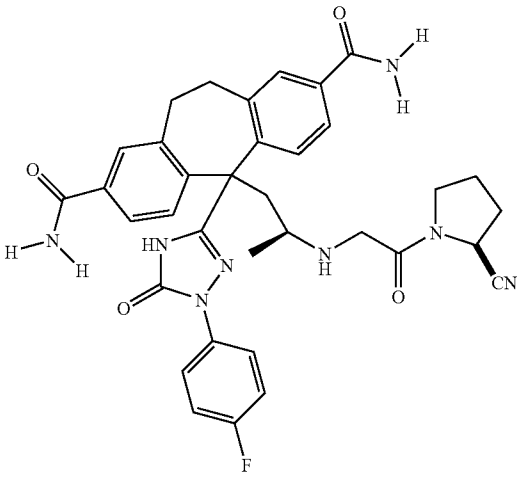
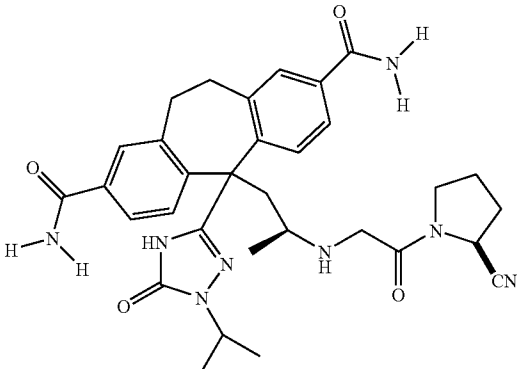
-continued

Example	Preparative Example	Preparative Example	Product
465	429	2	
466	430	2	
467	431	2	
468	432	2	

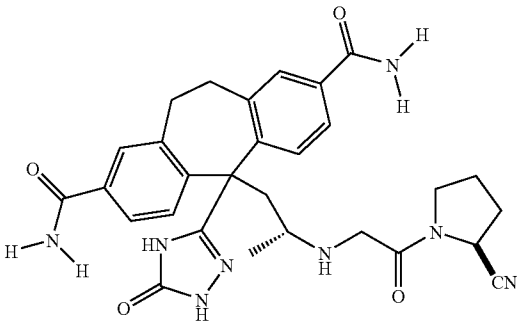
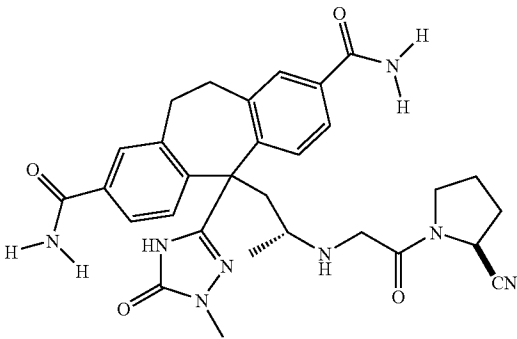
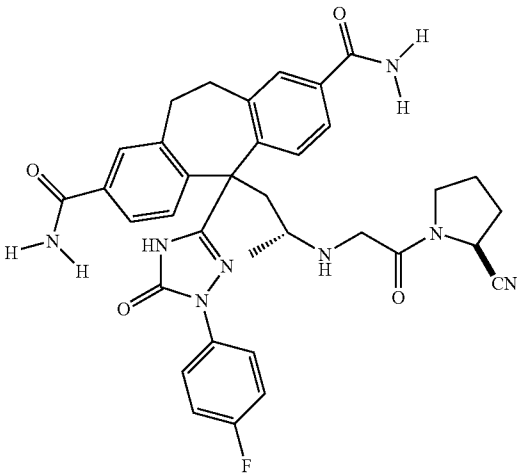
-continued

Example	Preparative Example	Preparative Example	Product
469	433	2	
470	434	2	
471	500	2	
472	501	2	

-continued

Example	Preparative Example	Preparative Example	Product
476	505	2	
477	506	2	
478	507	2	

-continued

Example	Preparative Example	Preparative Example	Product
479	508	2	
480	509	2	
481	510	2	

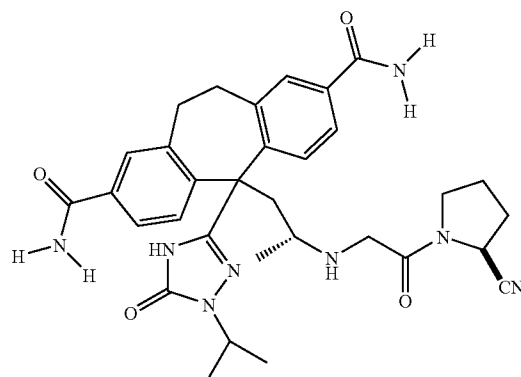
-continued

Example	Preparative Example	Preparative Example	Product
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482

511

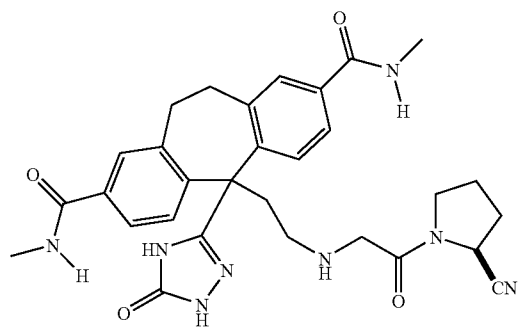
2



483

512

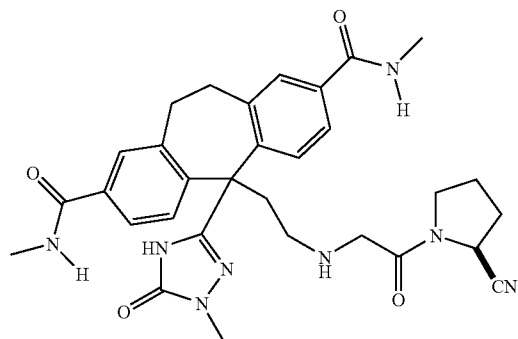
2



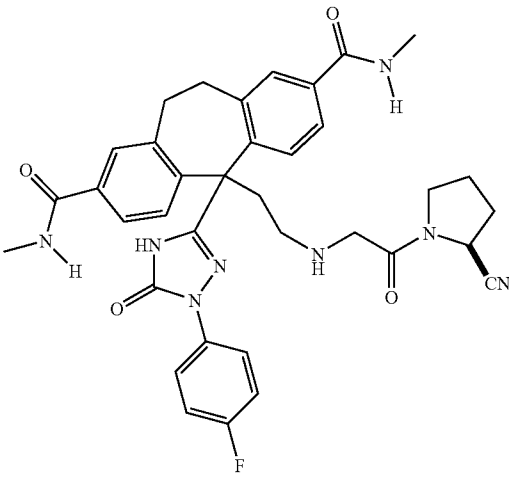
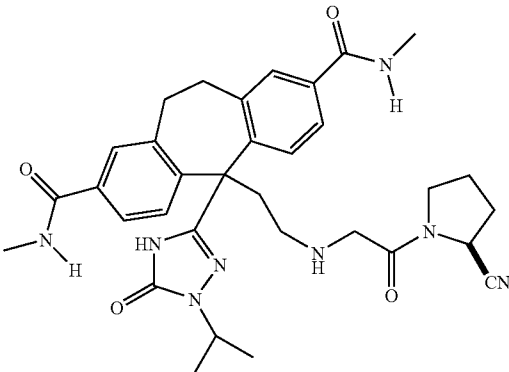
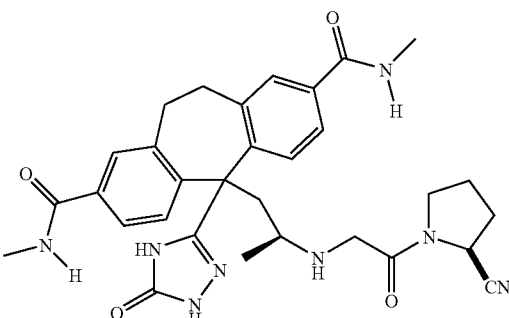
484

513

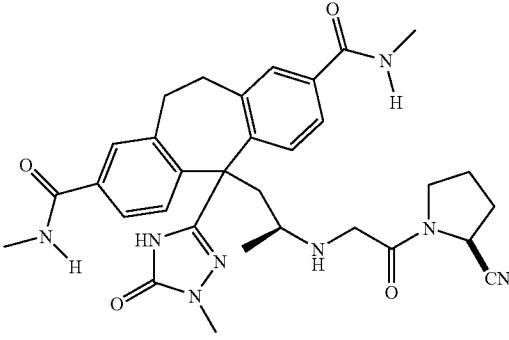
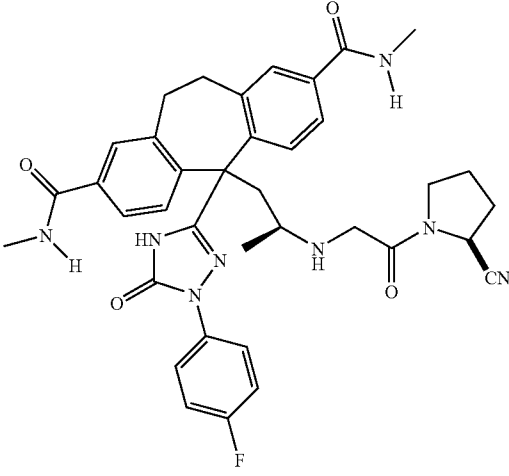
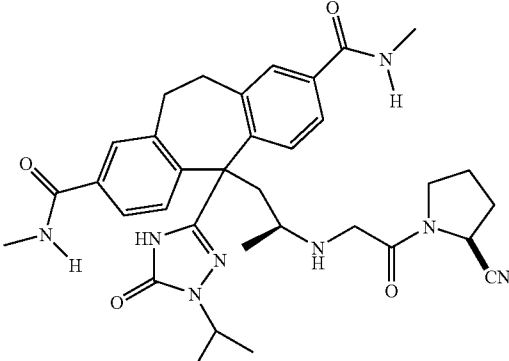
2



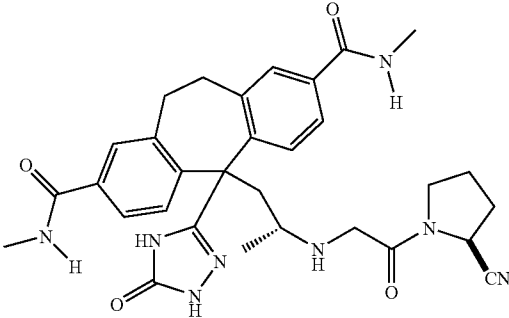
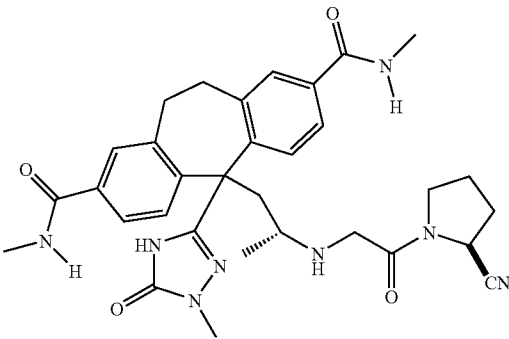
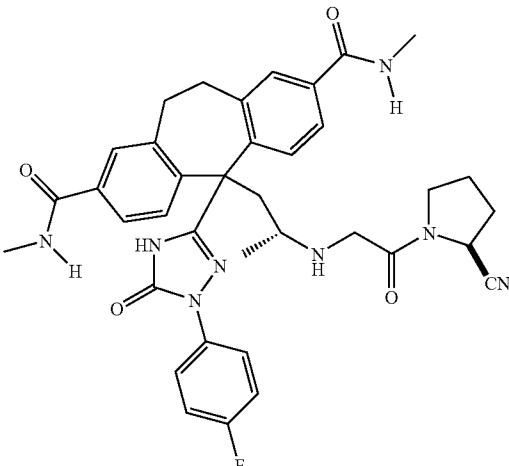
-continued

Example	Preparative Example	Preparative Example	Product
485	514	2	
486	515	2	
487	516	2	

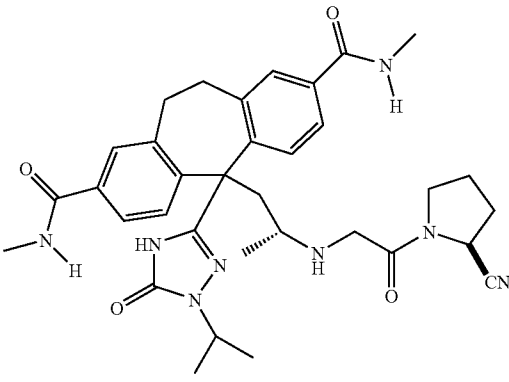
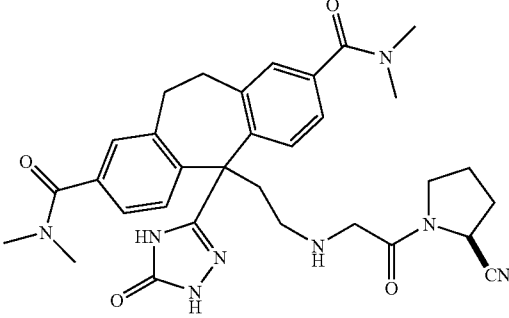
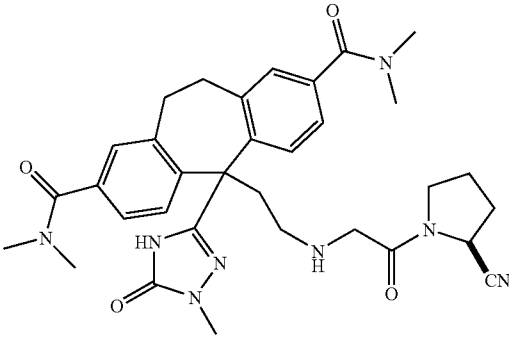
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Example	Preparative Example	Preparative Example	Product
488	517	2	
489	518	2	
490	519	2	

-continued

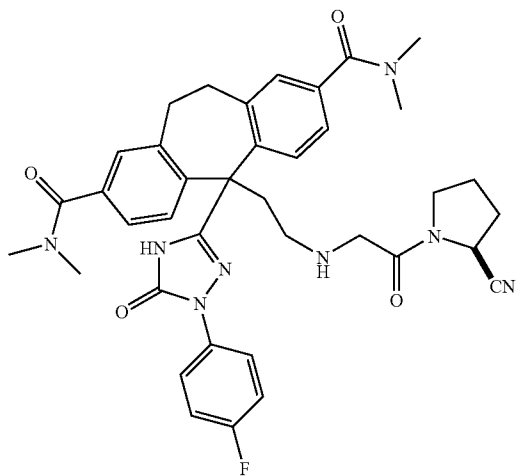
Example	Preparative Example	Preparative Example	Product
491	520	2	
492	521	2	
493	522	2	

-continued

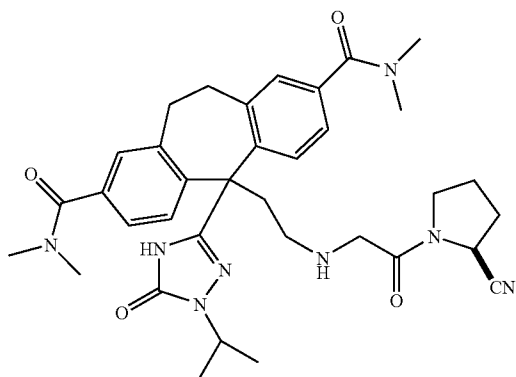
Example	Preparative Example	Preparative Example	Product
494	523	2	
495	524	2	
496	525	2	

-continued

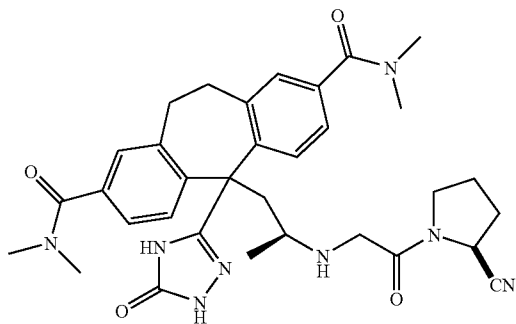
Example	Preparative Example	Preparative Example	Product
497	526	2	O



498	527	2
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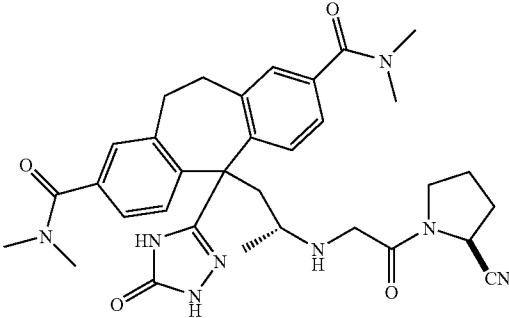
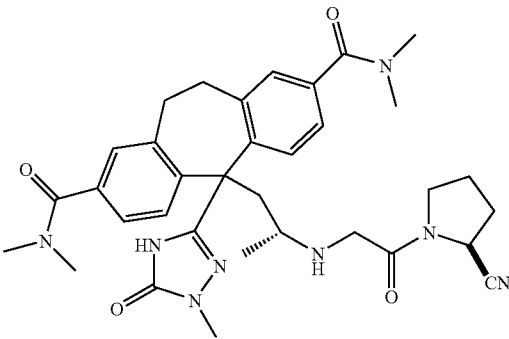
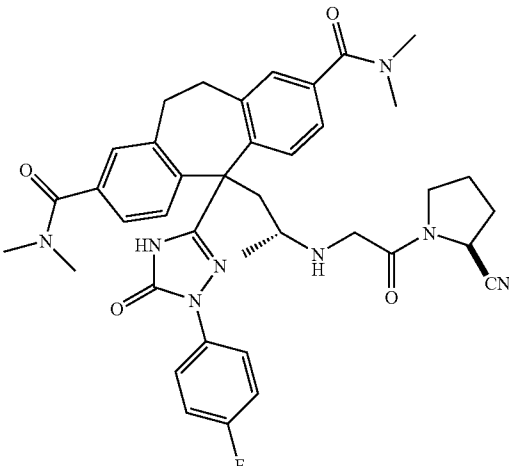
499	528	2
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Example	Preparative Example	Preparative Example	Product
500	529	2	
501	530	2	
502	531	2	

-continued

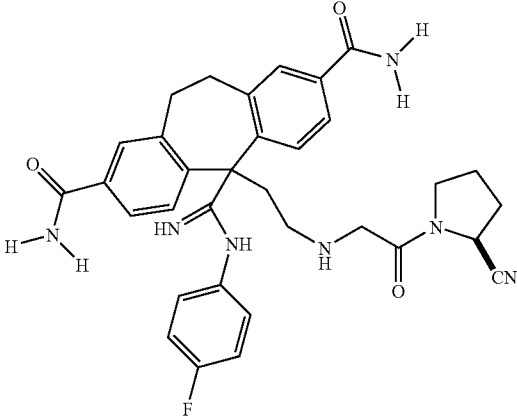
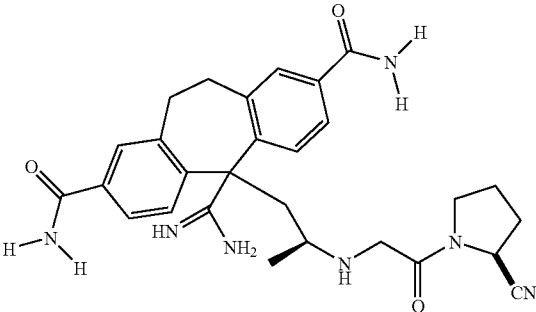
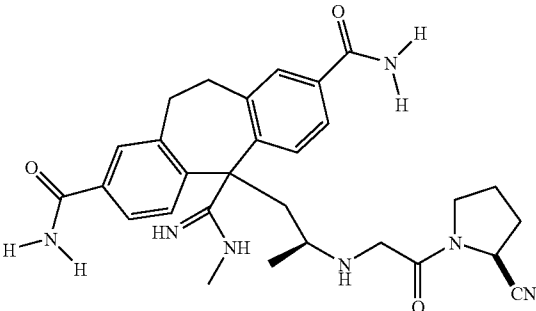
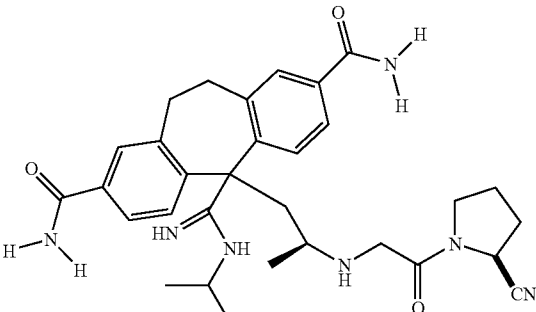
Example	Preparative Example	Preparative Example	Product
503	532	2	
504	533	2	
505	534	2	

-continued

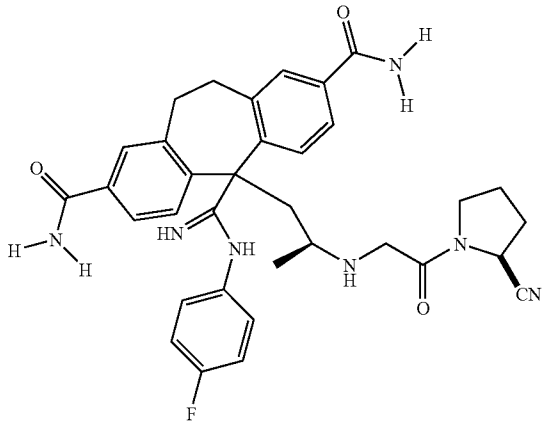
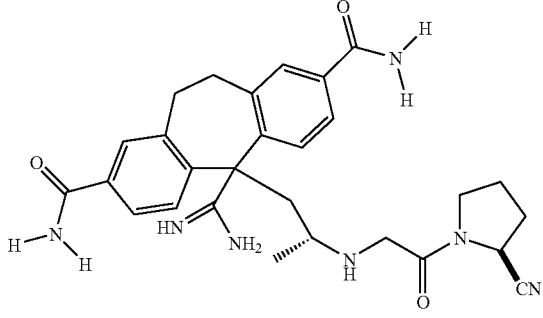
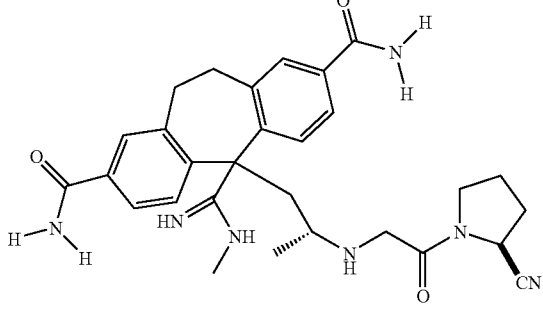
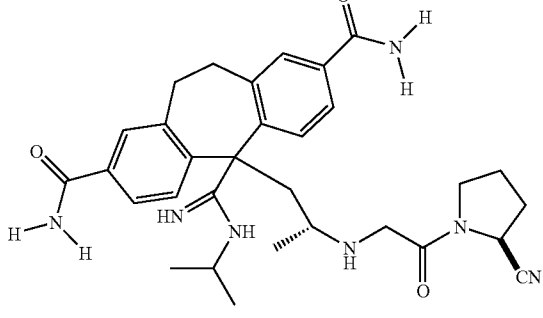
Example	Preparative Example	Preparative Example	Product
506	535	2	
507	600	2	
508	601	2	
509	602	2	

Example	Preparative Example	Preparative Example	Product
506	535	2	
507	600	2	
508	601	2	
509	602	2	

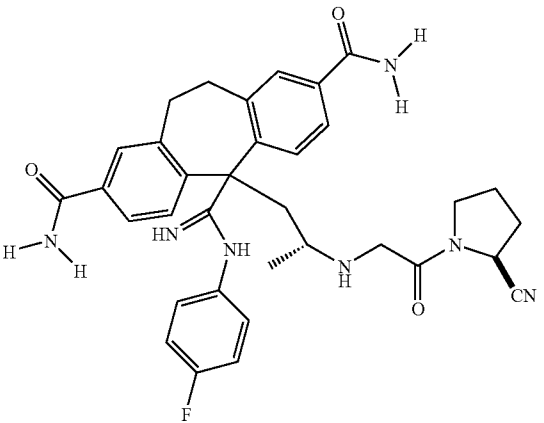
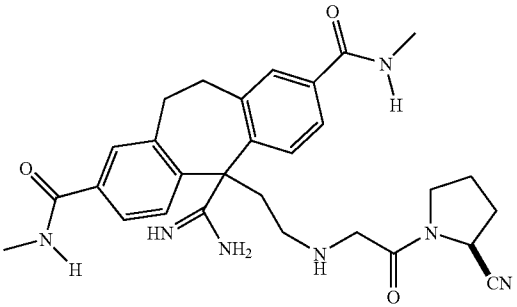
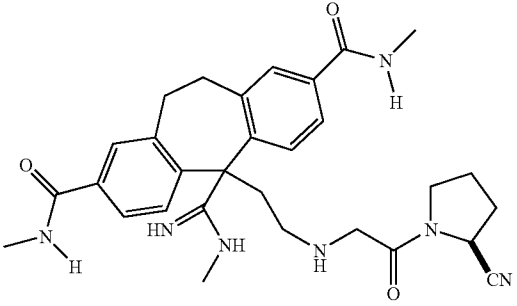
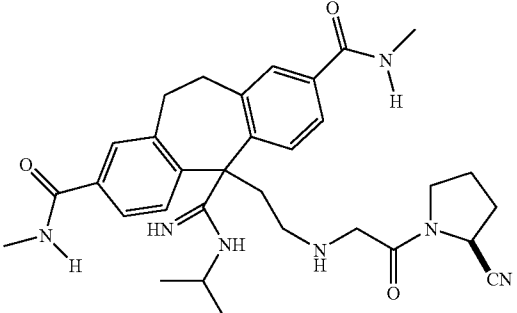
-continued

Example	Preparative Example	Preparative Example	Product
510	603	2	
511	604	2	
512	605	2	
513	606	2	

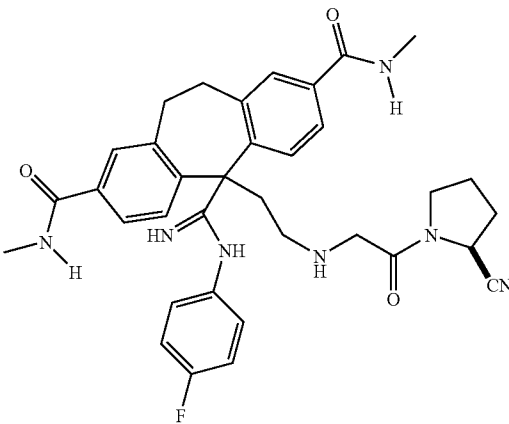
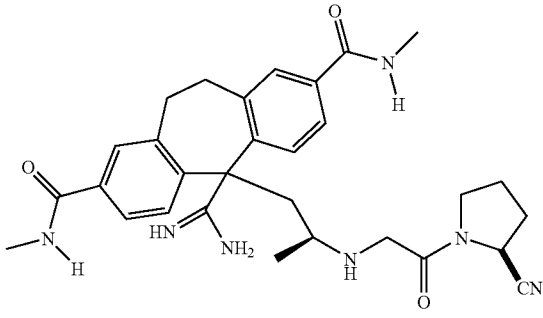
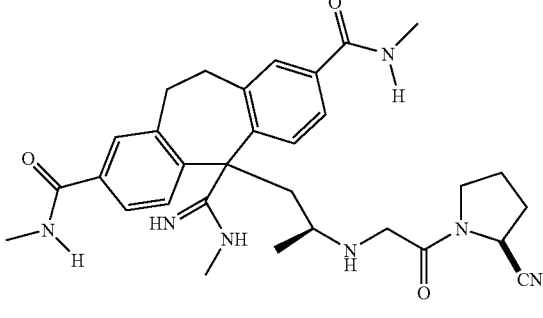
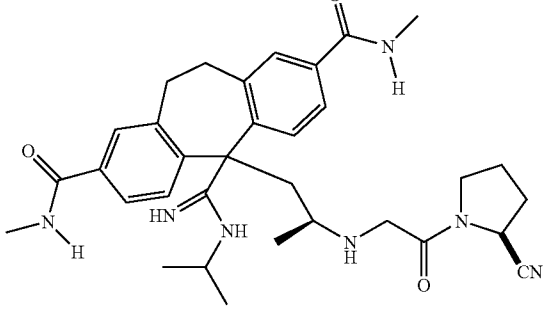
-continued

Example	Preparative Example	Preparative Example	Product
514	607	2	
515	608	2	
516	609	2	
517	610	2	

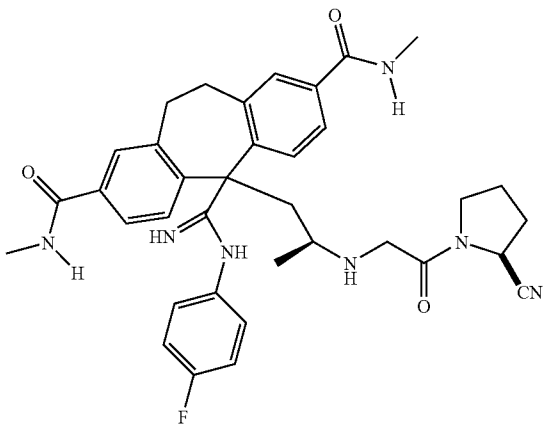
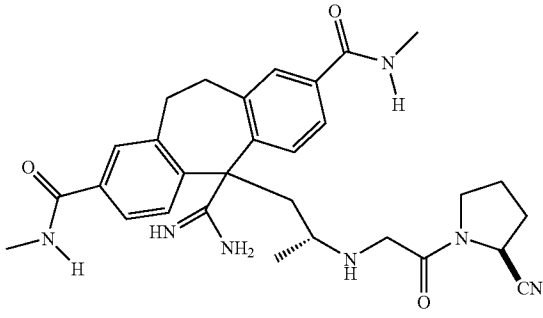
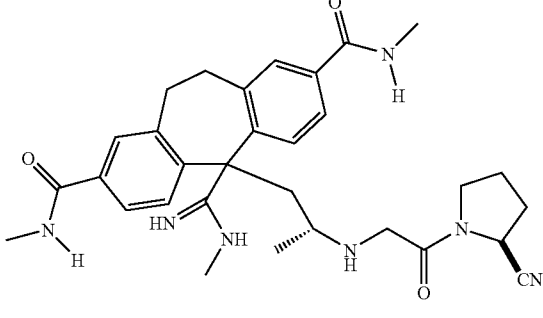
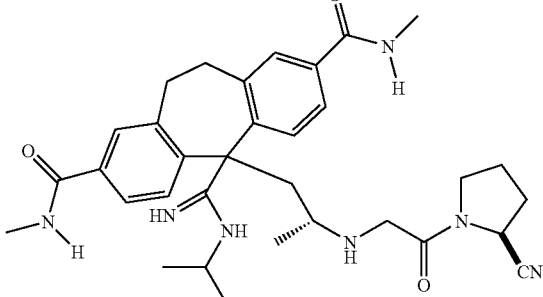
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Example	Preparative Example	Preparative Example	Product
518	611	2	
519	612	2	
520	613	2	
521	614	2	

-continued

Example	Preparative Example	Preparative Example	Product
522	615	2	
523	616	2	
524	617	2	
525	618	2	

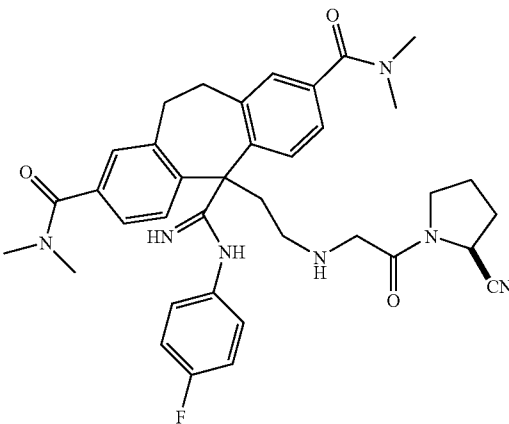
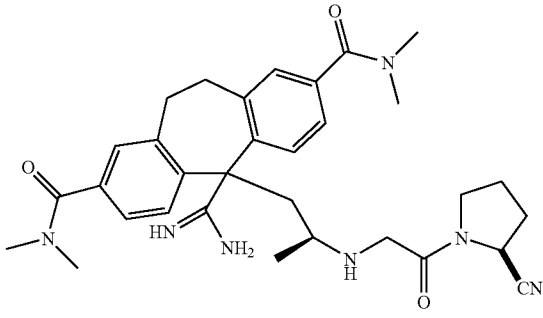
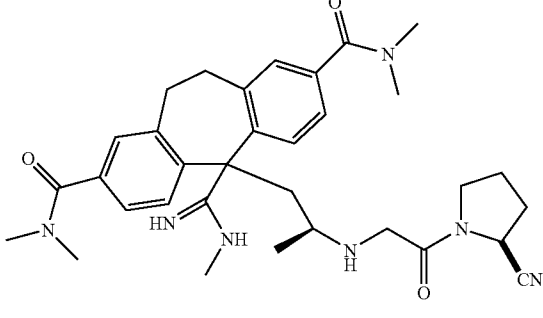
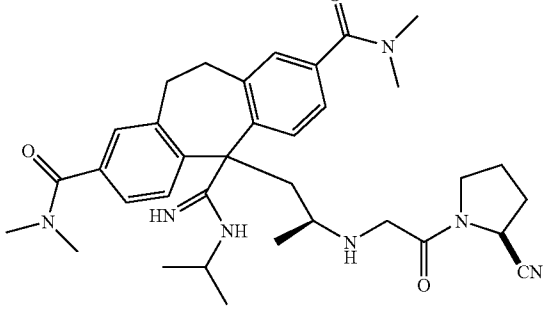
-continued

Example	Preparative Example	Preparative Example	Product
526	619	2	
527	620	2	
528	621	2	
529	622	2	

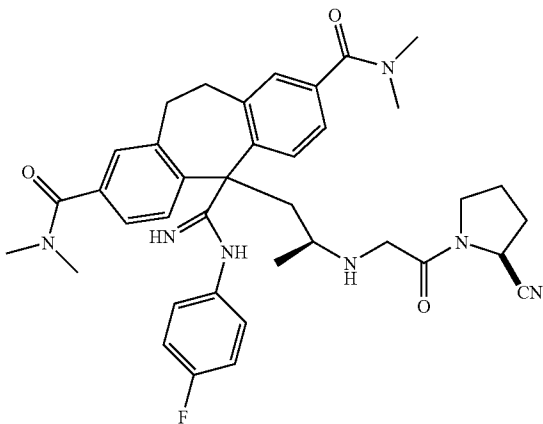
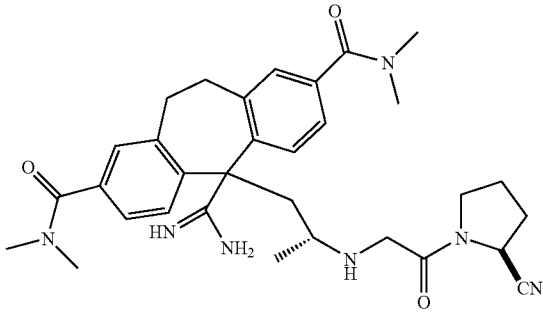
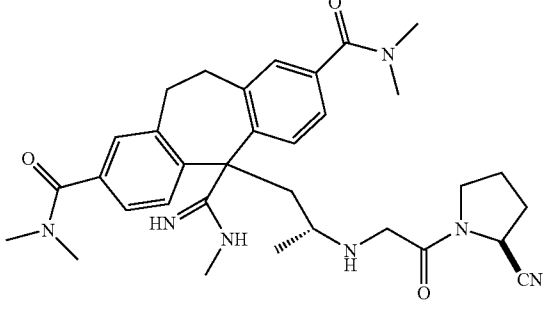
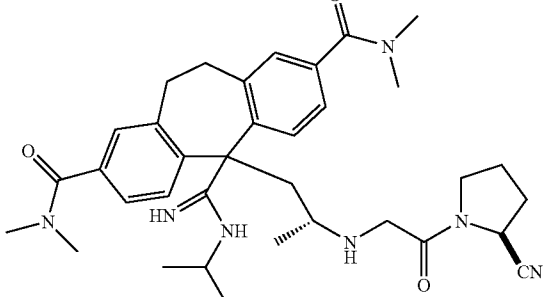
-continued

Example	Preparative Example	Preparative Example	Product
530	623	2	
531	624	2	
532	625	2	
533	626	2	

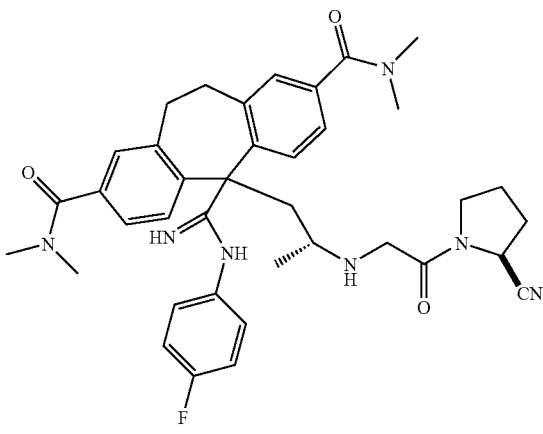
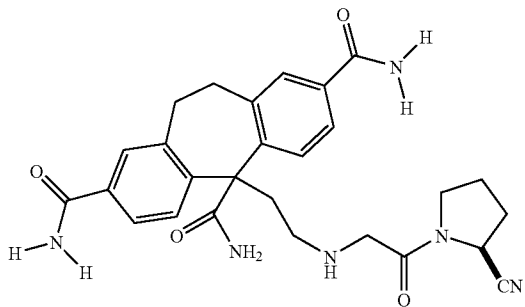
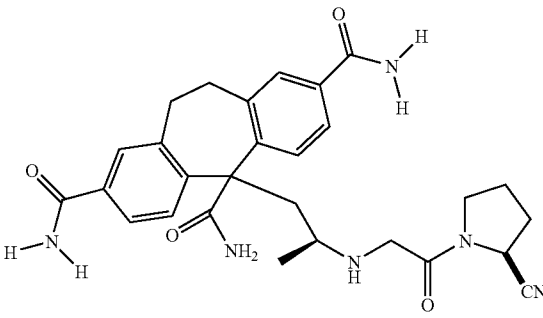
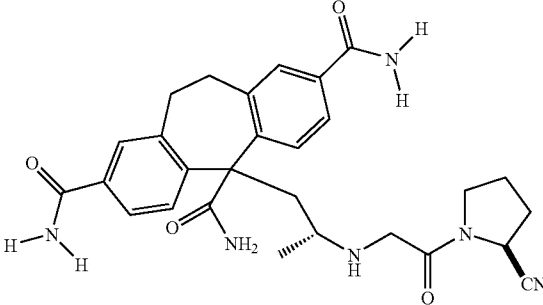
-continued

Example	Preparative Example	Preparative Example	Product
534	627	2	
535	628	2	
536	629	2	
537	630	2	

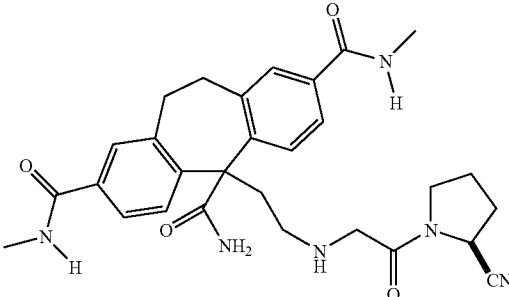
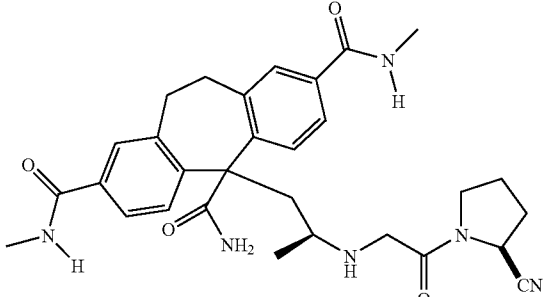
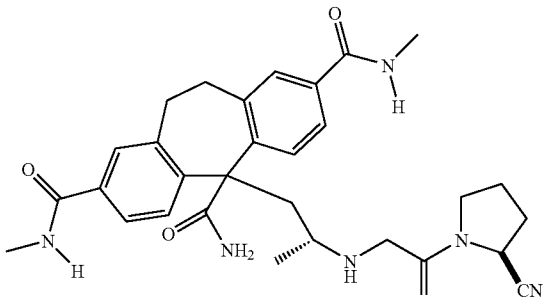
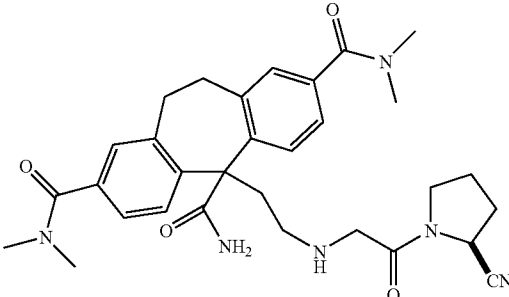
-continued

Example	Preparative Example	Preparative Example	Product
538	631	2	
539	632	2	
540	633	2	
541	634	2	

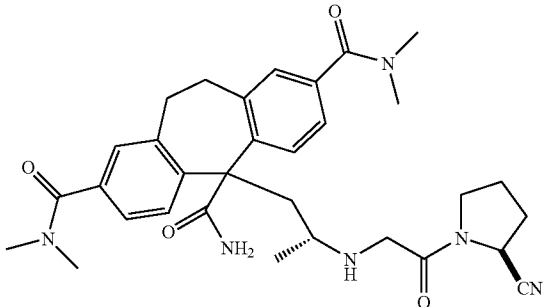
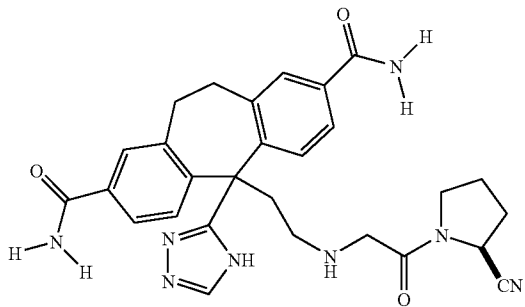
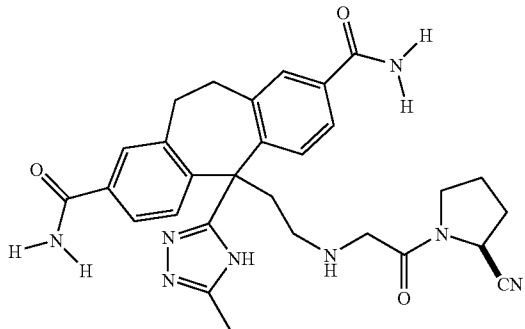
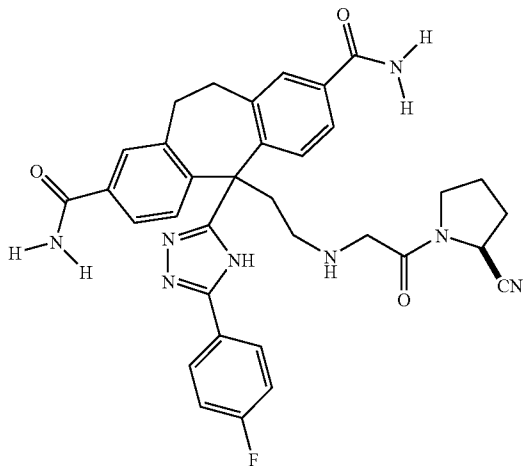
-continued

Example	Preparative Example	Preparative Example	Product
542	635	2	
543	680	2	
544	681	2	
545	682	2	

-continued

Example	Preparative Example	Preparative Example	Product
546	683	2	
547	684	2	
548	685	2	
549	686	2	

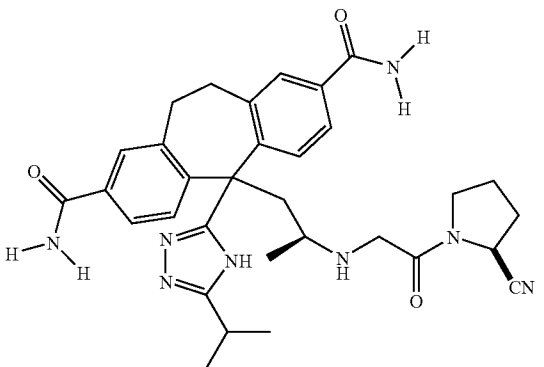
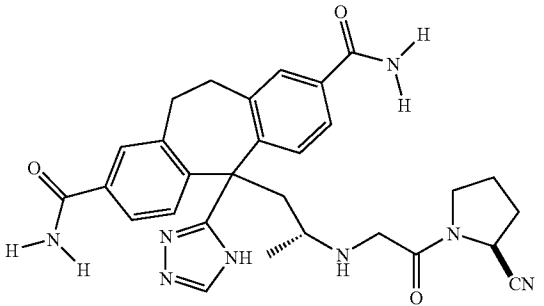
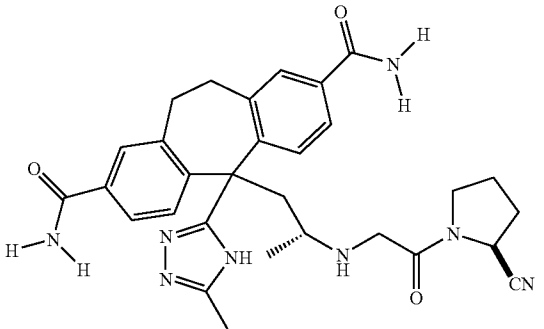
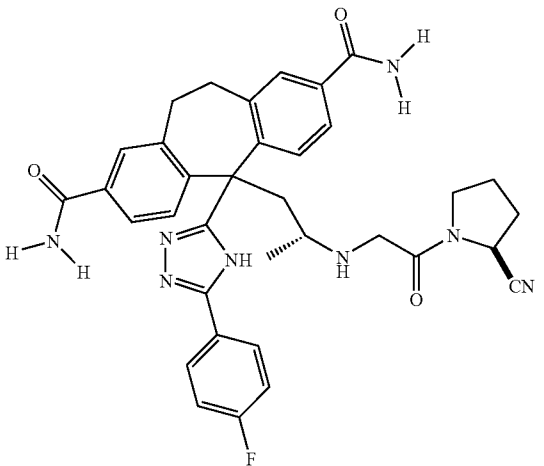
-continued

Example	Preparative Example	Preparative Example	Product
550	687	2	
551	700	2	
552	701	2	
553	702	2	

-continued

Example	Preparative Example	Preparative Example	Product
554	703	2	
555	704	2	
556	705	2	
557	706	2	

-continued

Example	Preparative Example	Preparative Example	Product
558	707	2	
559	708	2	
560	709	2	
561	710	2	

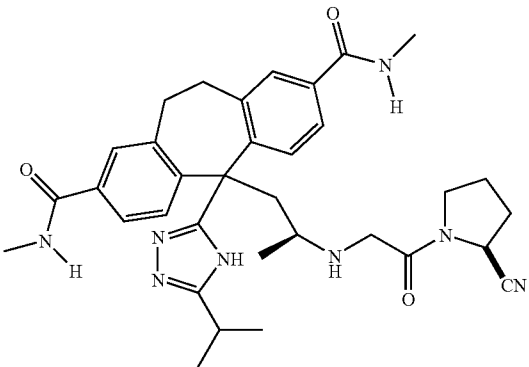
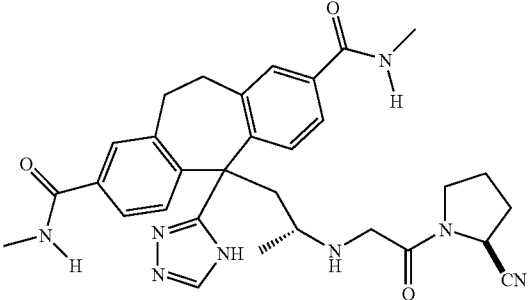
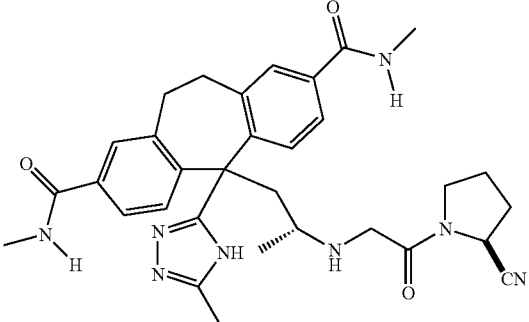
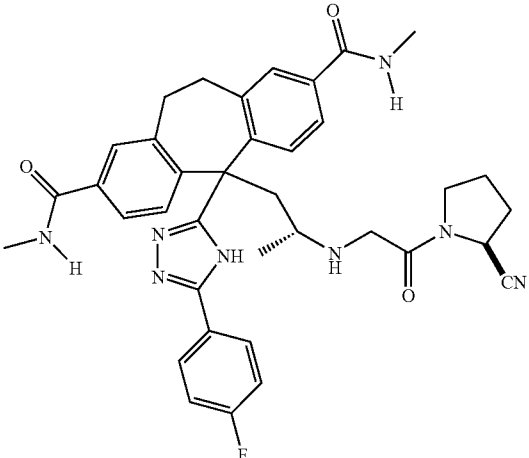
-continued

Example	Preparative Example	Preparative Example	Product
562	711	2	
563	712	2	
564	713	2	
565	714	2	

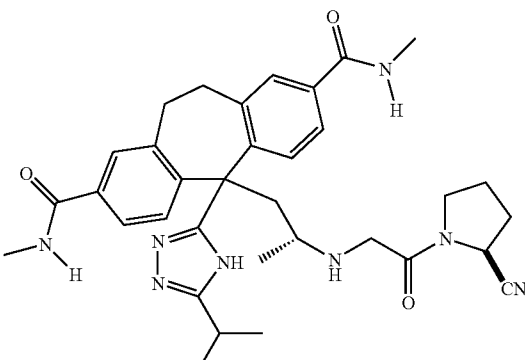
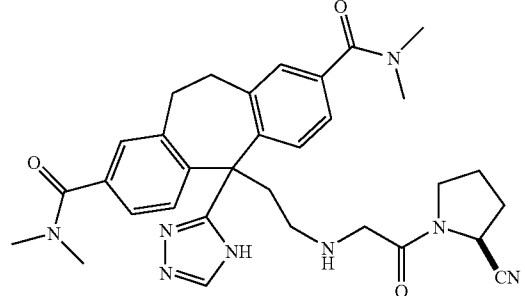
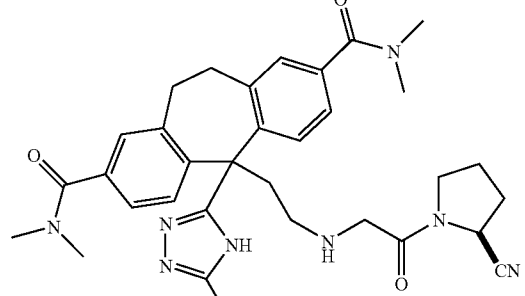
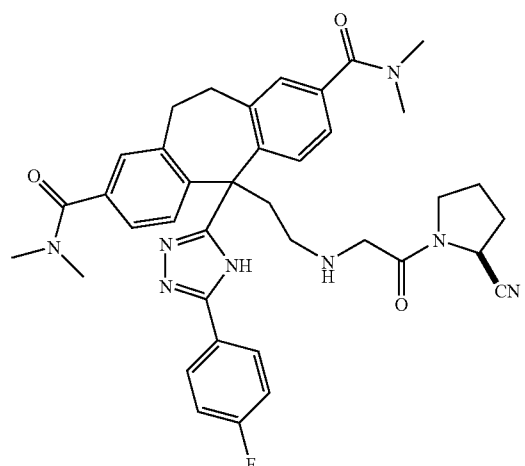
-continued

Example	Preparative Example	Preparative Example	Product
566	715	2	
567	716	2	
568	717	2	
569	718	2	

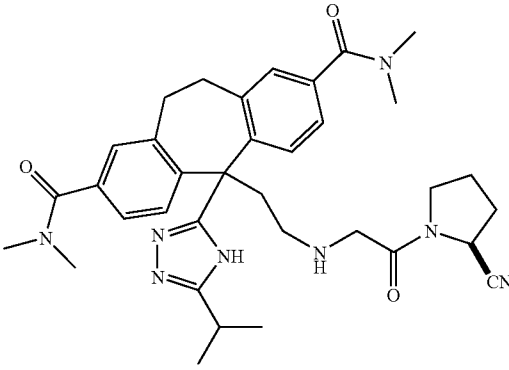
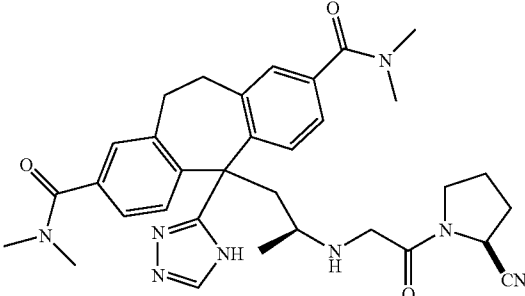
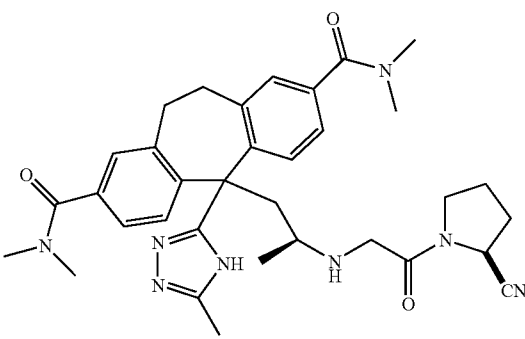
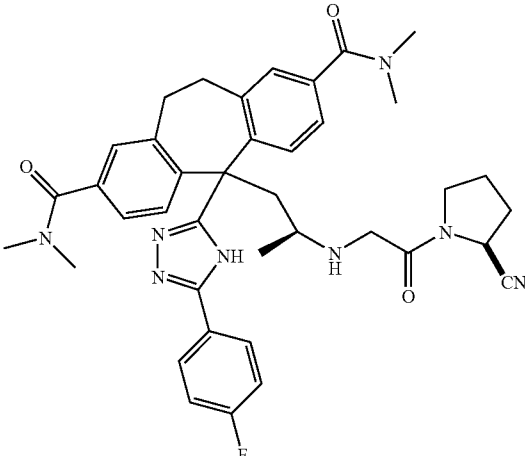
-continued

Example	Preparative Example	Preparative Example	Product
570	719	2	
571	720	2	
572	721	2	
573	722	2	

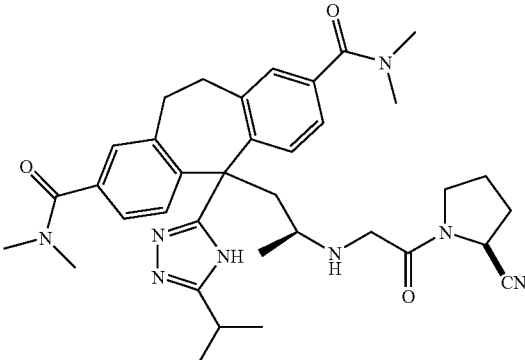
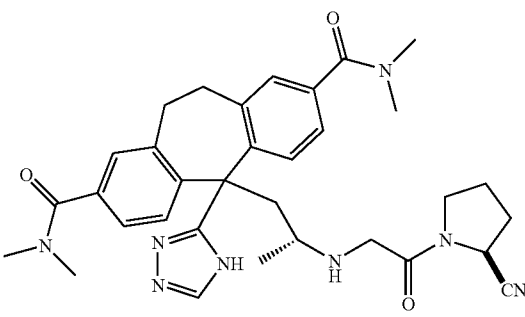
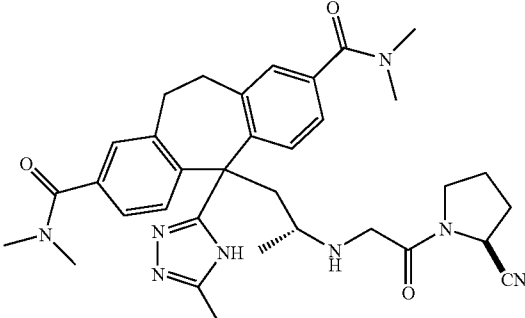
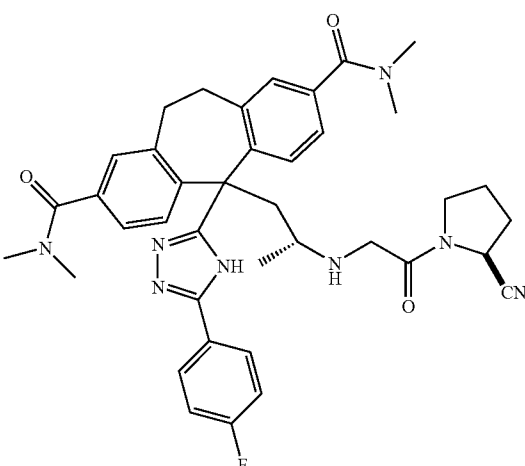
-continued

Example	Preparative Example	Preparative Example	Product
574	723	2	
575	724	2	
576	725	2	
577	726	2	

-continued

Example	Preparative Example	Preparative Example	Product
578	727	2	
579	728	2	
580	729	2	
581	730	2	

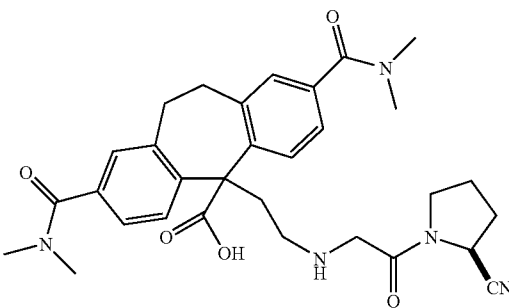
-continued

Example	Preparative Example	Preparative Example	Product
582	731	2	
583	732	2	
584	733	2	
585	734	2	

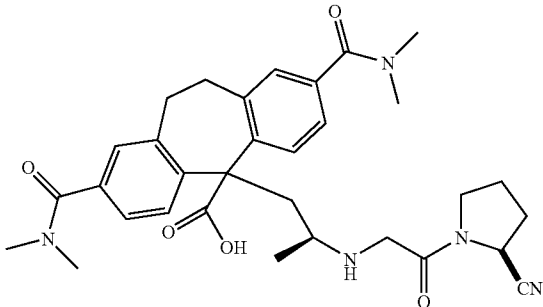
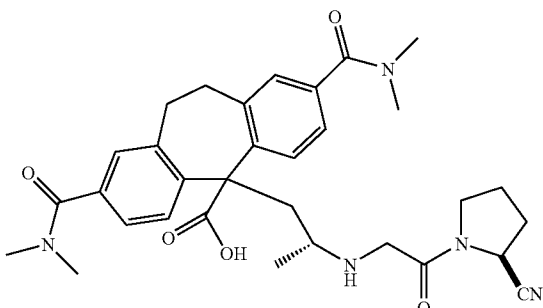
-continued

Example	Preparative Example	Preparative Example	Product
586	735	2	
587	780	2	
588	781	2	
589	782	2	

-continued

Example	Preparative Example	Preparative Example	Product
590	783	2	
591	784	2	
592	785	2	
593	786	2	

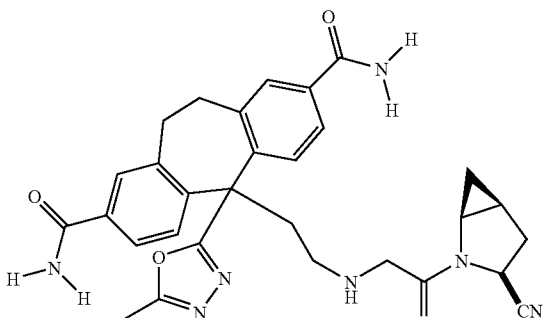
-continued

Example	Preparative Example	Preparative Example	Product
594	787	2	
595	788	2	

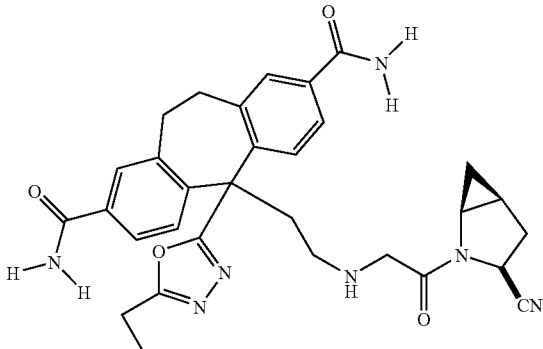
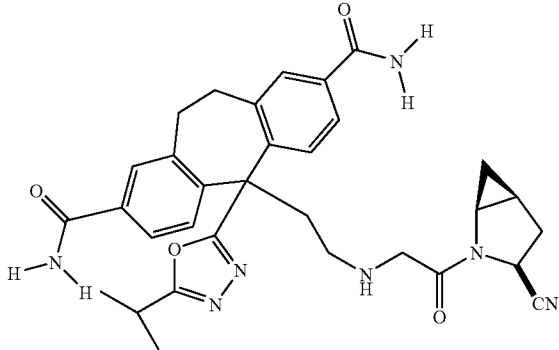
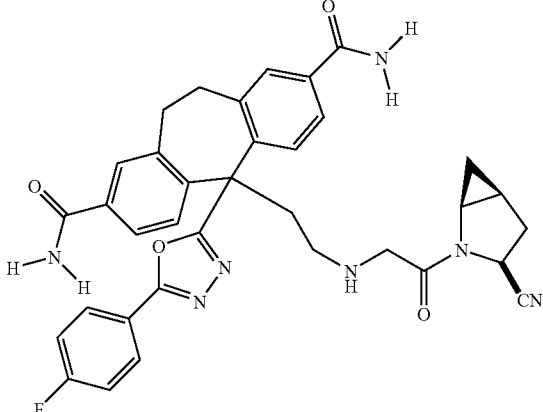
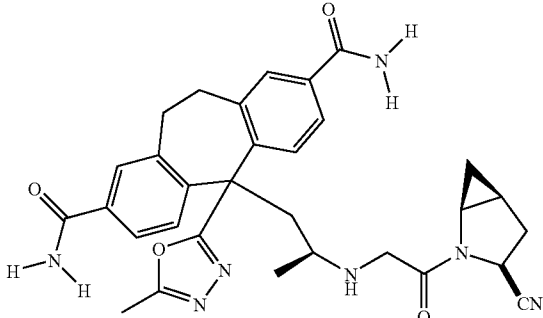
[0856] Examples 596-599 have been intentionally excluded.

Example 600-795

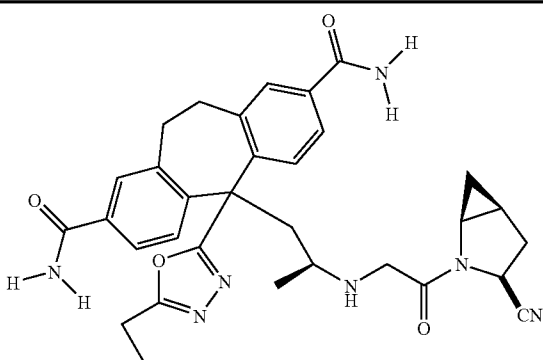
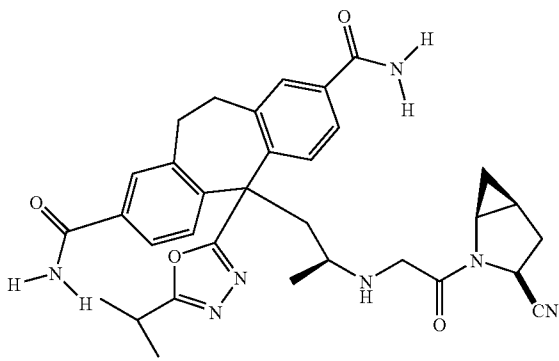
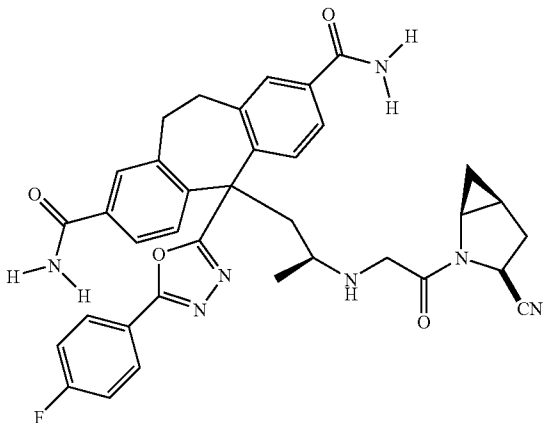
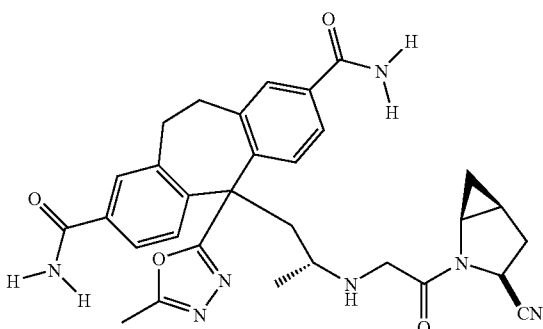
[0857] If one were to follow the procedures outlined in Examples 28 or 29 except using the compounds from the Preparative Examples as indicated in the Table below, one would obtain the indicated Product.

Example	Preparative Example	Preparative Example	Product
600	336	89	

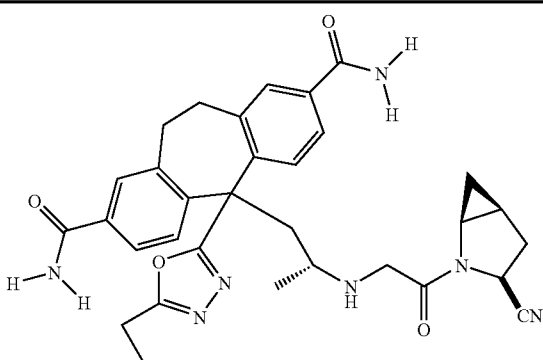
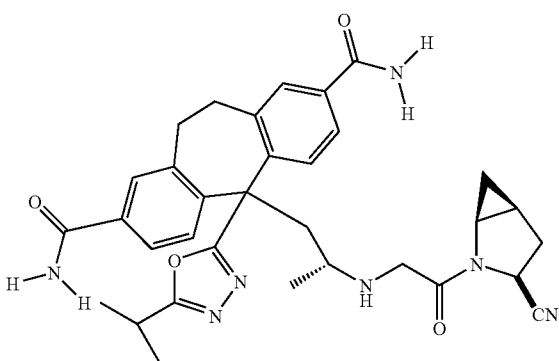
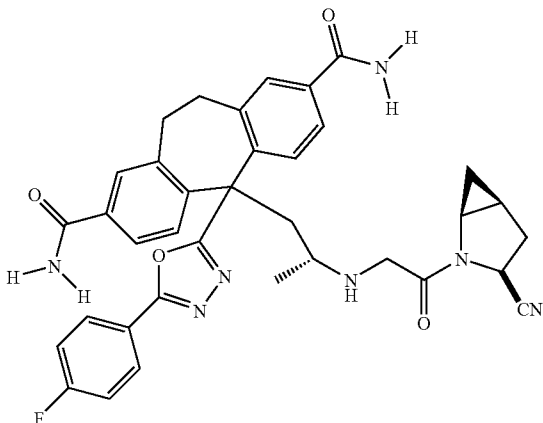
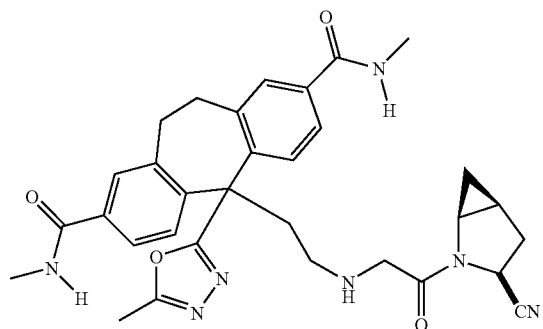
-continued

Example	Preparative Example	Preparative Example	Product
601	337	89	
602	338	89	
603	339	89	
604	340	89	

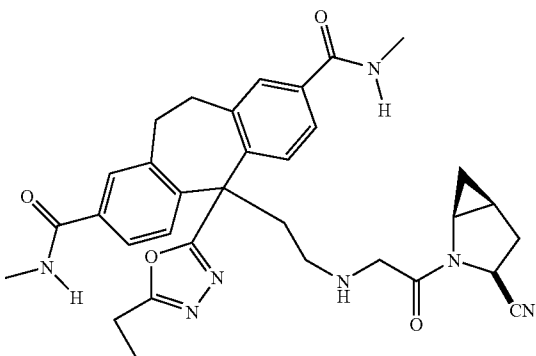
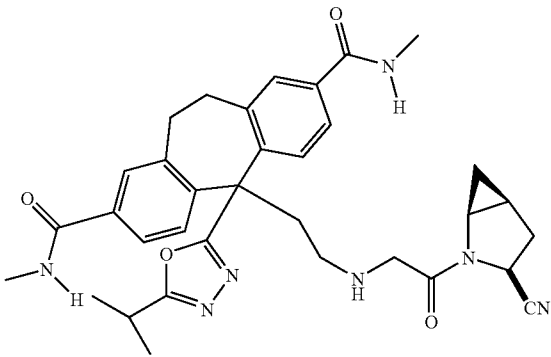
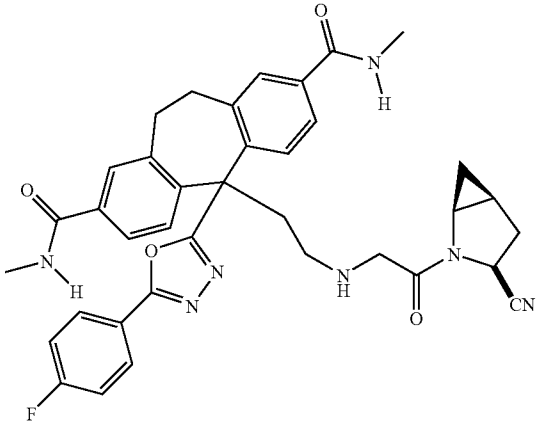
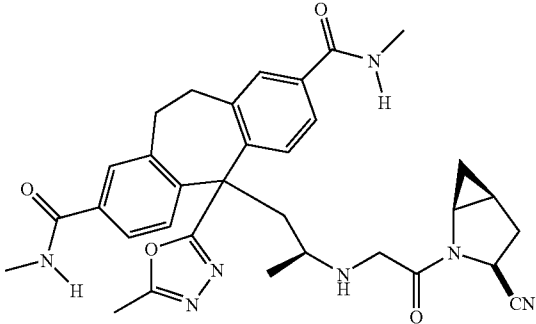
-continued

Example	Preparative Example	Preparative Example	Product
605	341	89	
606	342	89	
607	343	89	
608	344	89	

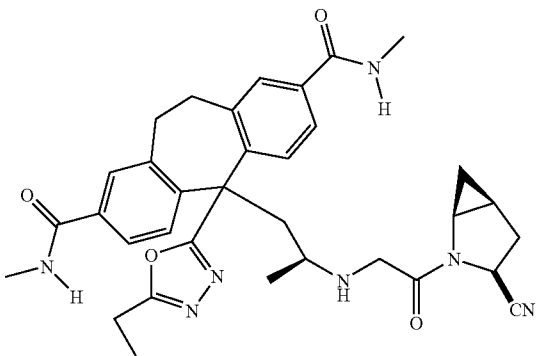
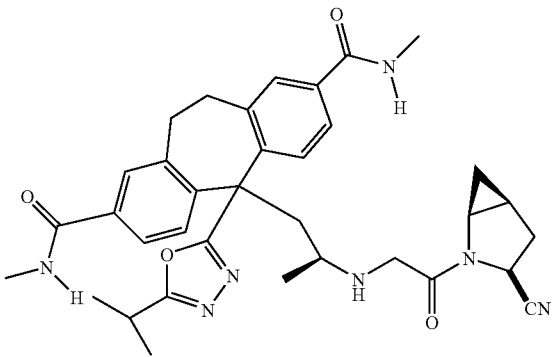
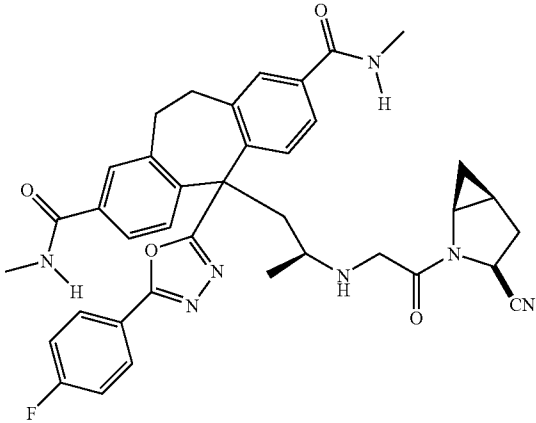
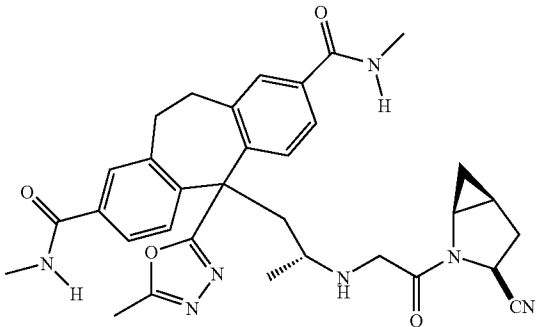
-continued

Example	Preparative Example	Preparative Example	Product
609	345	89	
610	346	89	
611	347	89	
612	348	89	

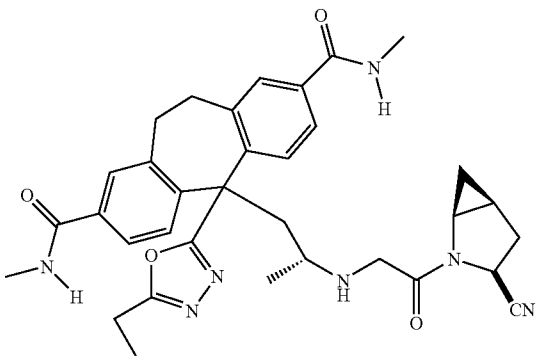
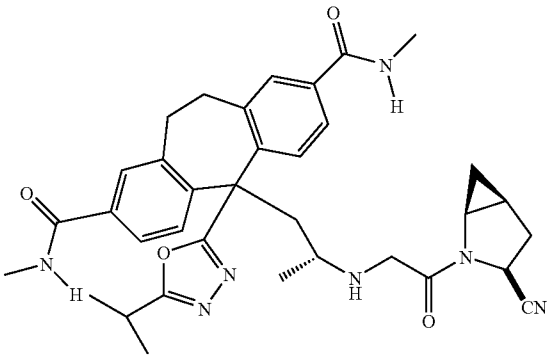
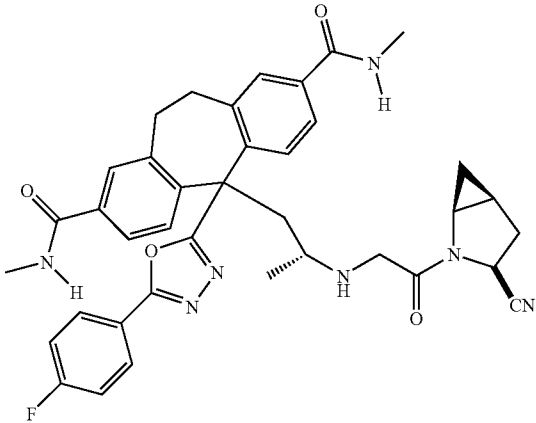
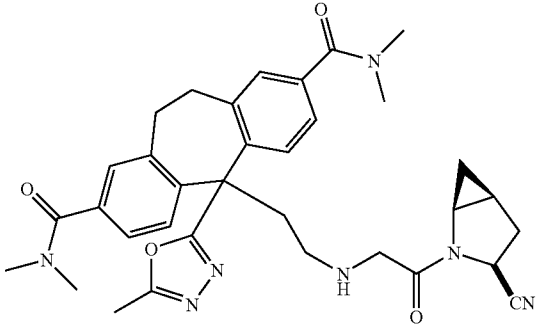
-continued

Example	Preparative Example	Preparative Example	Product
613	349	89	
614	350	89	
615	351	89	
616	352	89	

-continued

Example	Preparative Example	Preparative Example	Product
617	353	89	
618	354	89	
619	355	89	
620	356	89	

-continued

Example	Preparative Example	Preparative Example	Product
621	357	89	
622	358	89	
623	359	89	
624	360	89	

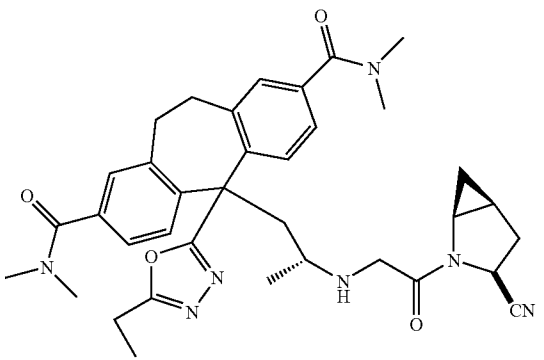
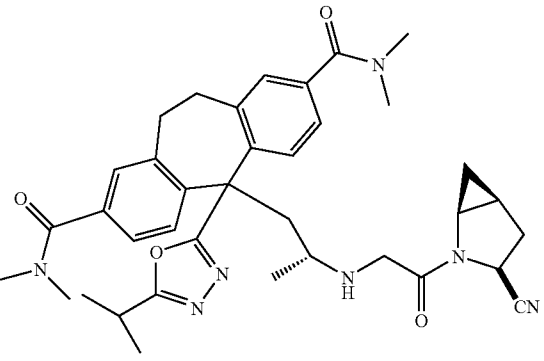
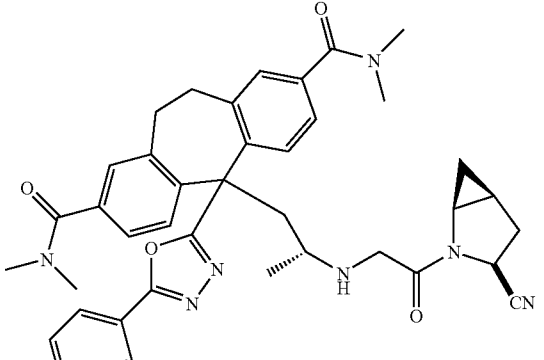
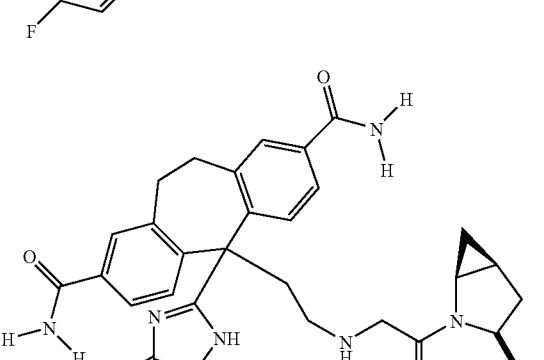
-continued

Example	Preparative Example	Preparative Example	Product
625	361	89	
626	362	89	
627	363	89	
628	364	89	

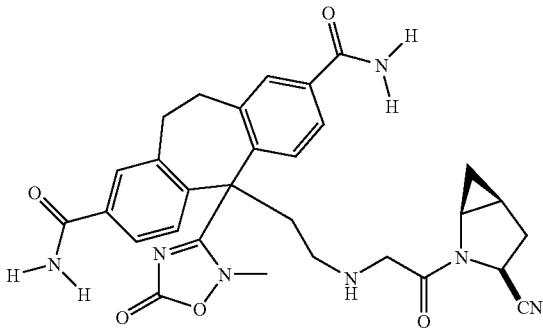
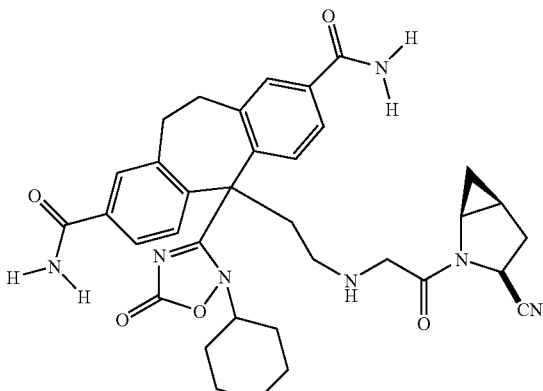
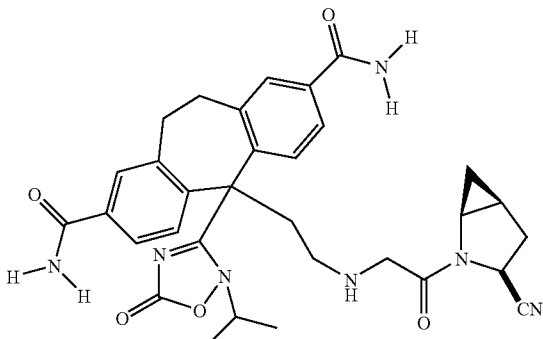
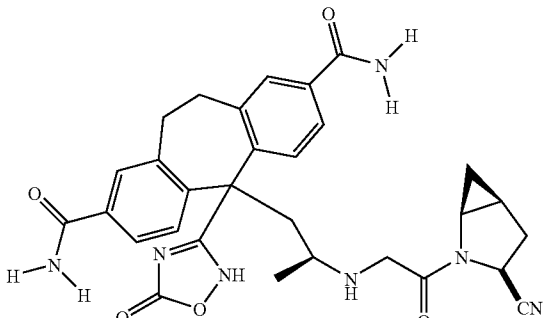
-continued

Example	Preparative Example	Preparative Example	Product
629	365	89	
630	366	89	
631	367	89	
632	368	89	

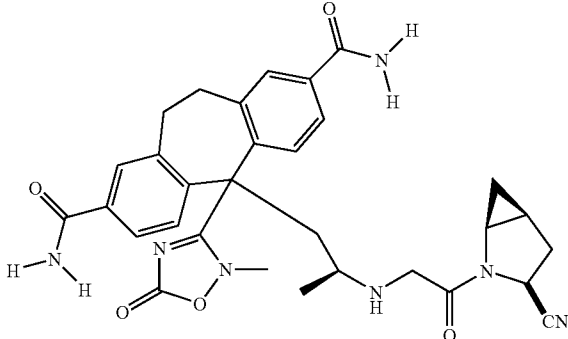
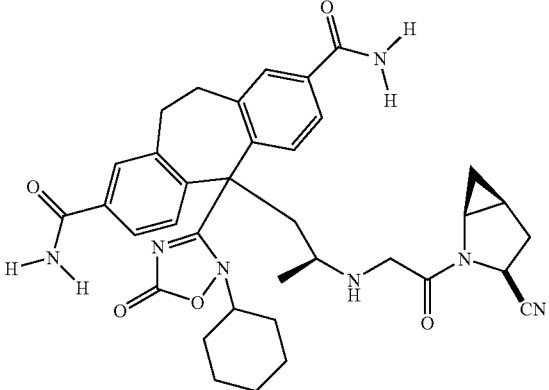
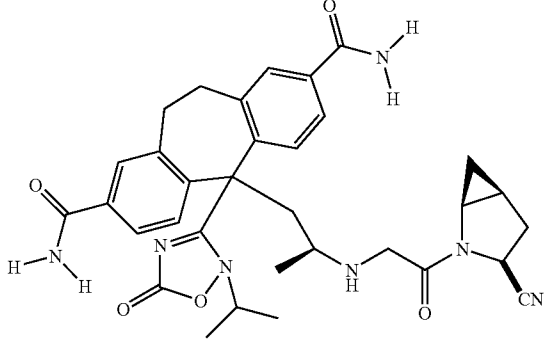
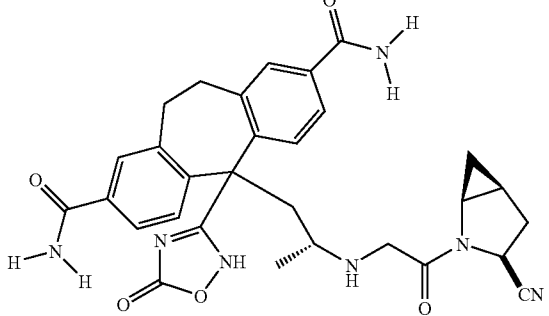
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Example	Preparative Example	Preparative Example	Product
633	369	89	
634	370	89	
635	371	89	
636	435	89	

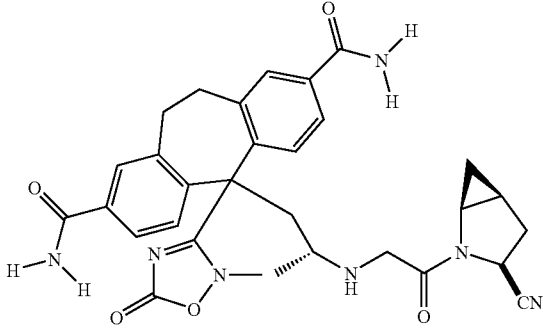
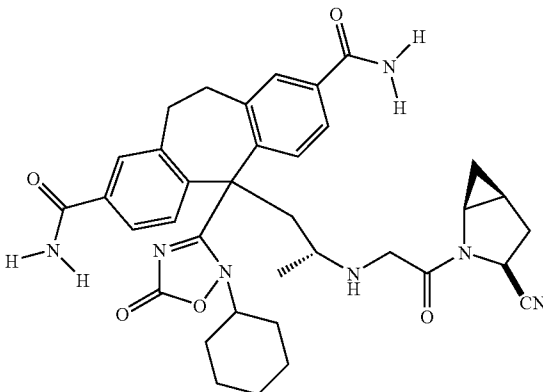
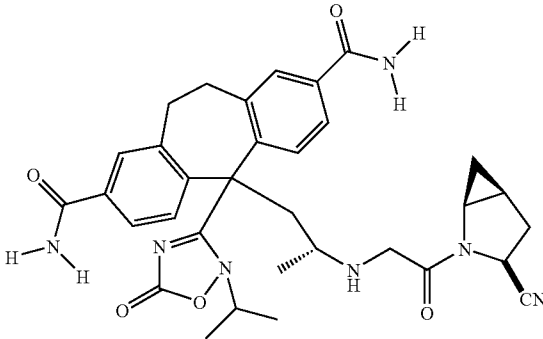
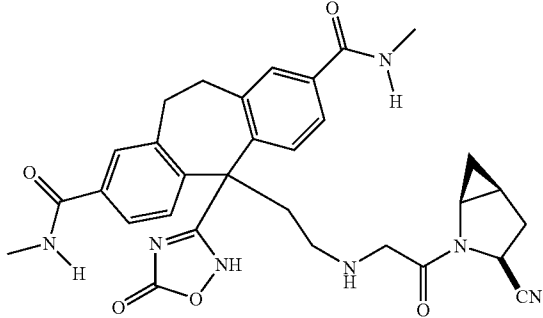
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Example	Preparative Example	Preparative Example	Product
637	436	89	
638	437	89	
639	438	89	
640	439	89	

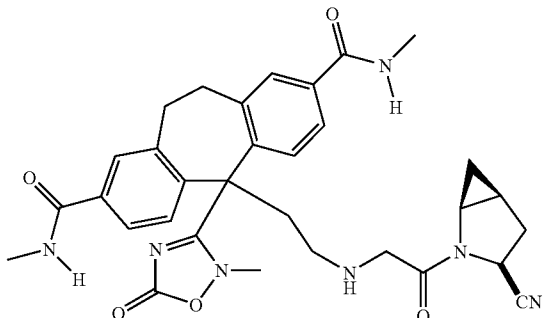
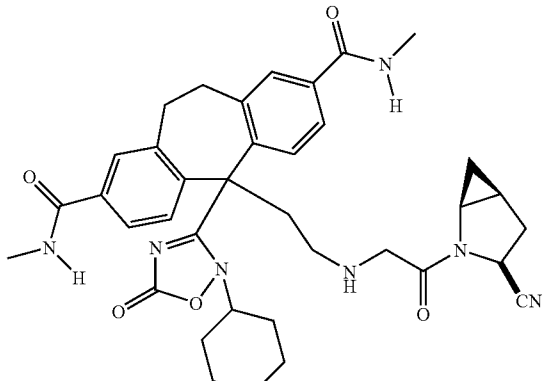
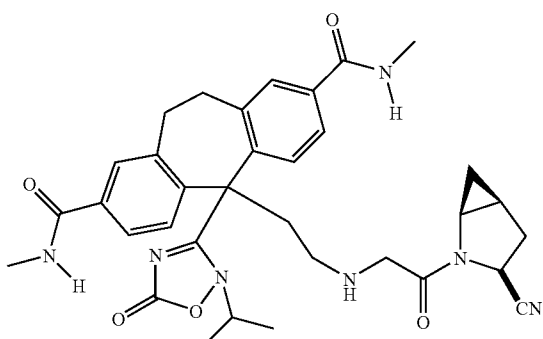
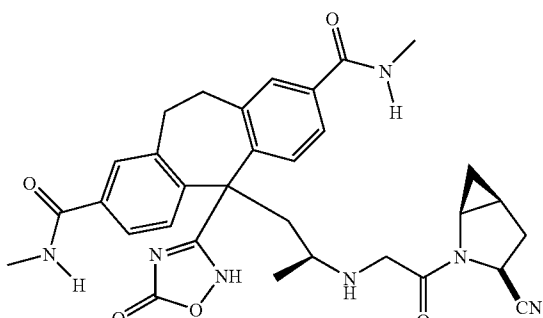
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Example	Preparative Example	Preparative Example	Product
641	440	89	
642	441	89	
643	442	89	
644	443	89	

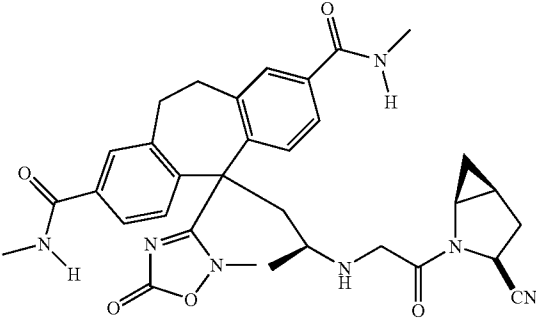
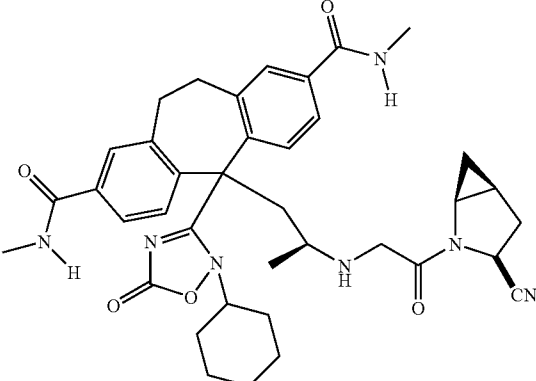
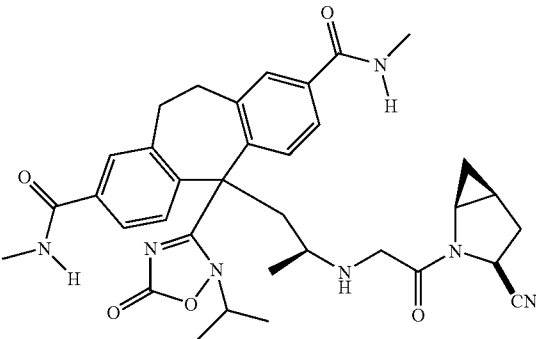
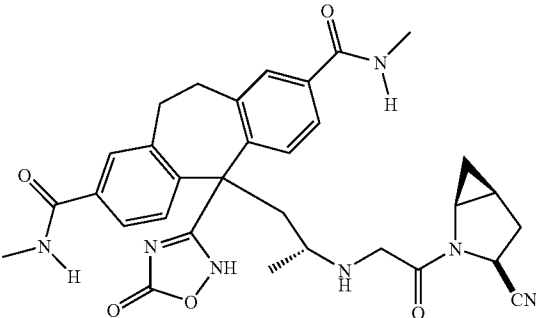
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Example	Preparative Example	Preparative Example	Product
645	444	89	
646	445	89	
647	446	89	
648	447	89	

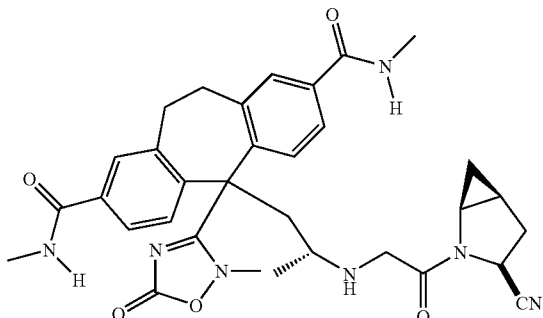
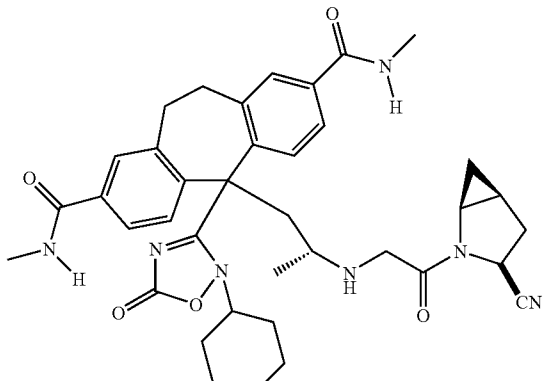
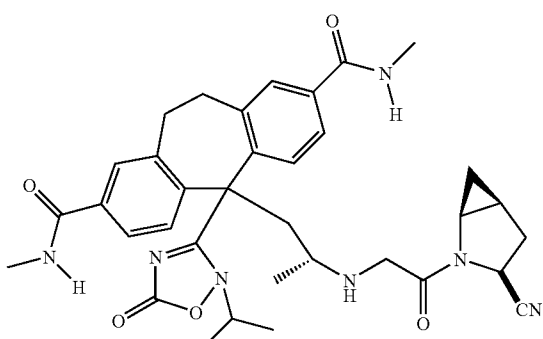
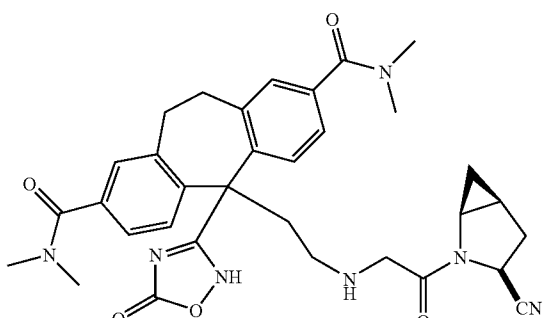
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Example	Preparative Example	Preparative Example	Product
649	448	89	
650	449	89	
651	450	89	
652	451	89	

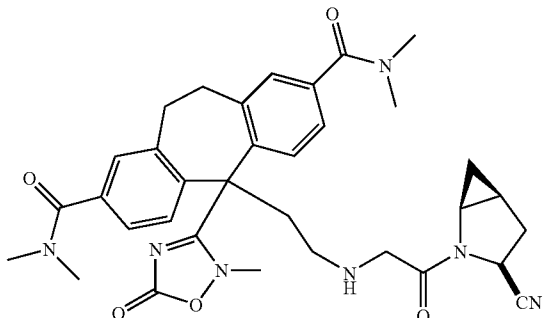
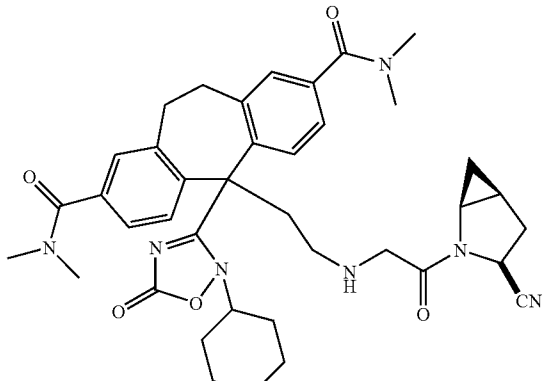
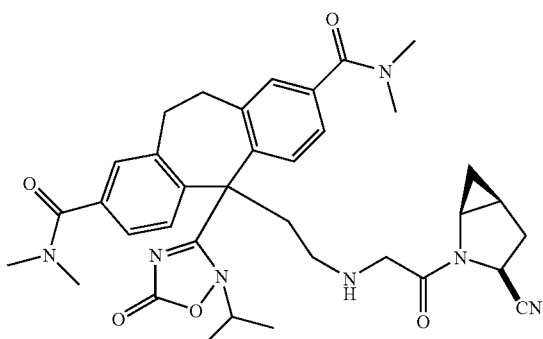
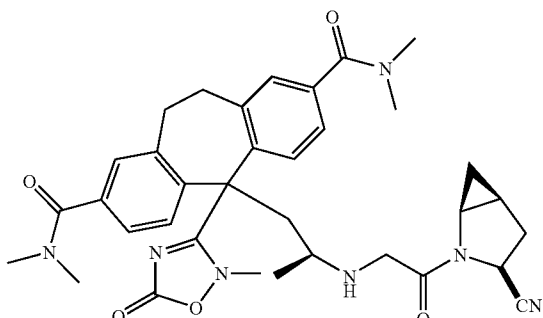
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Example	Preparative Example	Preparative Example	Product
653	452	89	
654	453	89	
655	454	89	
656	455	89	

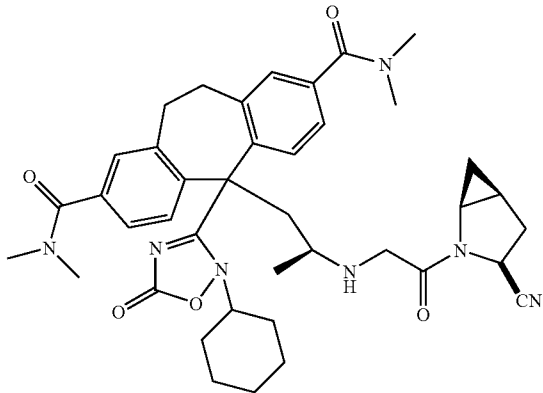
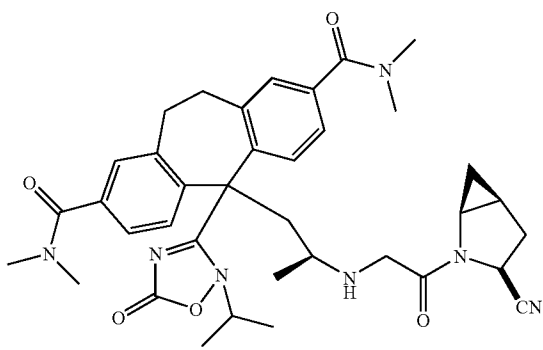
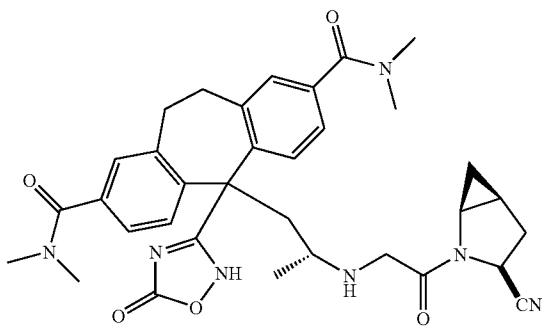
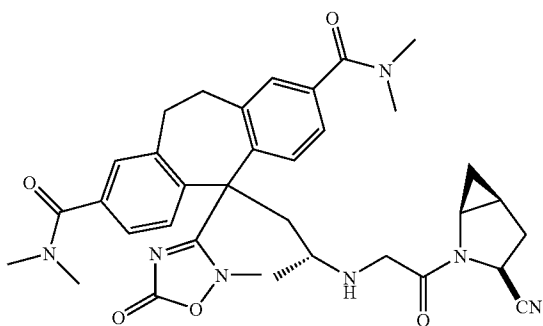
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Example	Preparative Example	Preparative Example	Product
657	456	89	
658	457	89	
659	458	89	
660	459	89	

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Example	Preparative Example	Preparative Example	Product
661	460	89	
662	461	89	
663	462	89	
664	463	89	

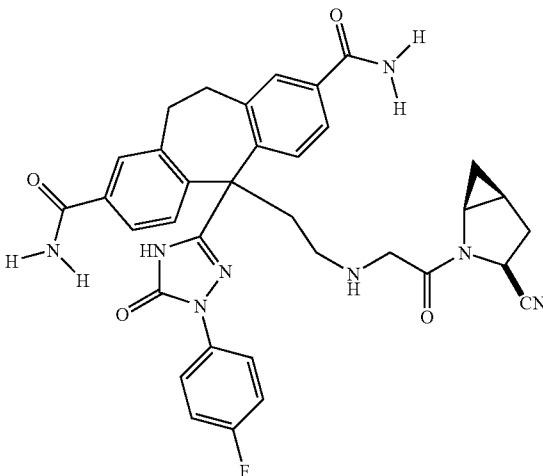
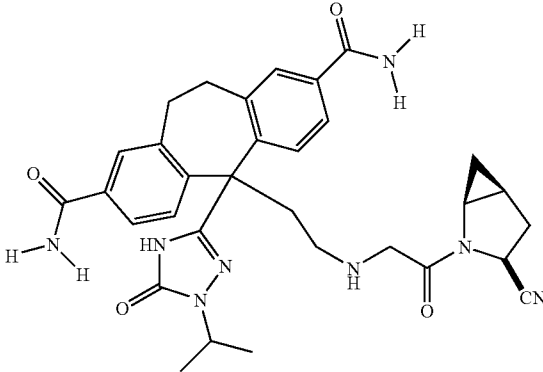
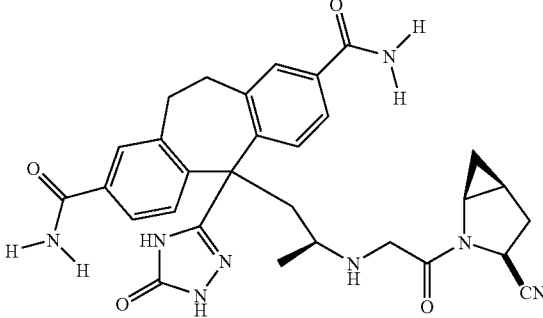
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Example	Preparative Example	Preparative Example	Product
665	464	89	
666	465	89	
667	466	89	
668	467	89	

-continued

Example	Preparative Example	Preparative Example	Product
669	468	89	
670	469	89	
671	536	89	
672	537	89	

-continued

Example	Preparative Example	Preparative Example	Product
673	538	89	
674	539	89	
675	540	89	

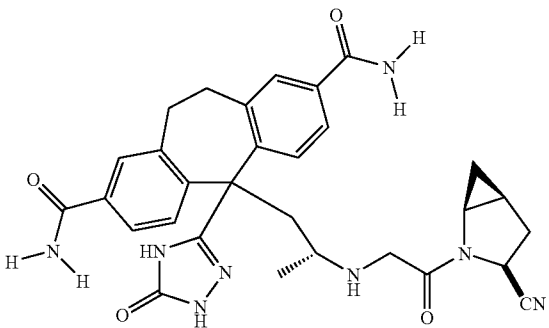
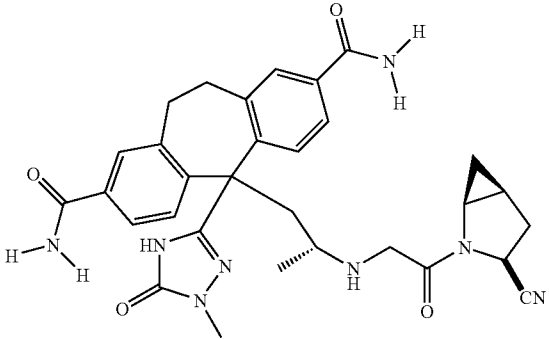
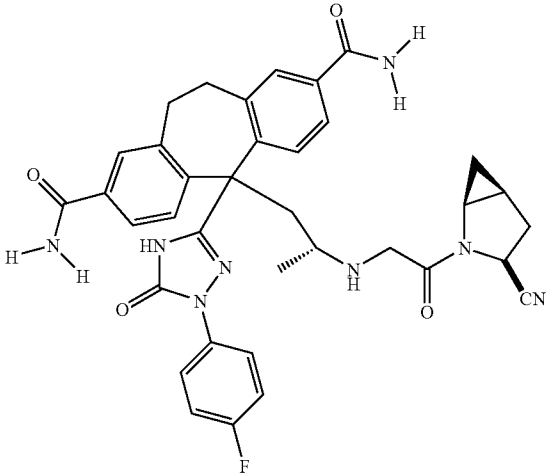
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Example	Preparative Example	Preparative Example	Product
676	541	89	
677	542	89	
678	543	89	

Example	Preparative Example	Preparative Example	Product
676	541	89	
677	542	89	
678	543	89	

Example	Preparative Example	Preparative Example	Product
676	541	89	
677	542	89	
678	543	89	

-continued

Example	Preparative Example	Preparative Example	Product
679	544	89	
680	545	89	
681	546	89	

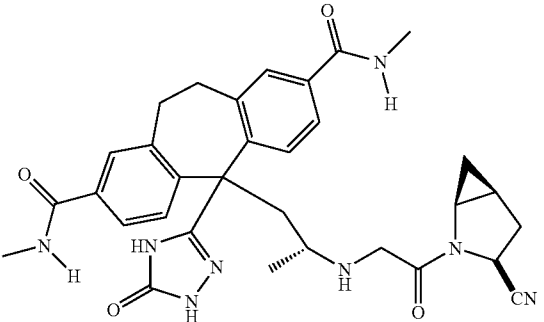
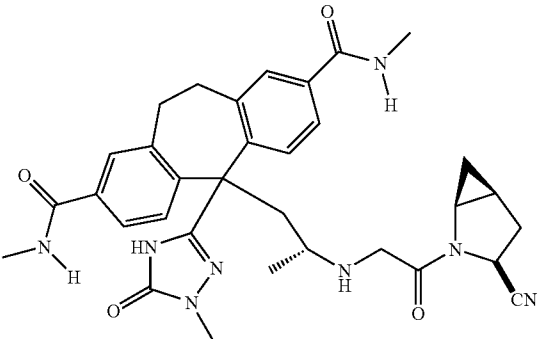
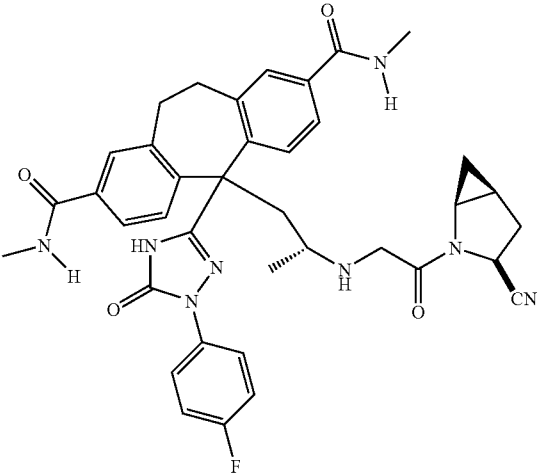
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Example	Preparative Example	Preparative Example	Product
682	547	89	
683	548	89	
684	549	89	

-continued

Example	Preparative Example	Preparative Example	Product
685	550	89	
686	551	89	
687	552	89	

-continued

Example	Preparative Example	Preparative Example	Product
691	556	89	
692	557	89	
693	558	89	

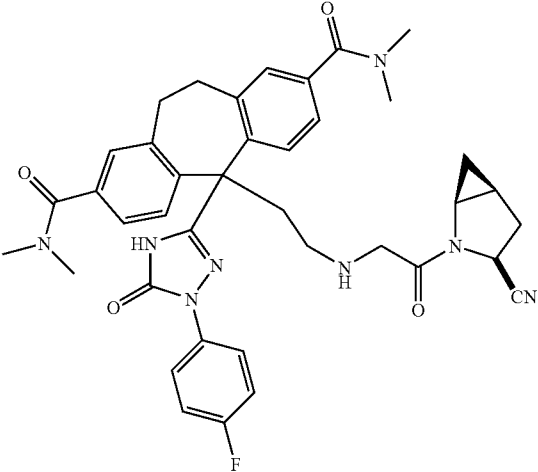
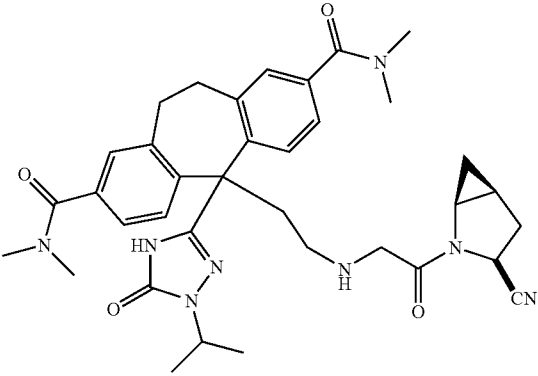
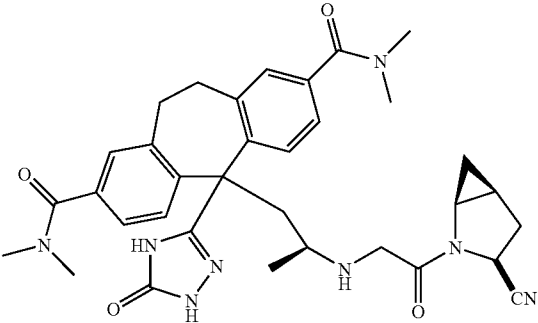
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Example	Preparative Example	Preparative Example	Product
694	559	89	
695	560	89	
696	561	89	

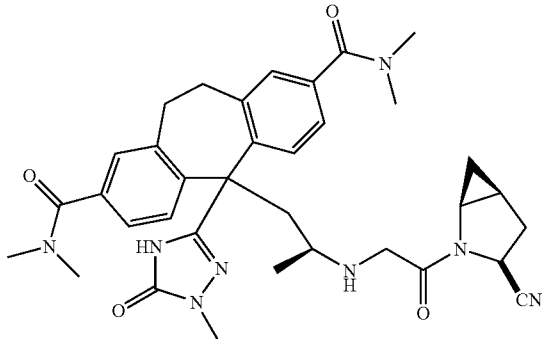
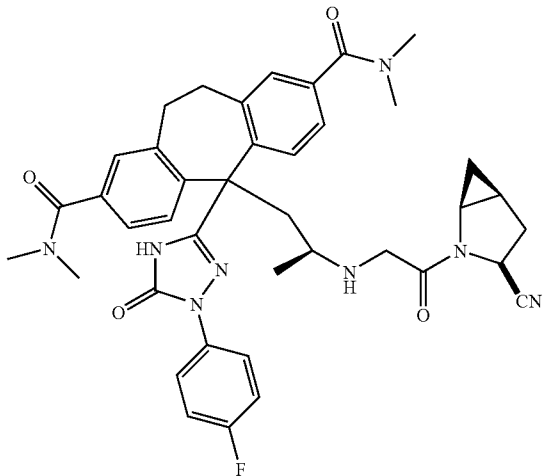
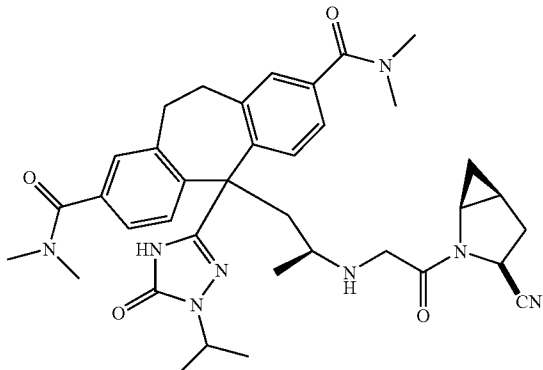
Example	Preparative Example	Preparative Example	Product
694	559	89	
695	560	89	
696	561	89	

Example	Preparative Example	Preparative Example	Product
694	559	89	
695	560	89	
696	561	89	

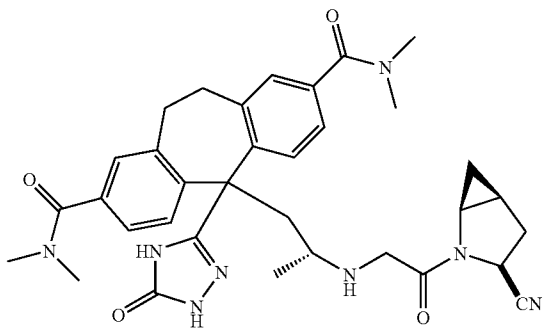
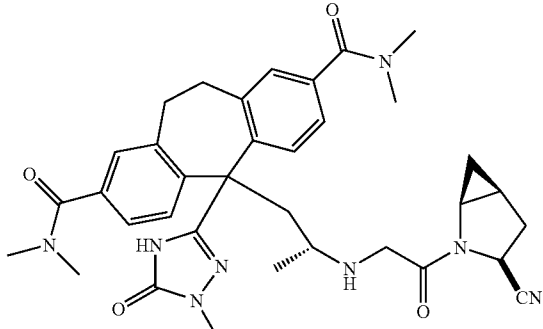
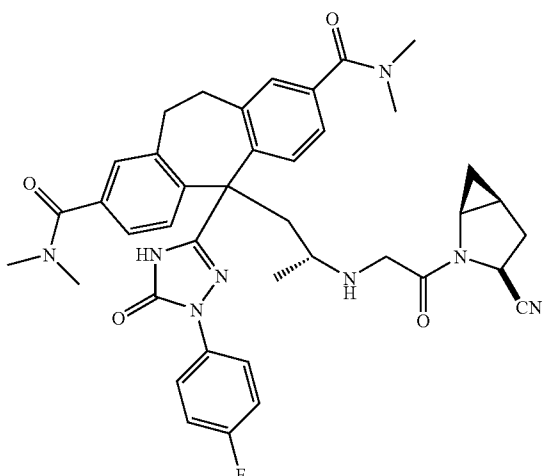
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Example	Preparative Example	Preparative Example	Product
697	562	89	
698	563	89	
699	564	89	

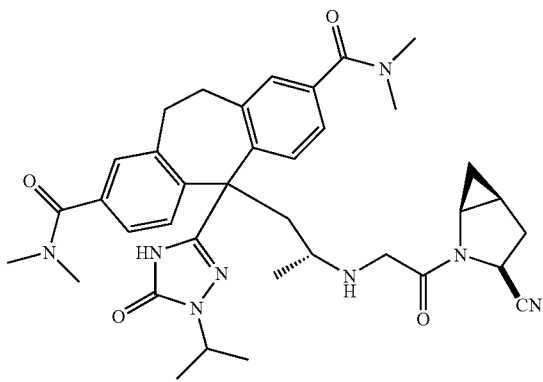
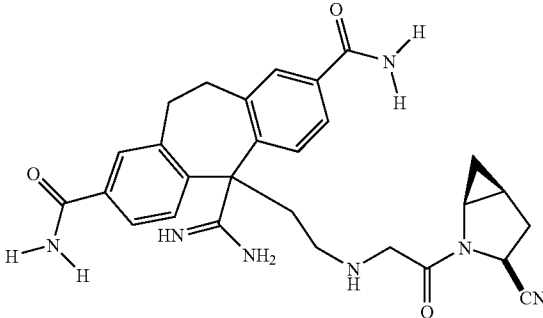
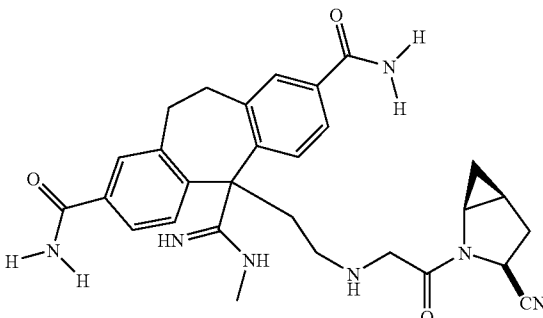
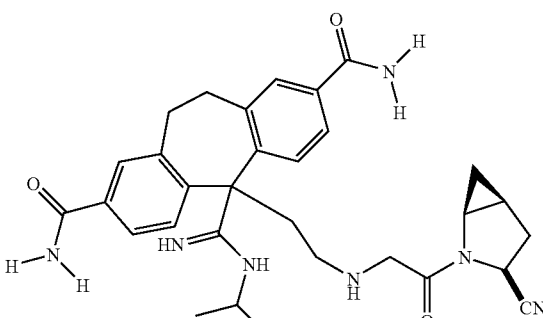
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Example	Preparative Example	Preparative Example	Product
700	565	89	
701	566	89	
702	567	89	

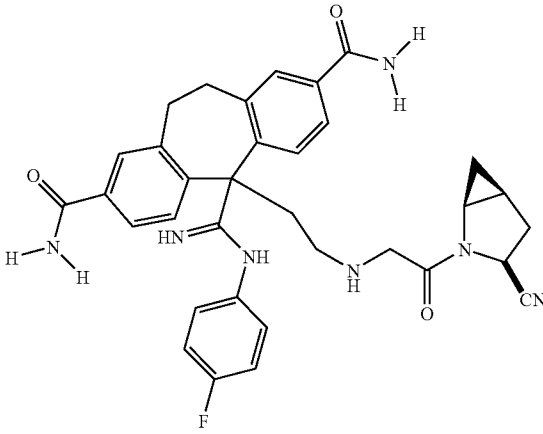
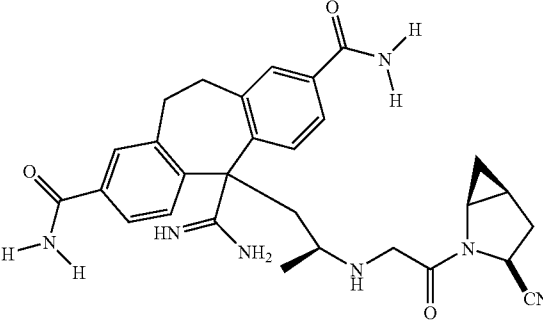
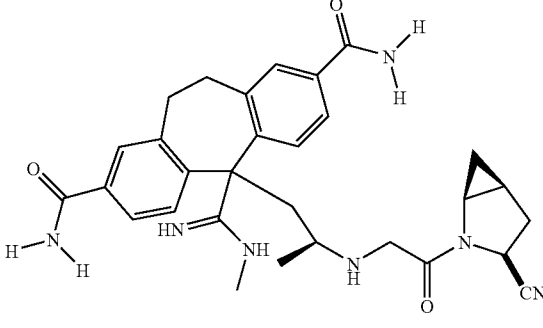
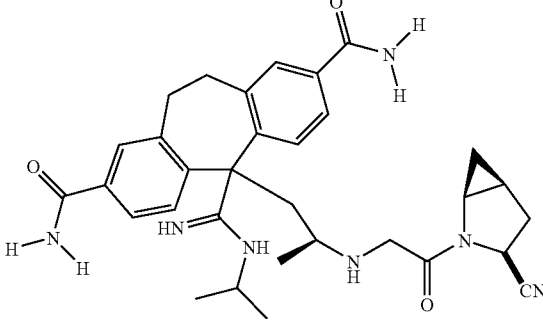
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Example	Preparative Example	Preparative Example	Product
703	568	89	
704	569	89	
705	570	89	

-continued

Example	Preparative Example	Preparative Example	Product
706	571	89	
707	636	89	
708	637	89	
709	638	89	

-continued

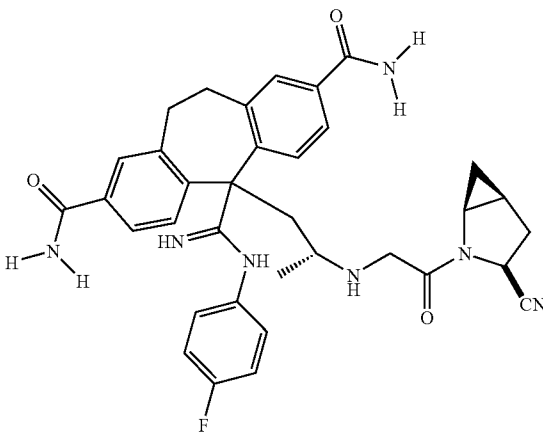
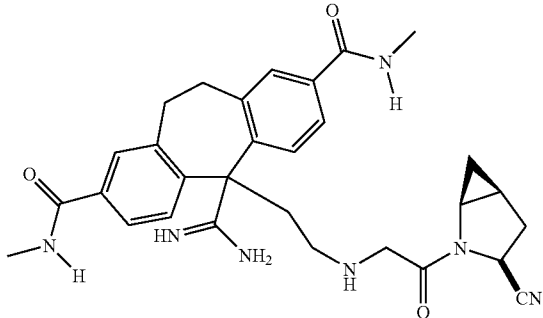
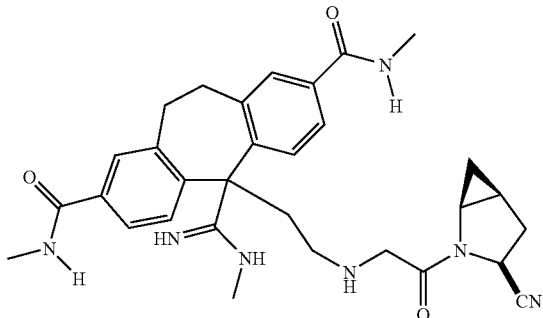
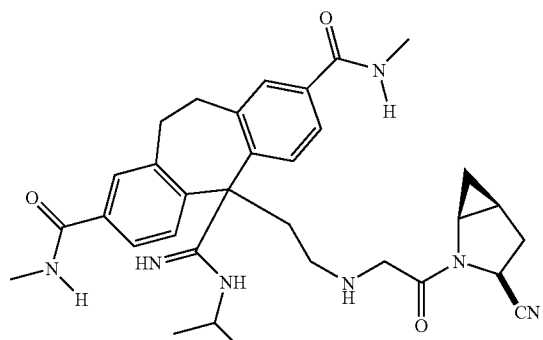
Example	Preparative Example	Preparative Example	Product
710	639	89	
711	640	89	
712	641	89	
713	642	89	

-continued

Example	Preparative Example	Preparative Example	Product
714	643	89	
715	644	89	
716	645	89	
717	646	89	

Example	Preparative Example	Preparative Example	Product
714	643	89	
715	644	89	
716	645	89	
717	646	89	

-continued

Example	Preparative Example	Preparative Example	Product
718	647	89	
719	648	89	
720	649	89	
721	650	89	

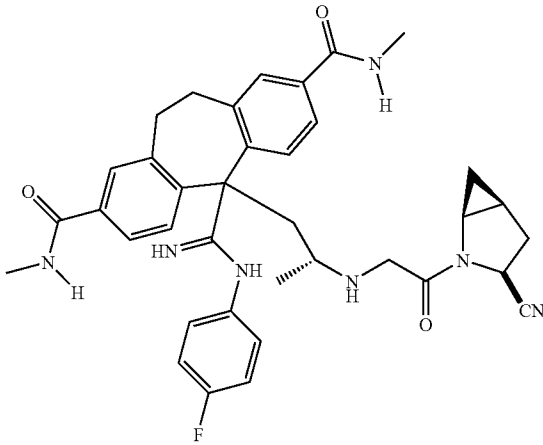
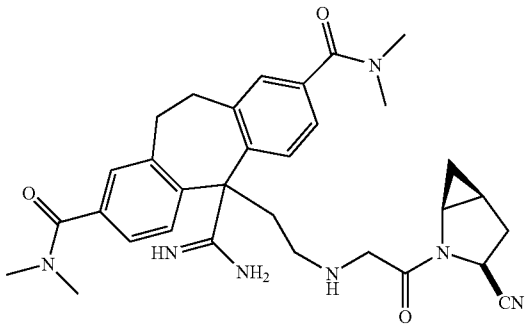
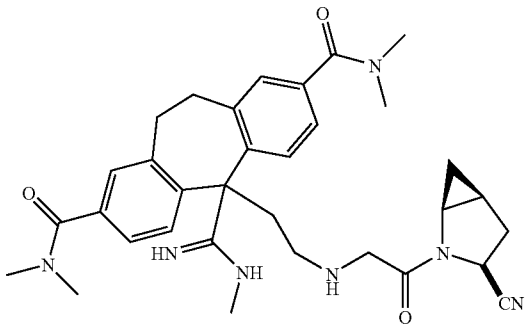
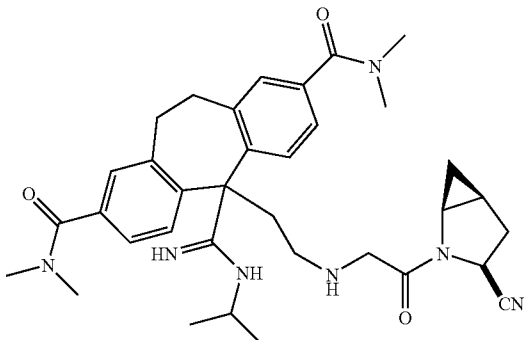
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Example	Preparative Example	Preparative Example	Product
722	651	89	
723	652	89	
724	653	89	
725	654	89	

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Example	Preparative Example	Preparative Example	Product
726	655	89	
727	656	89	
728	657	89	
729	658	89	

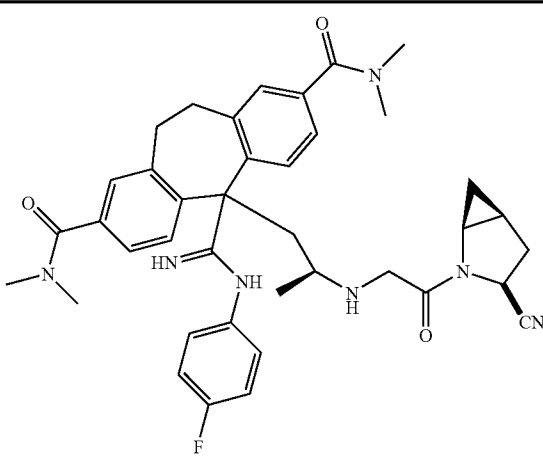
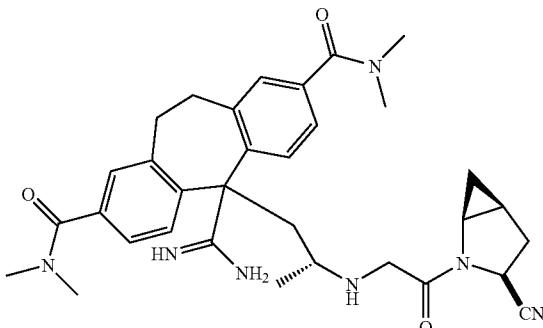
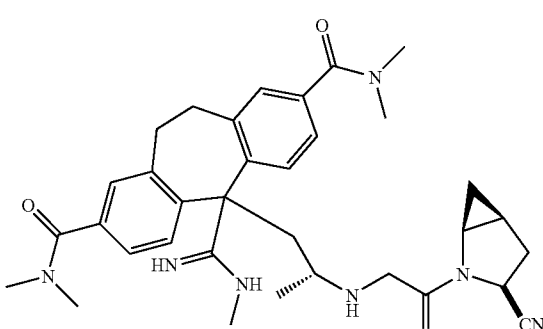
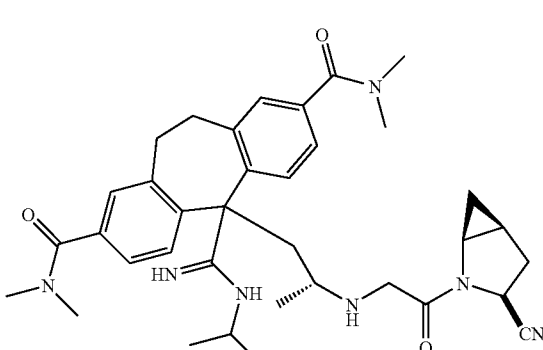
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Example	Preparative Example	Preparative Example	Product
730	659	89	
731	660	89	
732	661	89	
733	662	89	

-continued

Example	Preparative Example	Preparative Example	Product
734	663	89	
735	664	89	
736	665	89	
737	666	89	

-continued

Example	Preparative Example	Preparative Example	Product
738	667	89	
739	668	89	
740	669	89	
741	670	89	

-continued

Example	Preparative Example	Preparative Example	Product
742	671	89	
743	688	89	
744	689	89	
745	690	89	

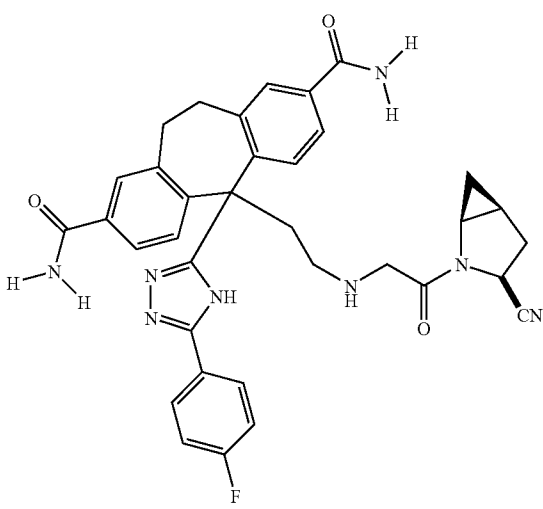
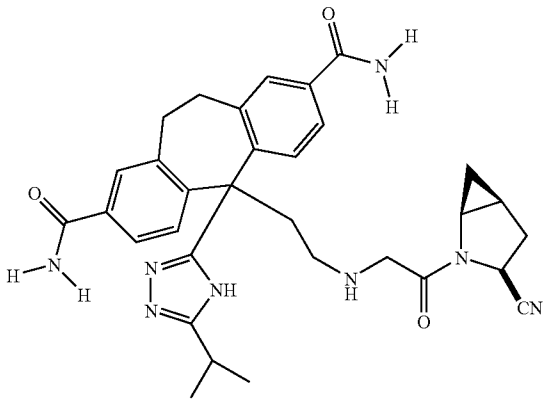
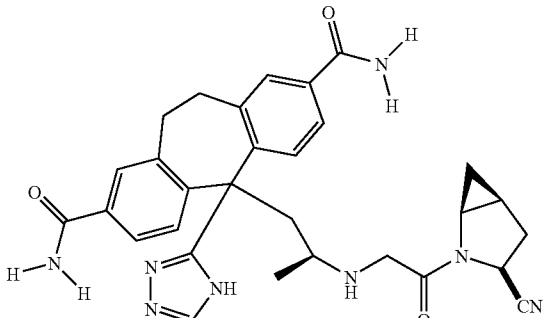
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Example	Preparative Example	Preparative Example	Product
746	691	89	
747	692	89	
748	693	89	
749	694	89	

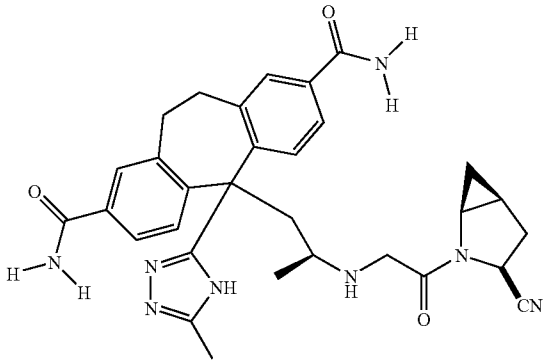
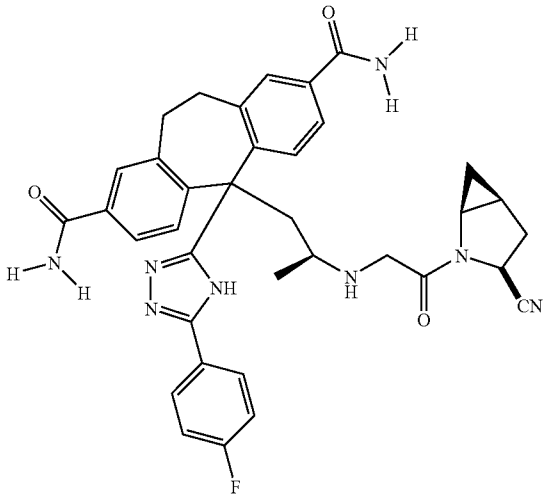
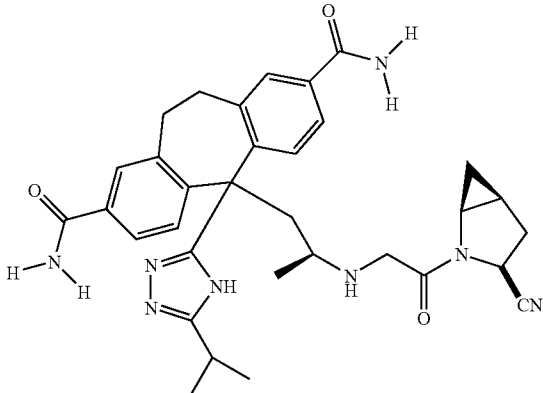
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Example	Preparative Example	Preparative Example	Product
750	695	89	
751	736	89	
752	737	89	

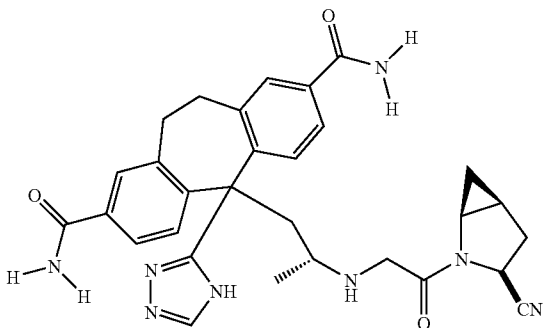
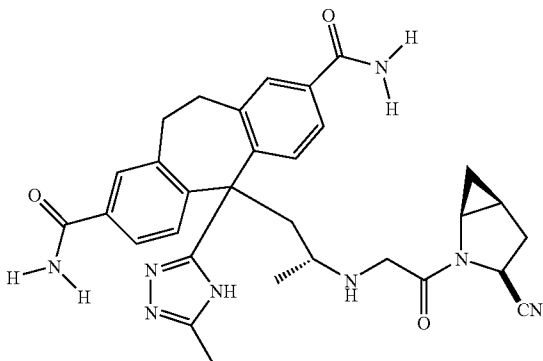
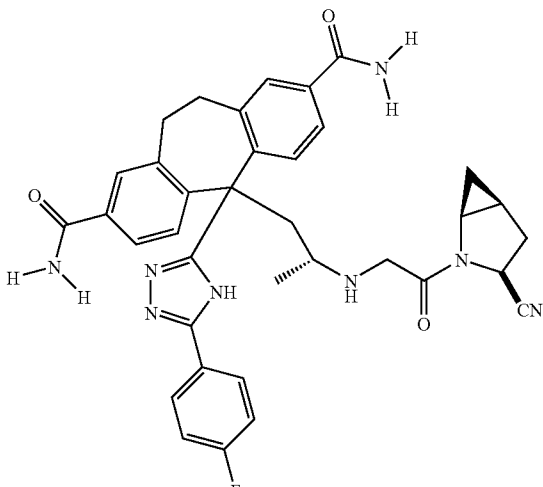
-continued

Example	Preparative Example	Preparative Example	Product
753	738	89	
754	739	89	
755	740	89	

-continued

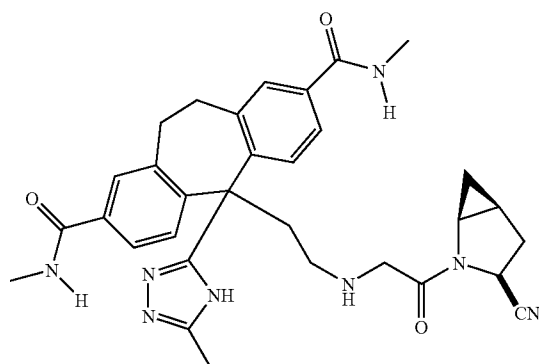
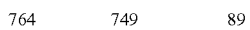
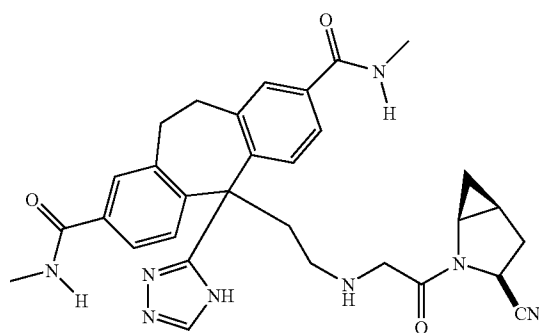
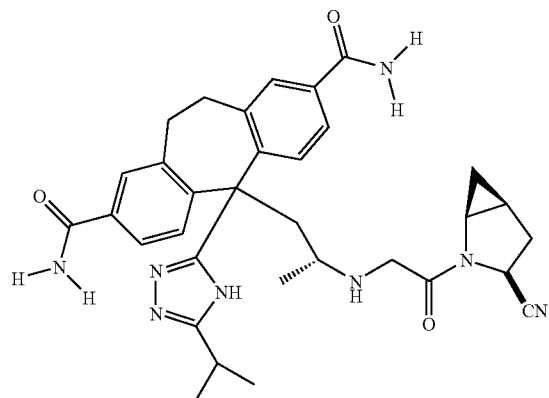
Example	Preparative Example	Preparative Example	Product
756	741	89	
757	742	89	
758	743	89	

-continued

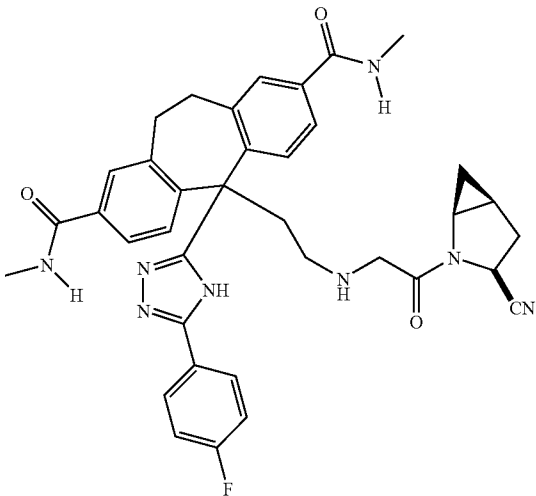
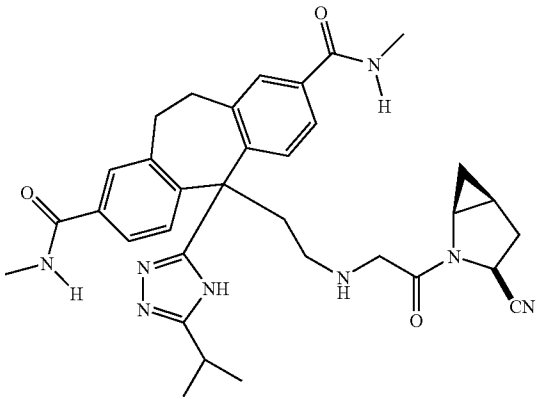
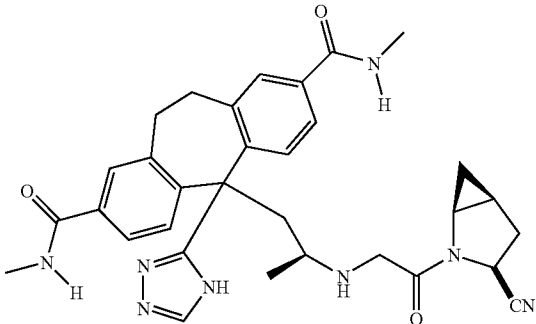
Example	Preparative Example	Preparative Example	Product
759	744	89	
760	745	89	
761	746	89	

-continued

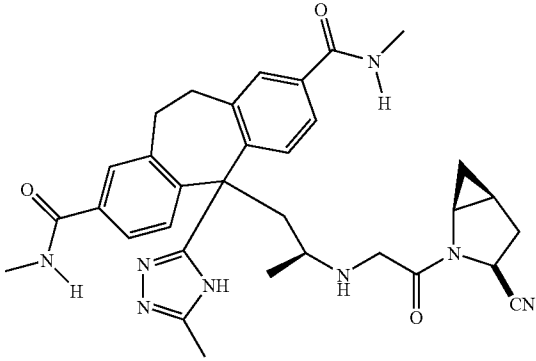
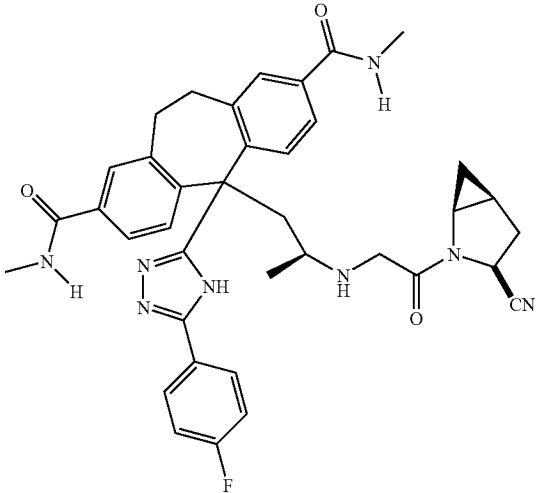
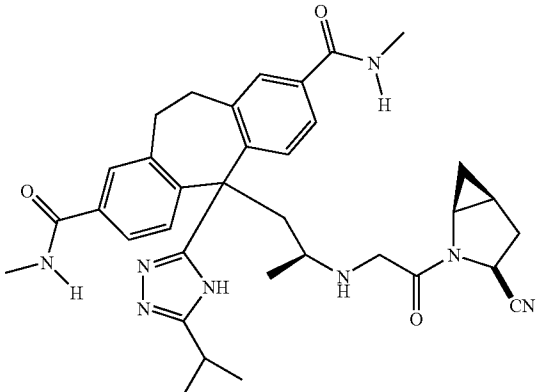
Example	Preparative Example	Preparative Example	Product
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-continued

Example	Preparative Example	Preparative Example	Product
765	750	89	
766	751	89	
767	752	89	

-continued

Example	Preparative Example	Preparative Example	Product
768	753	89	
769	754	89	
770	755	89	

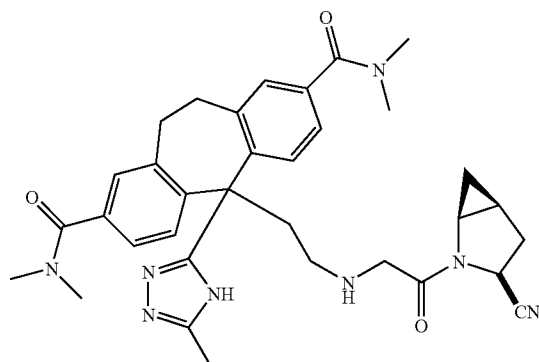
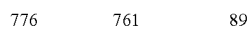
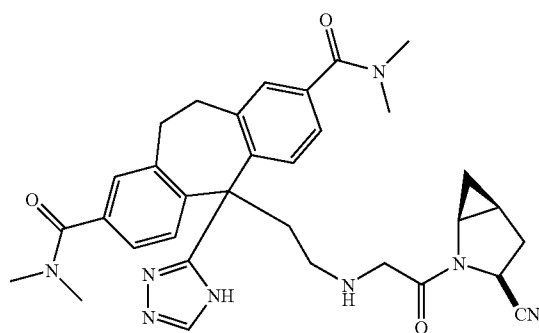
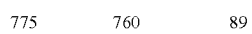
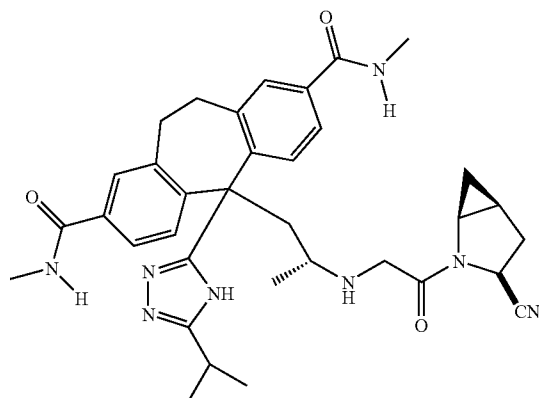
-continued

Example	Preparative Example	Preparative Example	Product
771	756	89	
772	757	89	
773	758	89	

Example	Preparative Example	Preparative Example	Product
771	756	89	
772	757	89	
773	758	89	

-continued

Example	Preparative Example	Preparative Example	Product
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-continued

Example	Preparative Example	Preparative Example	Product
777	762	89	
778	763	89	
779	764	89	

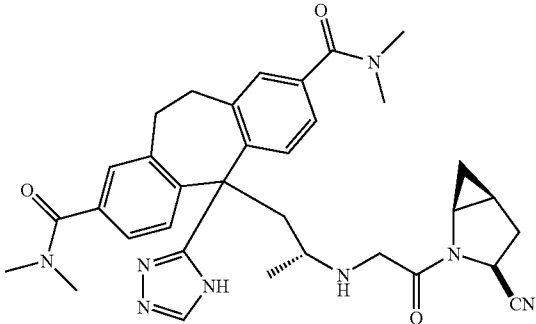
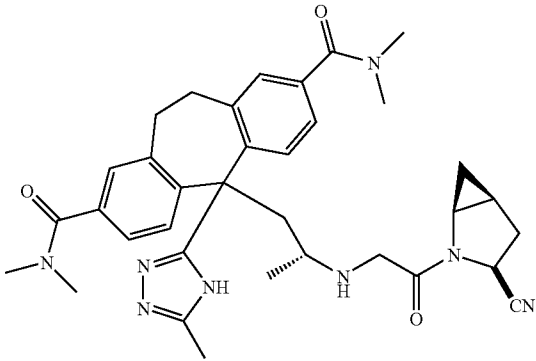
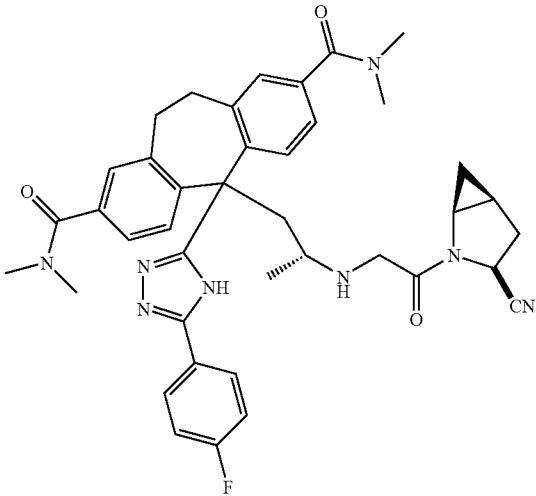
Example	Preparative Example	Preparative Example	Product
777	762	89	
778	763	89	
779	764	89	

Example	Preparative Example	Preparative Example	Product
777	762	89	
778	763	89	
779	764	89	

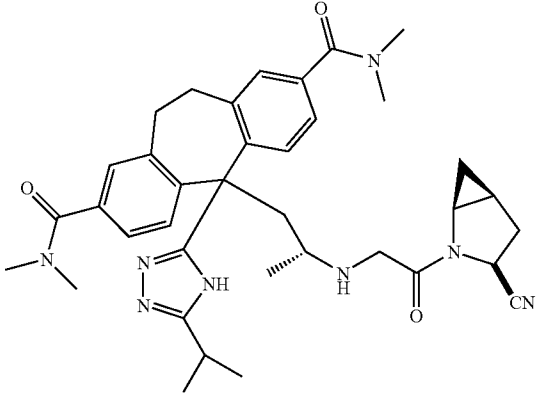
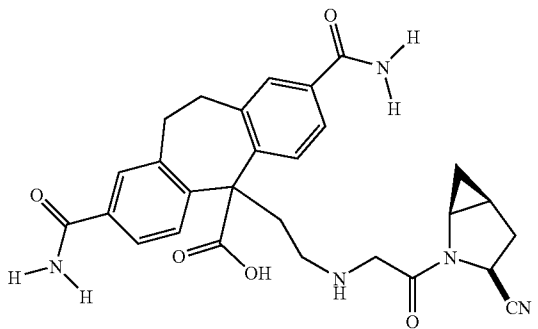
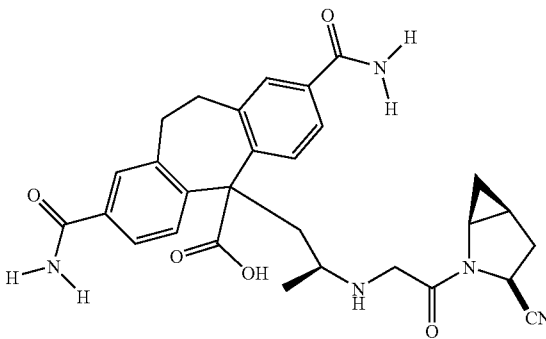
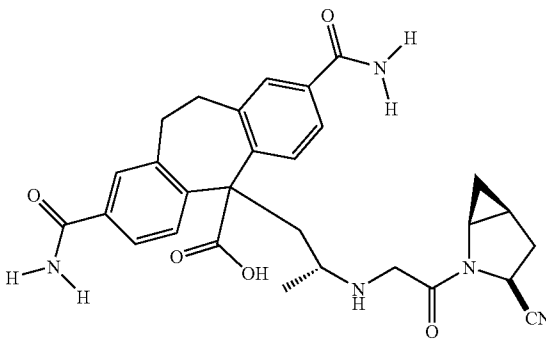
-continued

Example	Preparative Example	Preparative Example	Product
780	765	89	
781	766	89	
782	767	89	

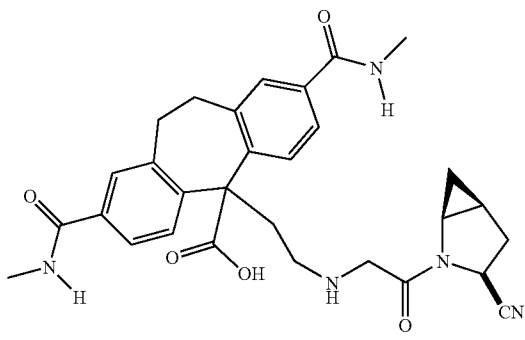
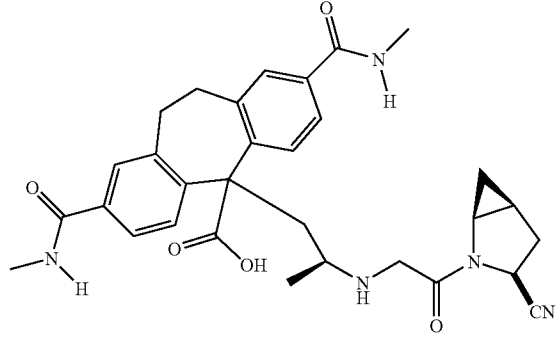
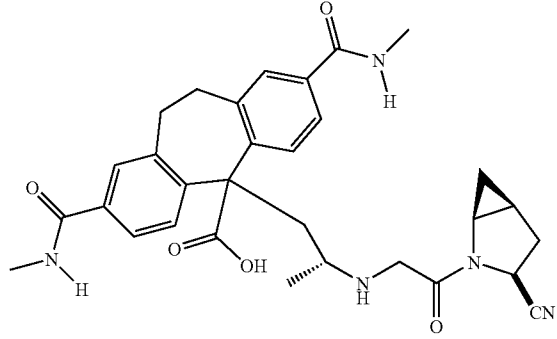
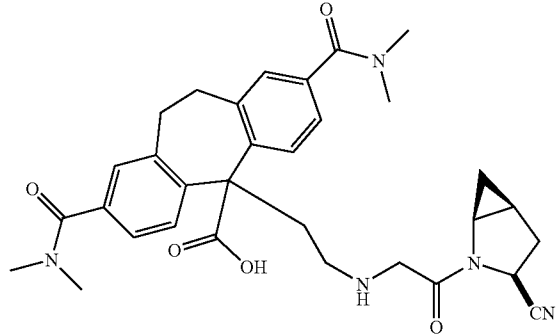
-continued

Example	Preparative Example	Preparative Example	Product
783	768	89	
784	769	89	
785	770	89	

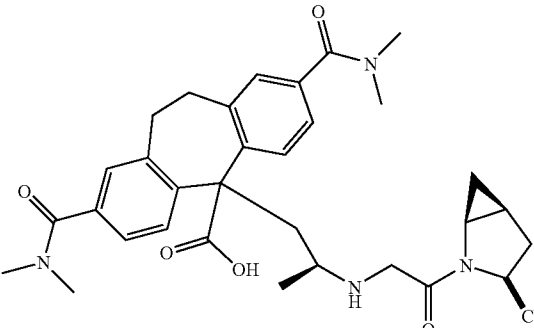
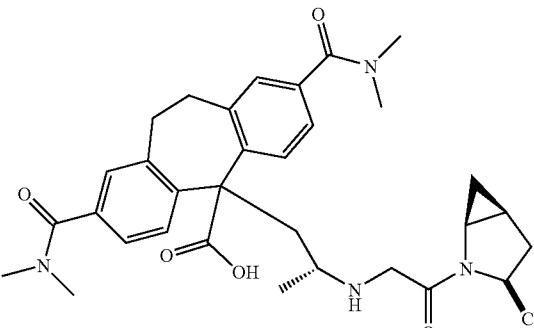
-continued

Example	Preparative Example	Preparative Example	Product
786	771	89	
787	789	89	
788	790	89	
789	791	89	

-continued

Example	Preparative Example	Preparative Example	Product
790	792	89	
791	793	89	
792	794	89	
793	795	89	

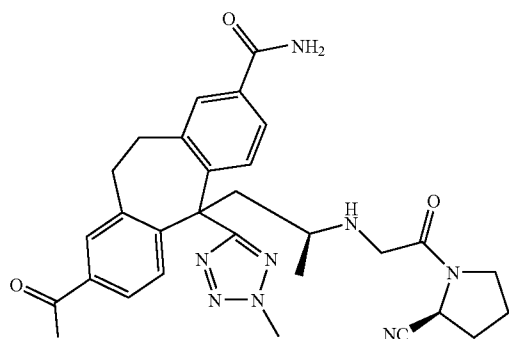
-continued

Example	Preparative Example	Preparative Example	Product
794	796	89	
795	797	89	

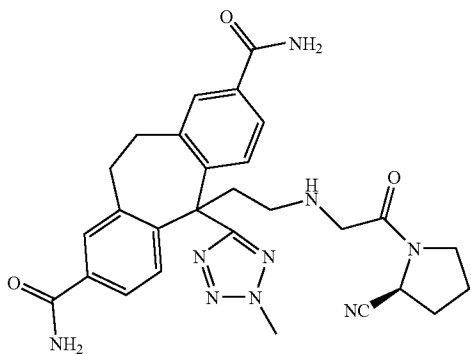
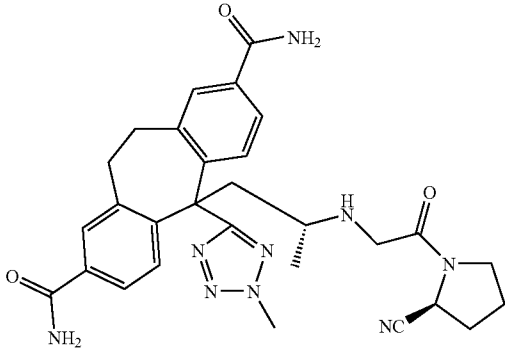
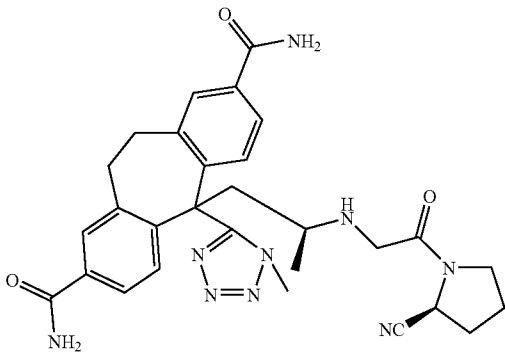
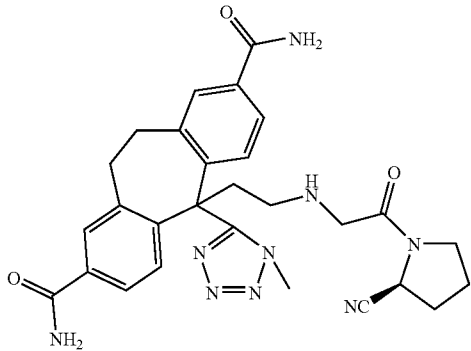
[0858] Examples 796-799 have been intentionally excluded.

Example 800-833

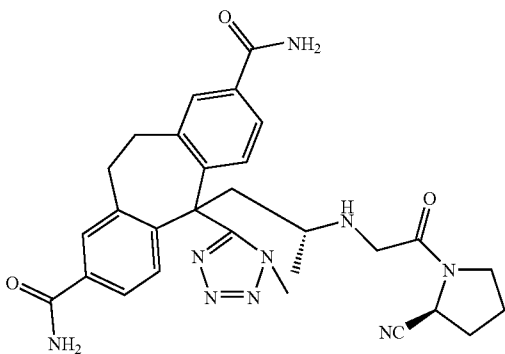
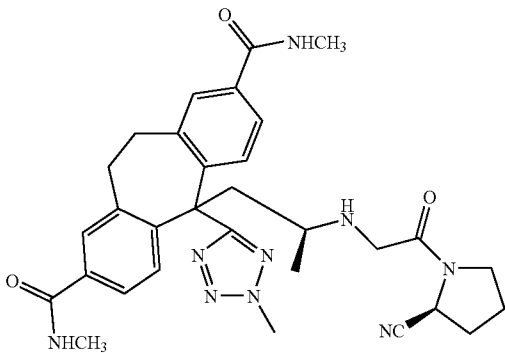
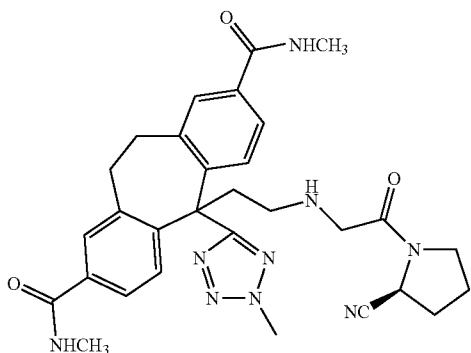
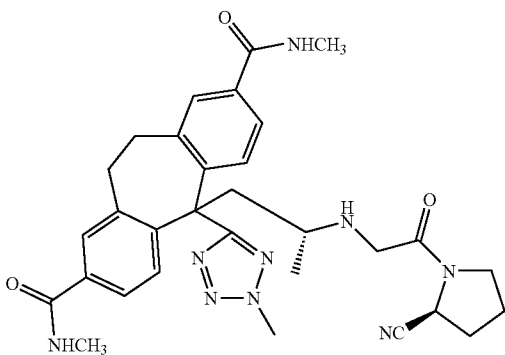
[0859] If one were to follow a similar procedure as that described in Examples 27 or 28, and treat the title compounds from the Preparative Examples in the table below as described in Preparative Example 69 and 71, except using the amines as indicated in the Table below, one would obtain the desired product.

Example	Preparative Example	Preparative Example	Amine	Product
800	61 Step B	2	NH ₃	

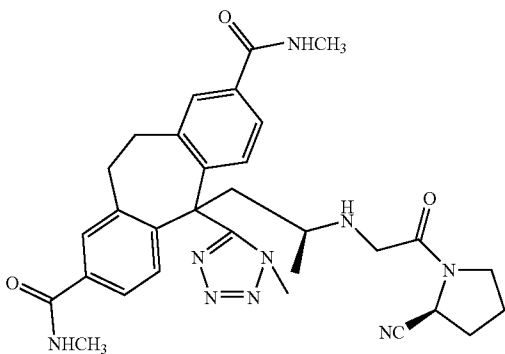
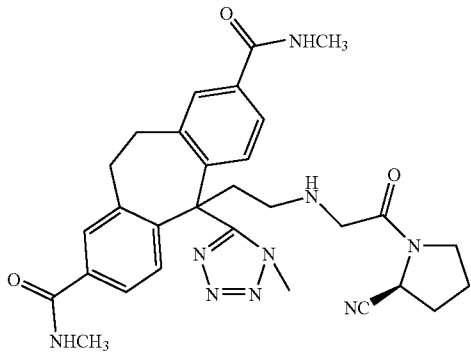
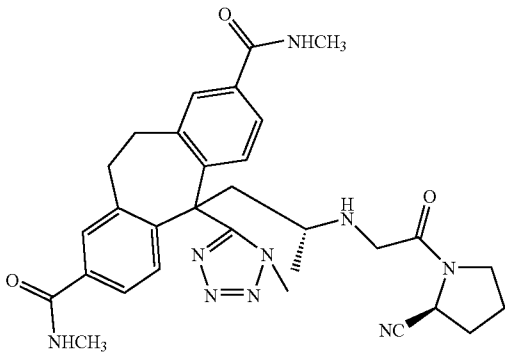
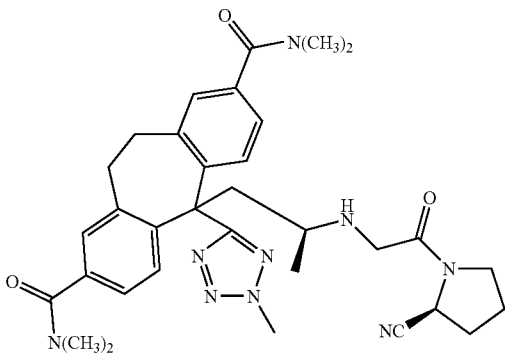
-continued

Example	Preparative Example	Preparative Example	Amine	Product
801	62	2	NH ₃	
802	65	2	NH ₃	
803	61 Step B	2	NH ₃	
804	62	2	NH ₃	

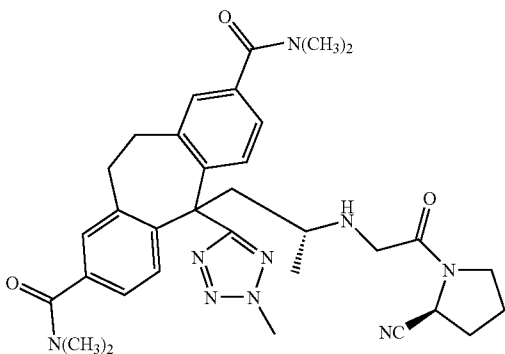
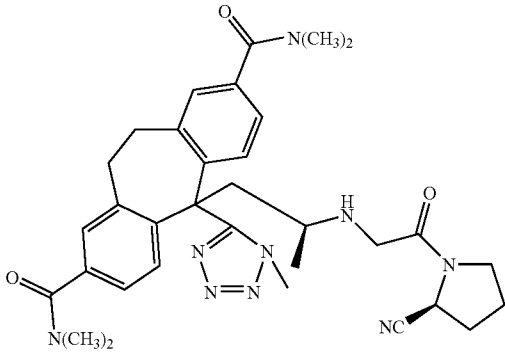
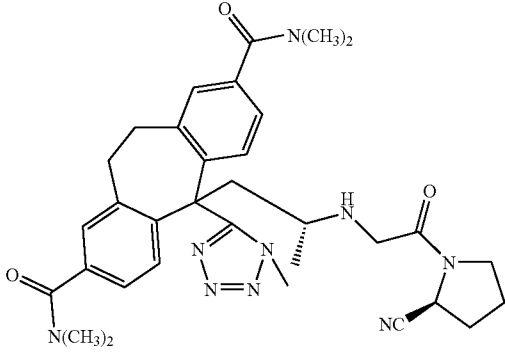
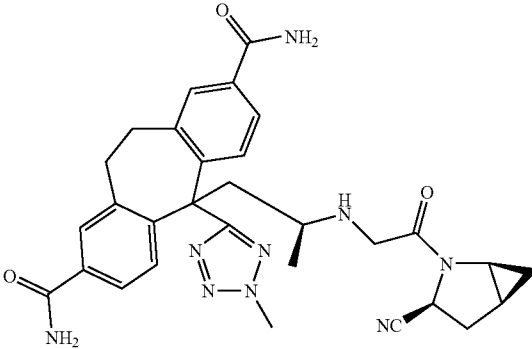
-continued

Example	Preparative Example	Preparative Example	Amine	Product
805	65	2	NH ₃	
806	61 Step B	2	CH ₃ NH ₂	
807	62	2	CH ₃ NH ₂	
808	65	2	CH ₃ NH ₂	

-continued

Example	Preparative Example	Preparative Example	Amine	Product
809	61 Step B	2	CH_3NH_2	
810	62	2	CH_3NH_2	
811	65	2	CH_3NH_2	
812	61 Step B	2	$(\text{CH}_3)_2\text{NH}$	

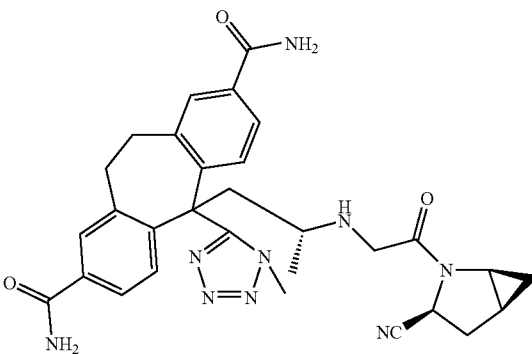
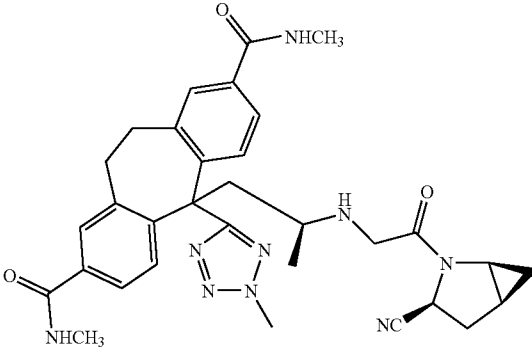
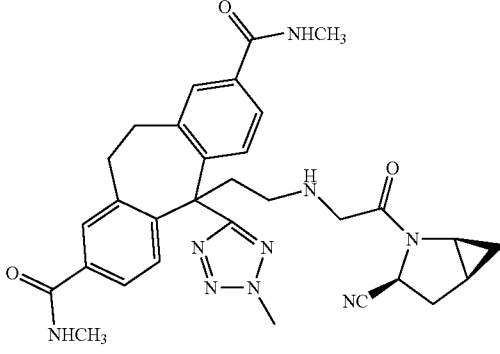
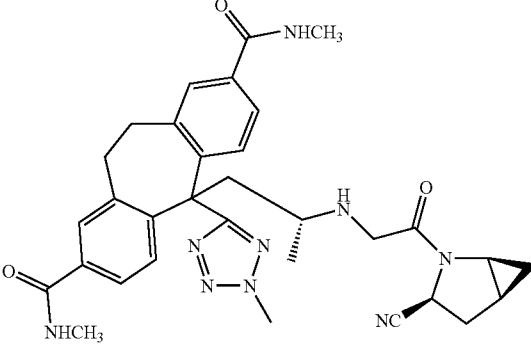
-continued

Example	Preparative Example	Preparative Example	Amine	Product
813	65	2	$(\text{CH}_3)_2\text{NH}$	
814	61 Step B	2	$(\text{CH}_3)_2\text{NH}$	
815	65	2	$(\text{CH}_3)_2\text{NH}$	
816	61 Step B	89	NH_3	

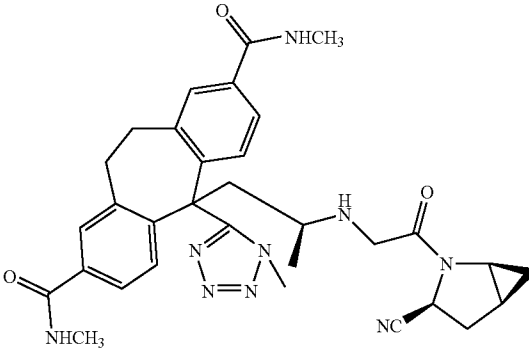
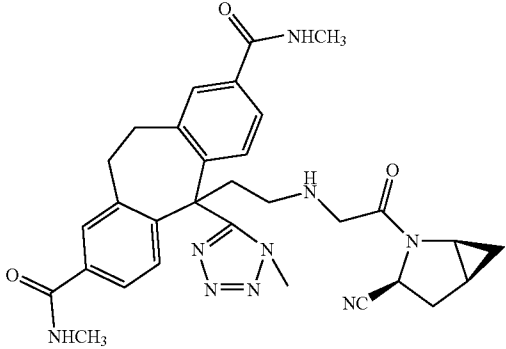
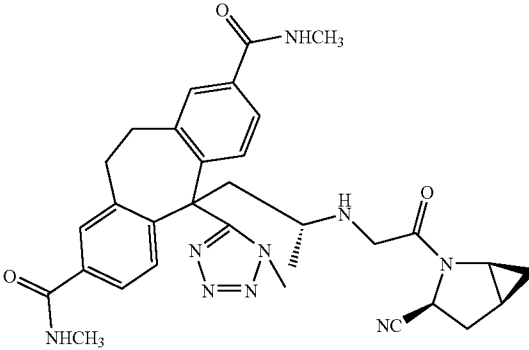
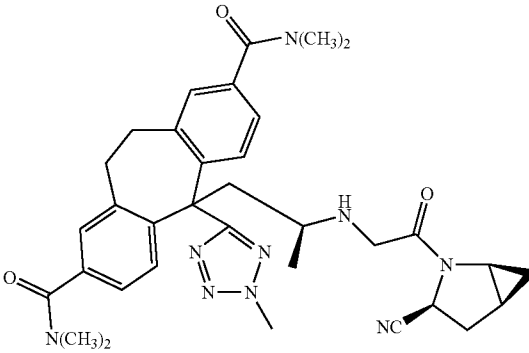
-continued

Example	Preparative Example	Preparative Example	Amine	Product
817	62	89	NH ₃	
818	65	89	NH ₃	
819	61 Step B	89	NH ₃	
820	62	89	NH ₃	

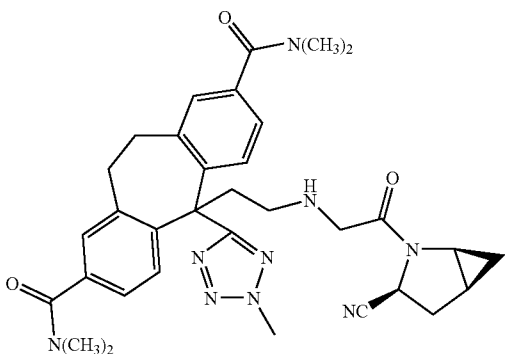
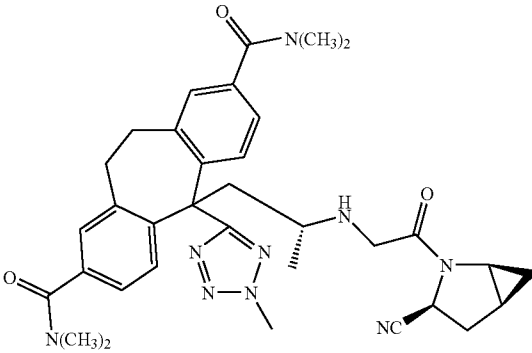
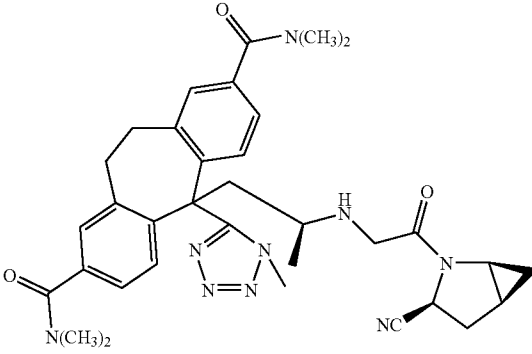
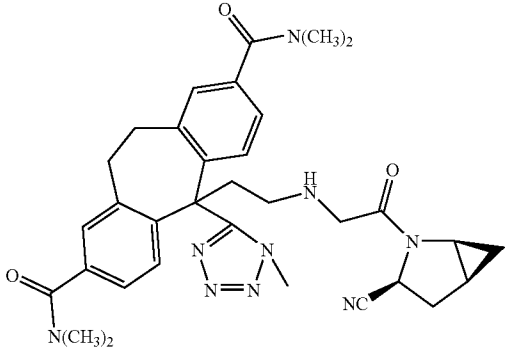
-continued

Example	Preparative Example	Preparative Example	Amine	Product
821	65	89	NH_3	
822	61 Step B	89	CH_3NH_2	
823	62	89	CH_3NH_2	
824	65	89	CH_3NH_2	

-continued

Example	Preparative Example	Preparative Example	Amine	Product
825	61 Step B	89	CH_3NH_2	
826	62	89	CH_3NH_2	
827	65	89	CH_3NH_2	
828	61 Step B	89	$(\text{CH}_3)_2\text{NH}$	

-continued

Example	Preparative Example	Preparative Example	Amine	Product
829	62	89	$(\text{CH}_3)_2\text{NH}$	
830	65	89	$(\text{CH}_3)_2\text{NH}$	
831	61 Step B	89	$(\text{CH}_3)_2\text{NH}$	
832	62	89	$(\text{CH}_3)_2\text{NH}$	

-continued

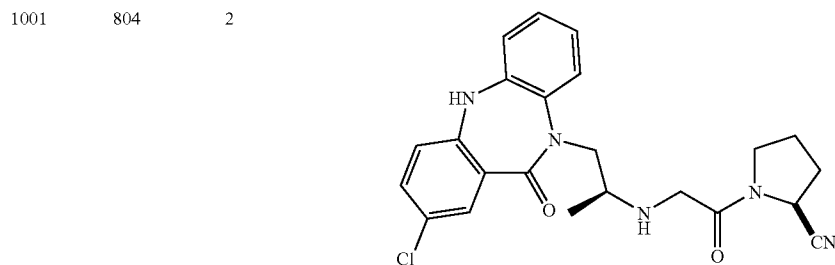
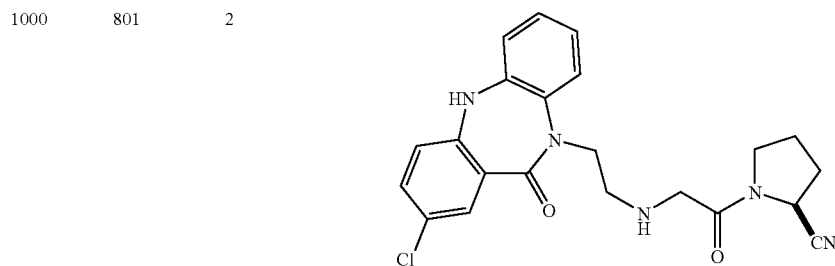
Example	Preparative Example	Preparative Example	Amine	Product
833	65	89	$(\text{CH}_3)_2\text{NH}$	

[0860] Examples 834-999 have been intentionally excluded.

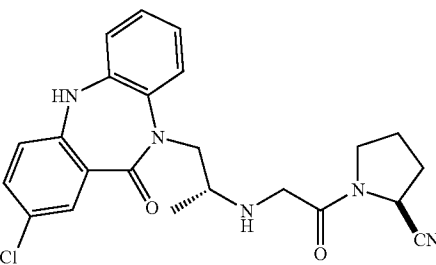
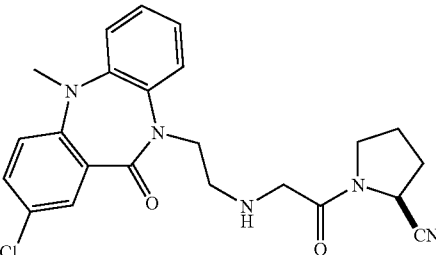
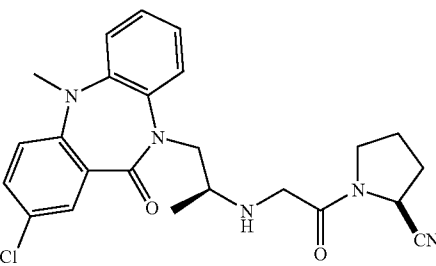
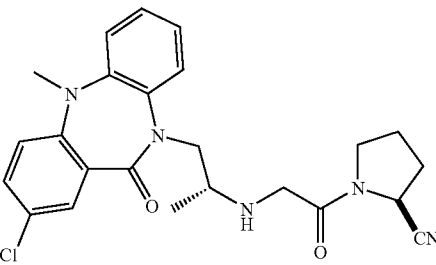
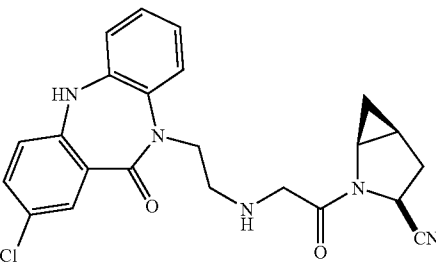
Example 1000-1168

[0861] If one were to follow the procedures outlined in Examples 28 or 29 except using the compounds from the Preparative Examples as indicated in the Table below, one would obtain the indicated Product.

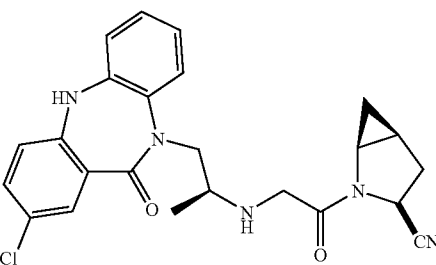
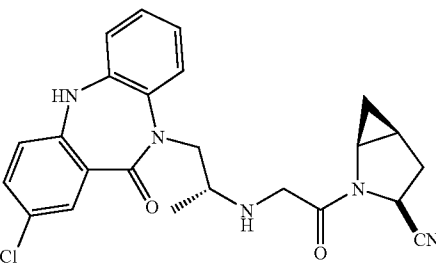
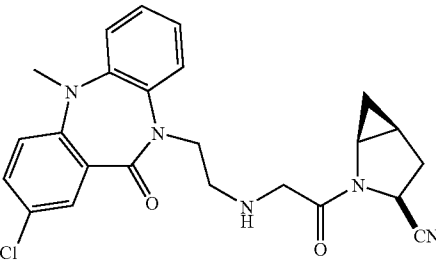
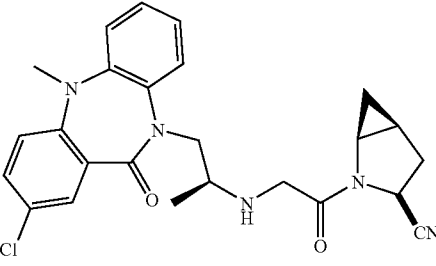
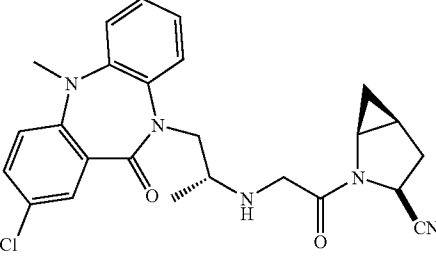
Example	Preparative Example	Preparative Example	Product
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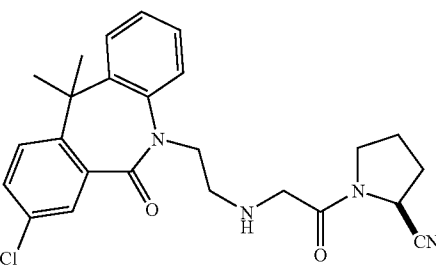
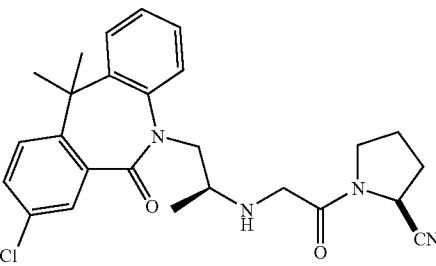
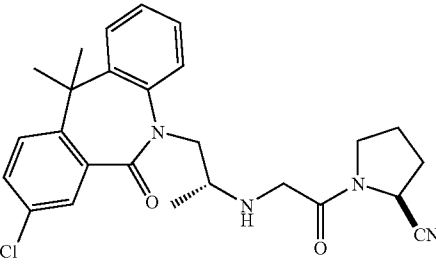
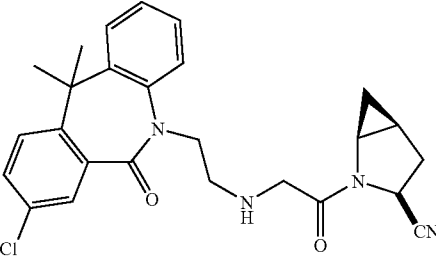
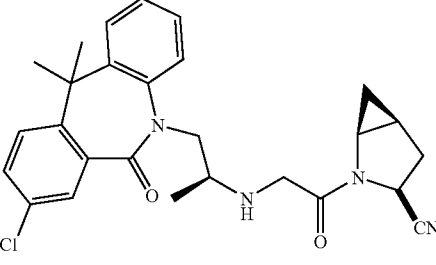
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Example	Preparative Example	Preparative Example	Product
1002	805	2	
1003	800	2	
1004	802	2	
1005	803	2	
1006	801	89	

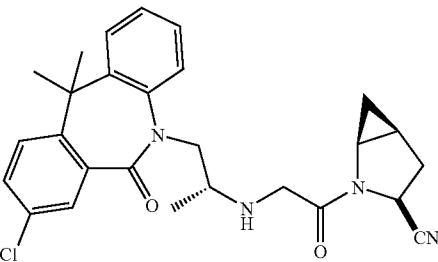
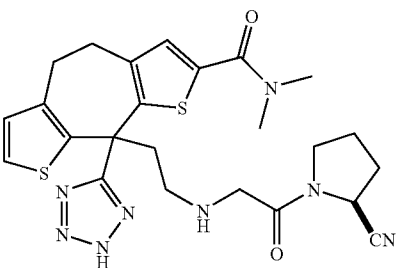
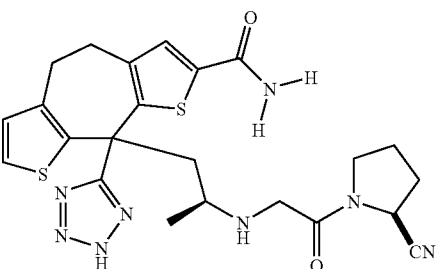
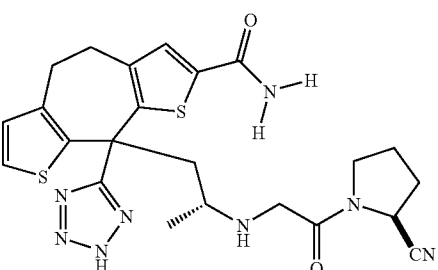
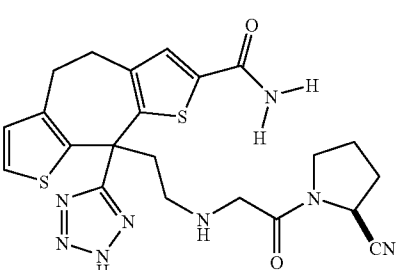
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Example	Preparative Example	Preparative Example	Product
1007	804	89	
1008	805	89	
1009	800	89	
1010	802	89	
1011	803	89	

-continued

Example	Preparative Example	Preparative Example	Product
1012	810	2	
1013	812	2	
1014	811	2	
1015	810	89	
1016	812	89	

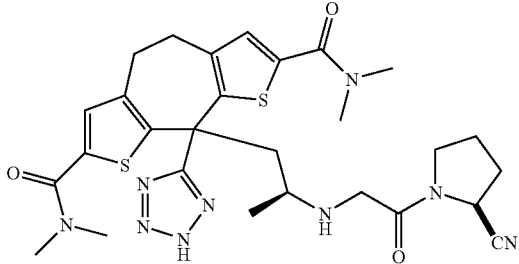
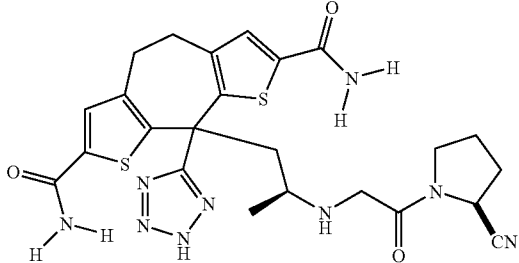
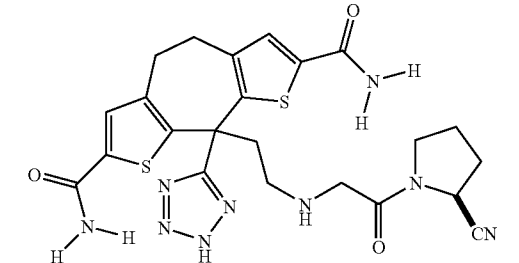
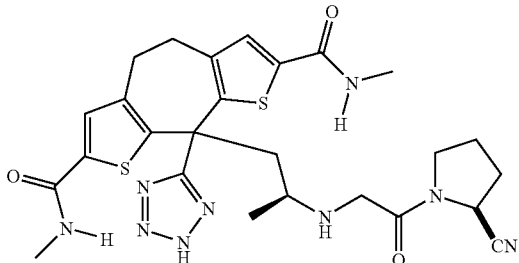
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Example	Preparative Example	Preparative Example	Product
1017	811	89	
1018	831	2	
1019	832	2	
1020	833	2	
1021	834	2	

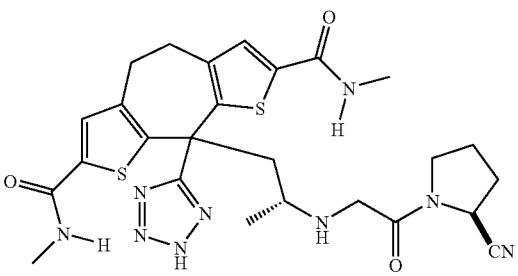
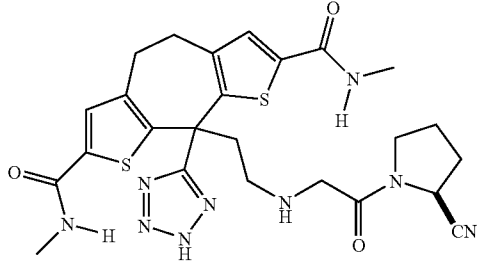
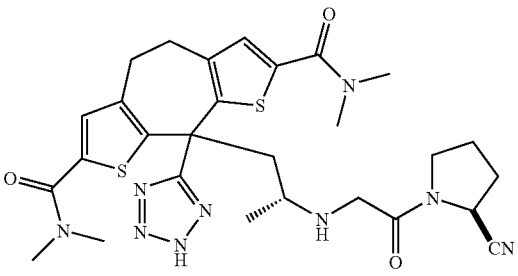
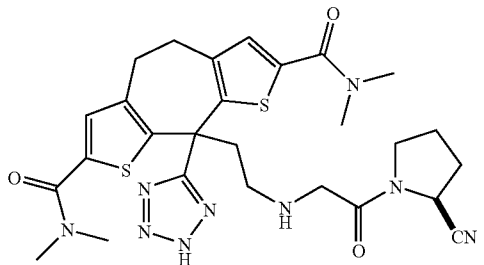
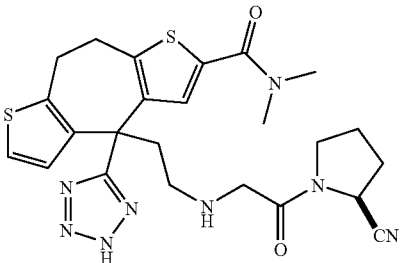
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Example	Preparative Example	Preparative Example	Product
1022	835	2	
1023	836	2	
1024	837	2	
1025	838	2	
1026	839	2	

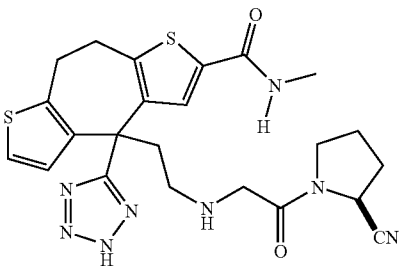
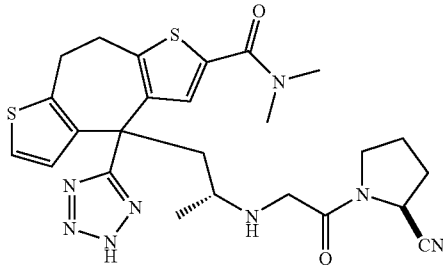
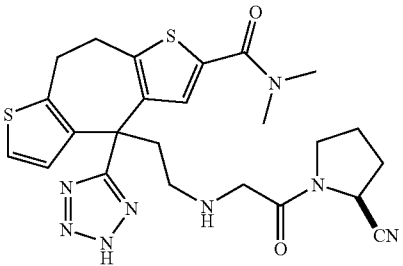
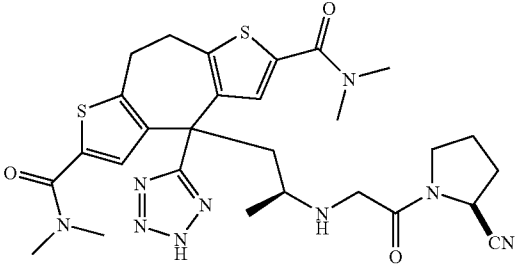
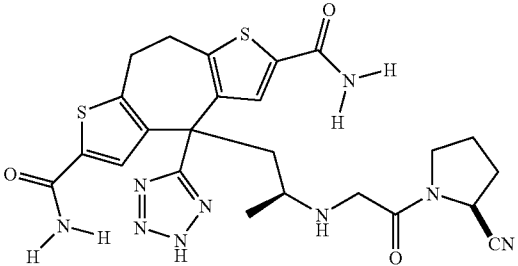
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Example	Preparative Example	Preparative Example	Product
1027	851	2	
1028	852	2	
1029	853	2	
1030	854	2	
1031	855	2	

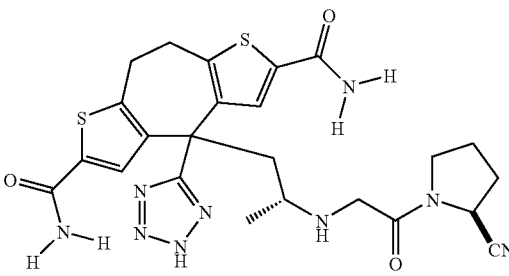
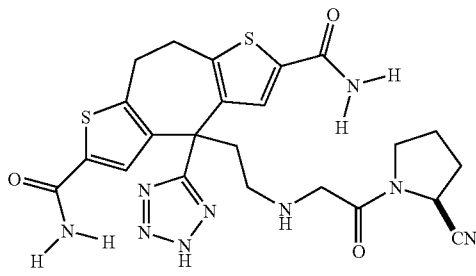
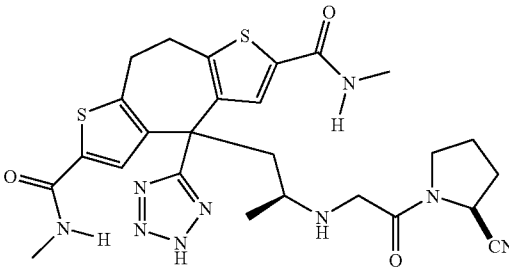
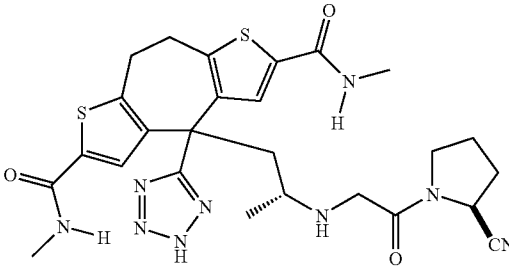
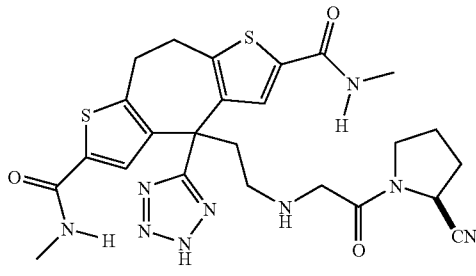
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Example	Preparative Example	Preparative Example	Product
1032	856	2	
1033	857	2	
1034	858	2	
1035	859	2	
1036	901	2	

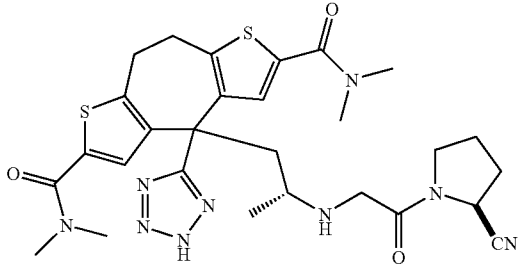
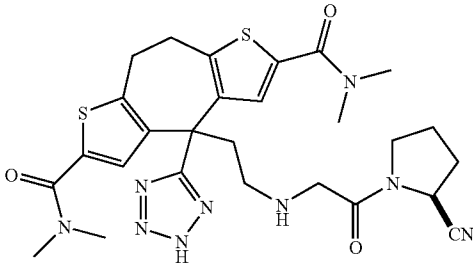
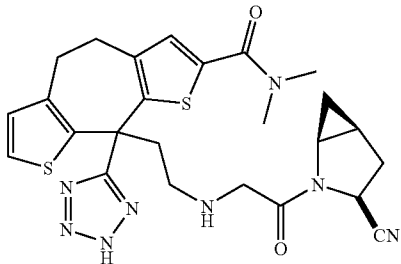
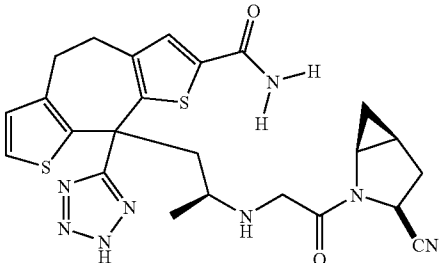
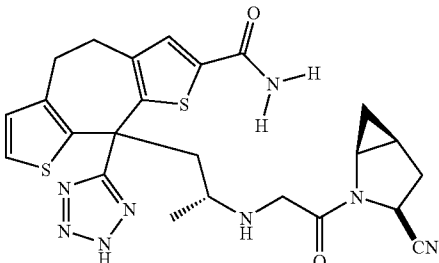
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Example	Preparative Example	Preparative Example	Product
1042	907	2	
1043	908	2	
1044	909	2	
1045	921	2	
1046	922	2	

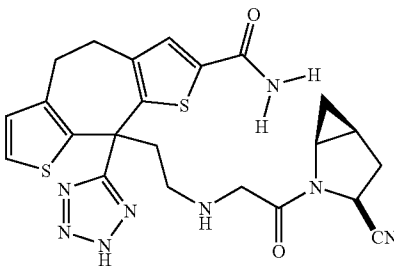
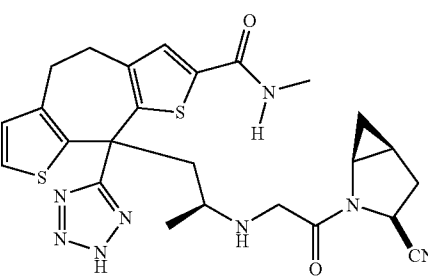
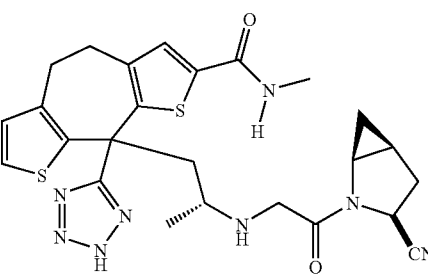
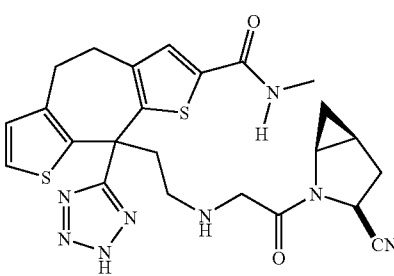
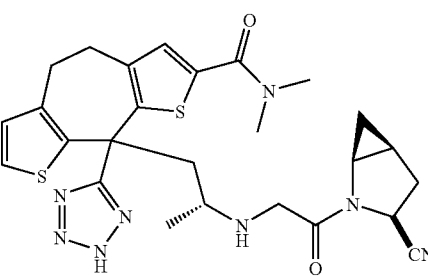
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Example	Preparative Example	Preparative Example	Product
1047	923	2	
1048	924	2	
1049	925	2	
1050	926	2	
1051	927	2	

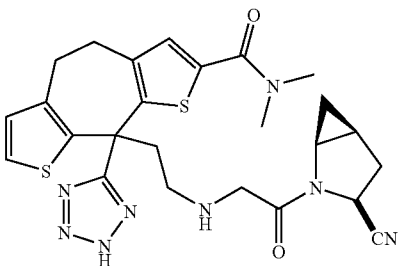
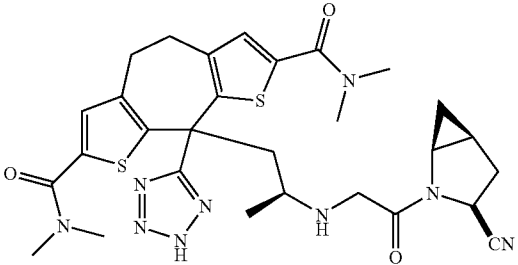
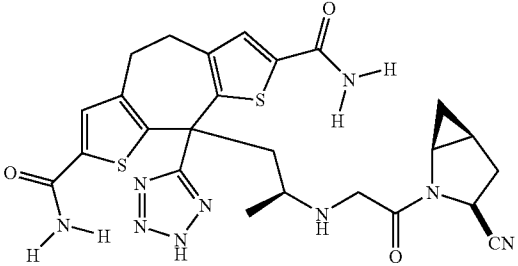
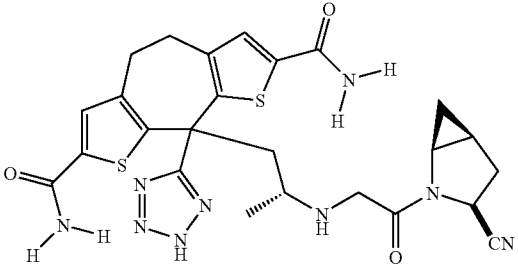
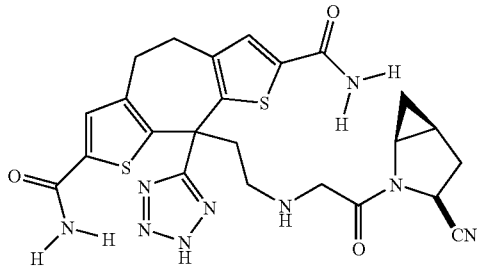
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Example	Preparative Example	Preparative Example	Product
1052	928	2	
1053	929	2	
1054	831	89	
1055	832	89	
1056	833	89	

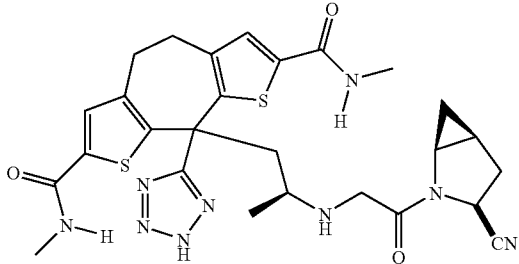
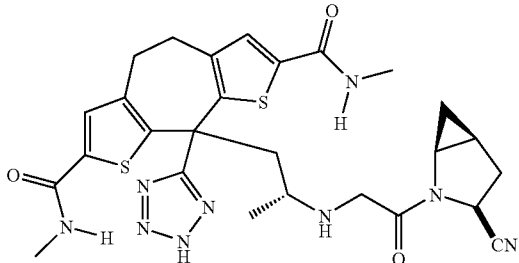
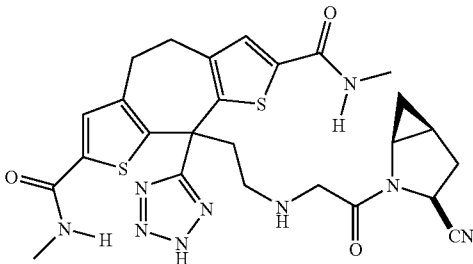
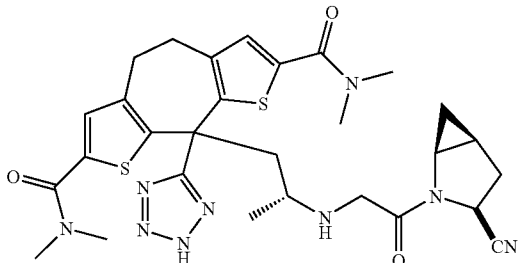
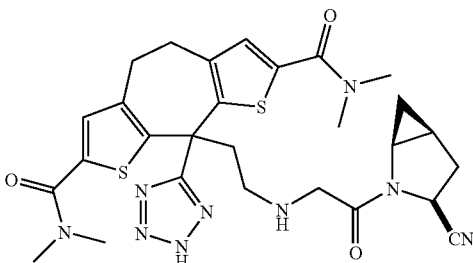
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Example	Preparative Example	Preparative Example	Product
1057	834	89	
1058	835	89	
1059	836	89	
1060	837	89	
1061	838	89	

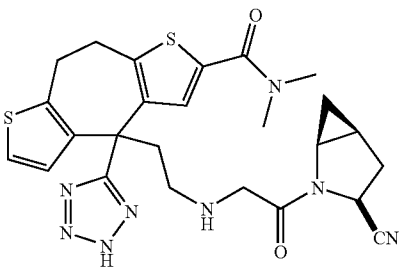
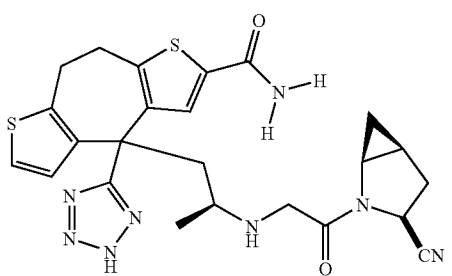
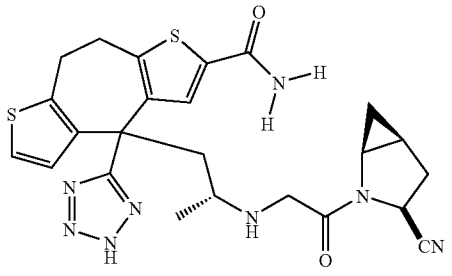
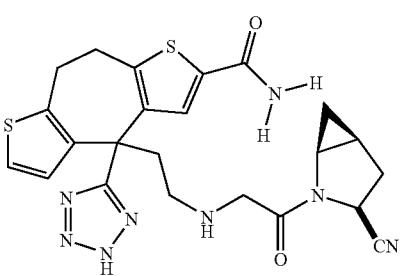
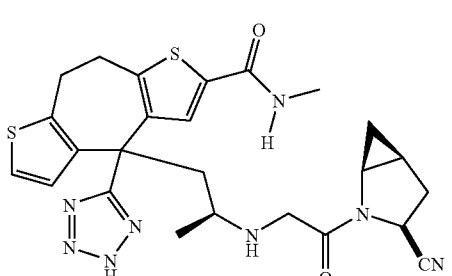
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Example	Preparative Example	Preparative Example	Product
1062	839	89	
1063	851	89	
1064	852	89	
1065	853	89	
1066	854	89	

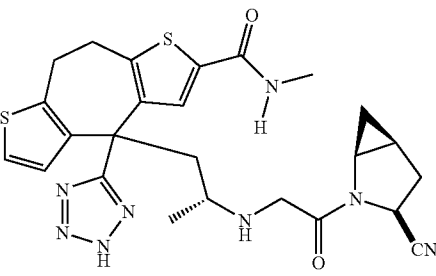
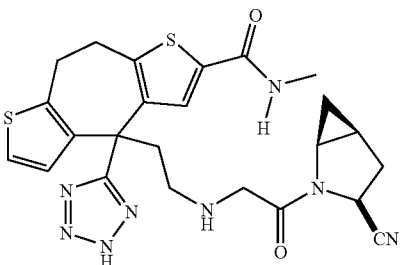
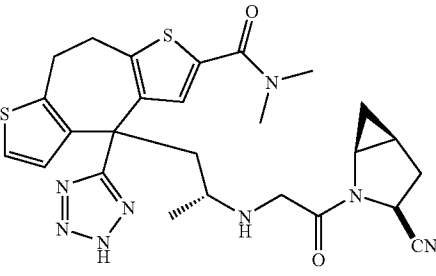
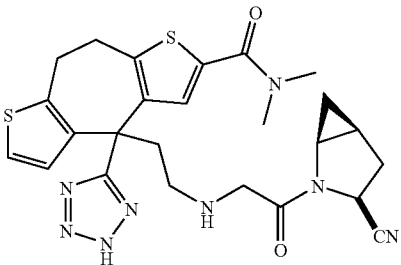
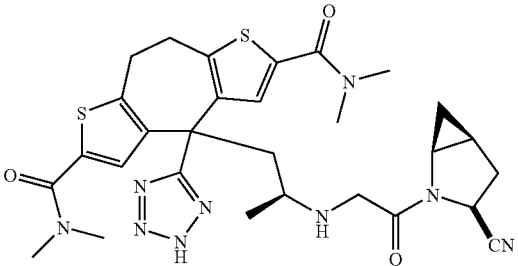
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Example	Preparative Example	Preparative Example	Product
1067	855	89	
1068	856	89	
1069	857	89	
1070	858	89	
1071	859	89	

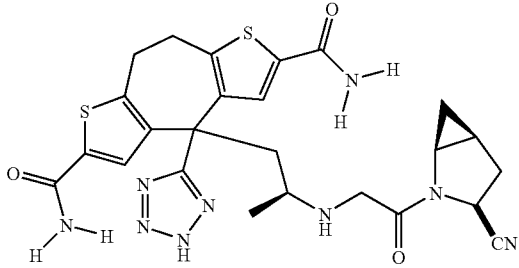
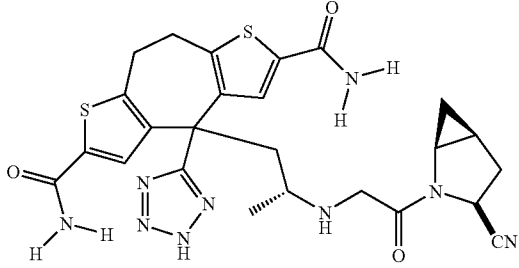
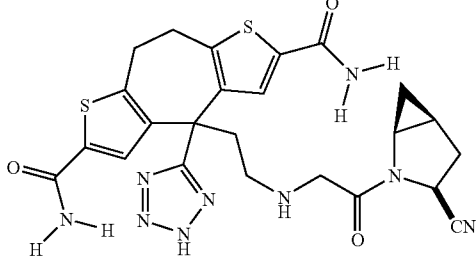
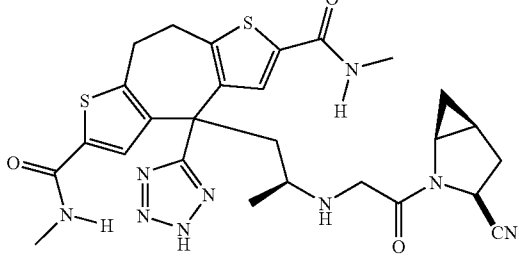
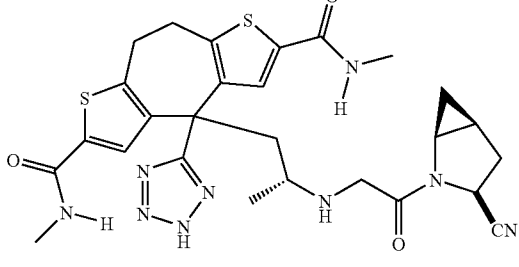
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Example	Preparative Example	Preparative Example	Product
1072	901	89	
1073	902	89	
1074	903	89	
1075	904	89	
1076	905	89	

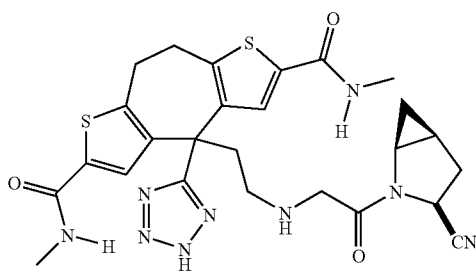
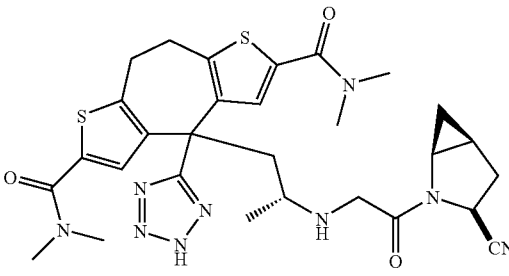
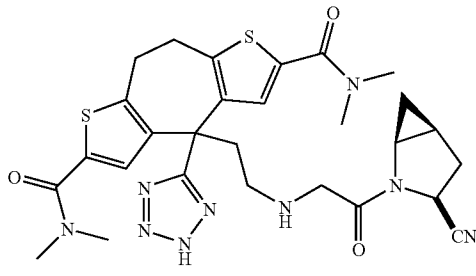
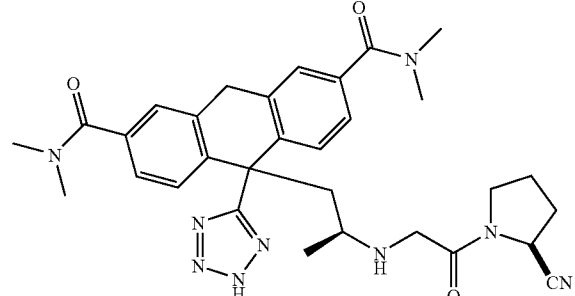
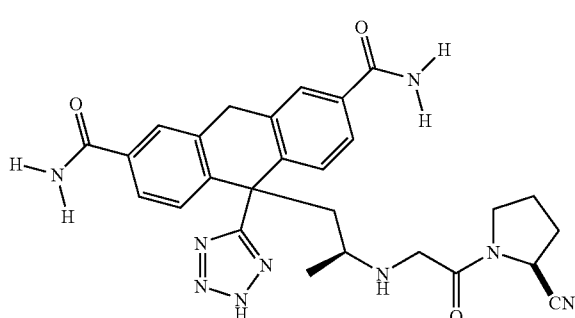
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Example	Preparative Example	Preparative Example	Product
1077	906	89	
1078	907	89	
1079	908	89	
1080	909	89	
1081	921	89	

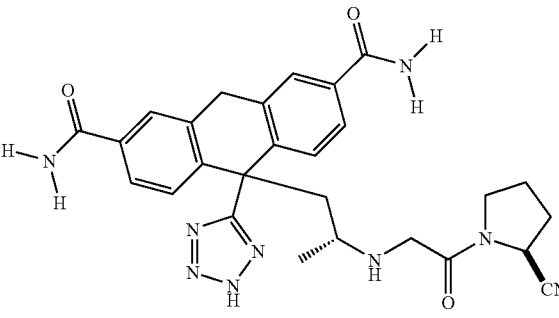
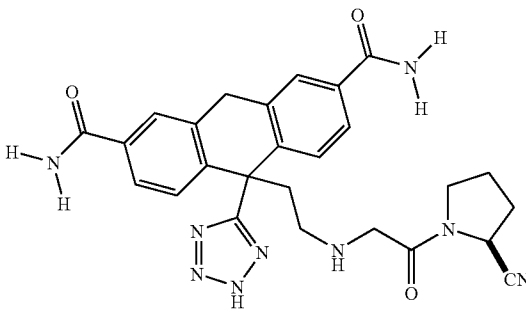
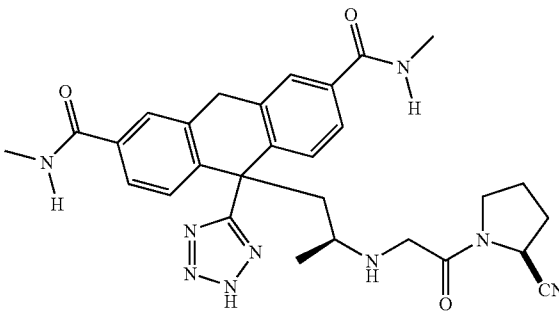
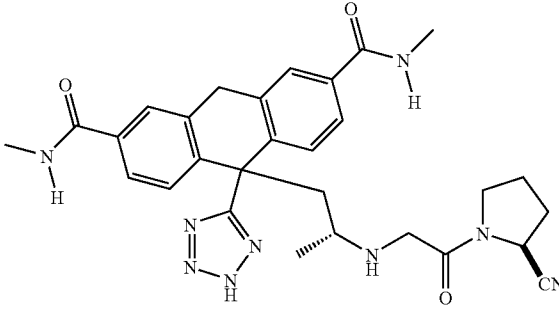
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Example	Preparative Example	Preparative Example	Product
1082	922	89	
1083	923	89	
1084	924	89	
1085	925	89	
1086	926	89	

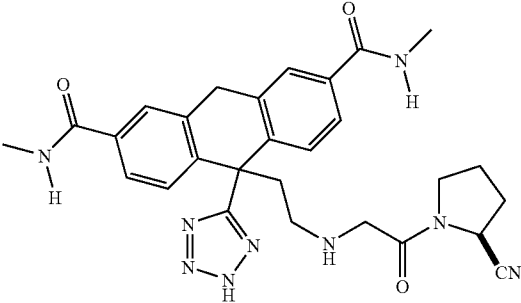
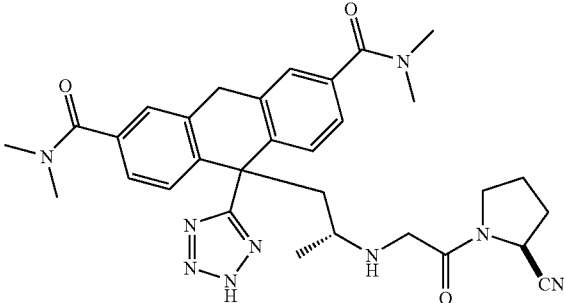
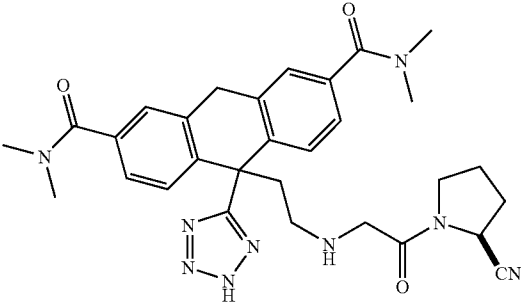
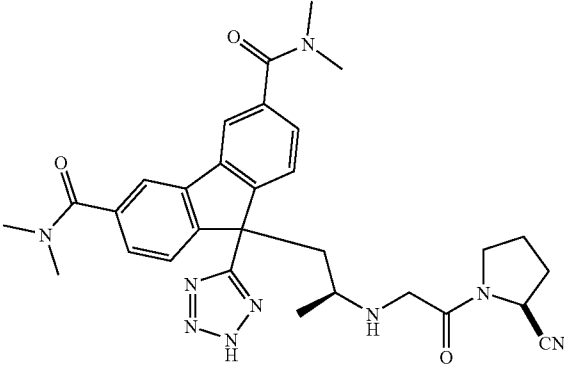
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Example	Preparative Example	Preparative Example	Product
1087	927	89	
1088	928	89	
1089	929	89	
1090	1301	2	
1091	1302	2	

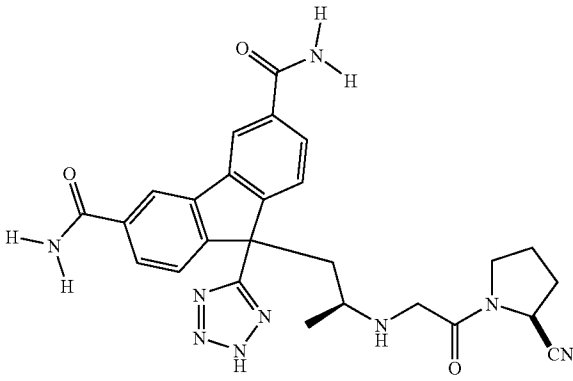
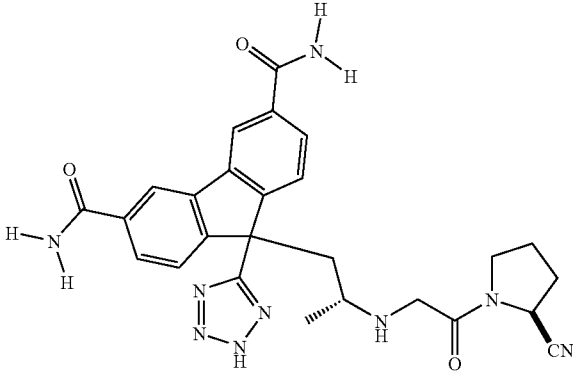
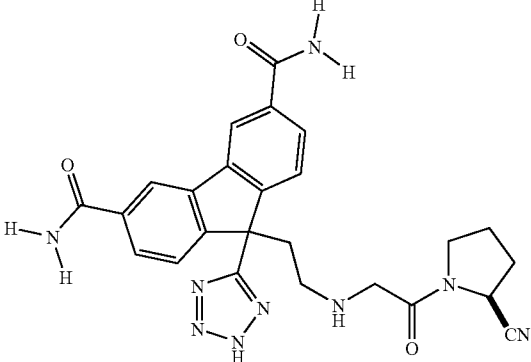
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Example	Preparative Example	Preparative Example	Product
1092	1303	2	
1093	1304	2	
1094	1305	2	
1095	1306	2	

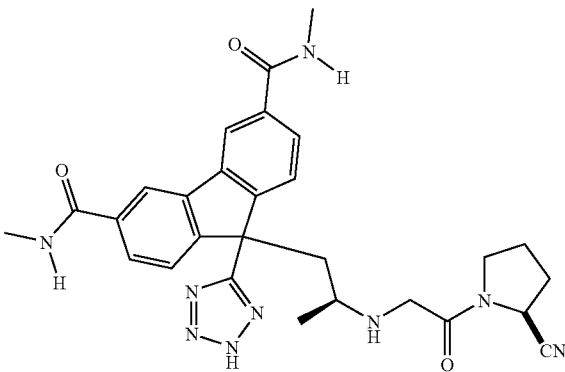
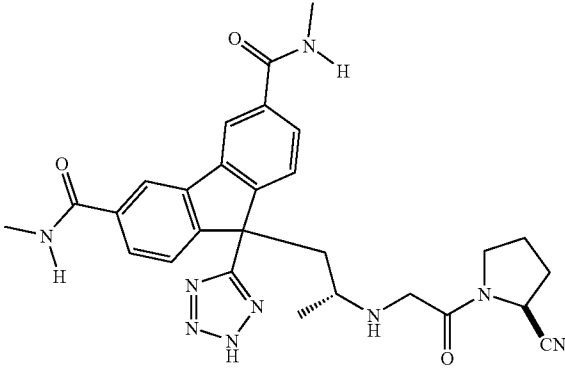
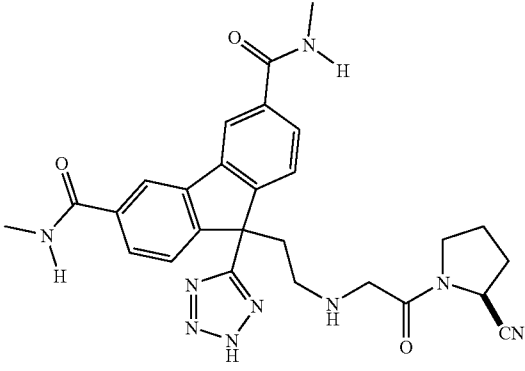
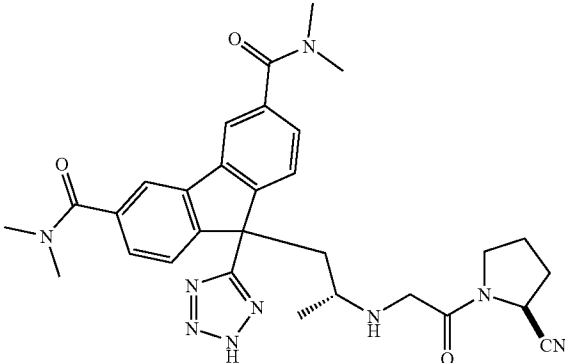
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Example	Preparative Example	Preparative Example	Product
1096	1307	2	
1097	1308	2	
1098	1309	2	
1099	1351	2	

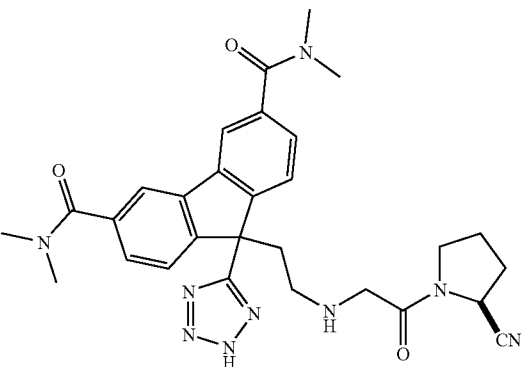
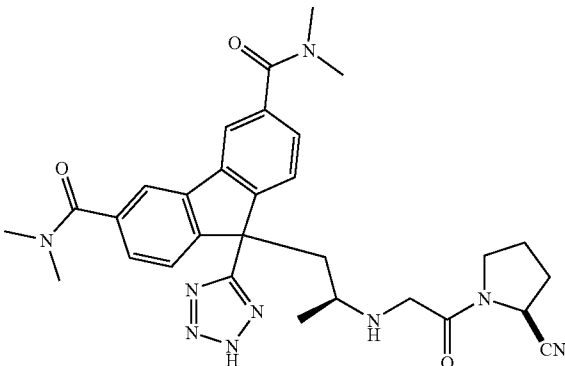
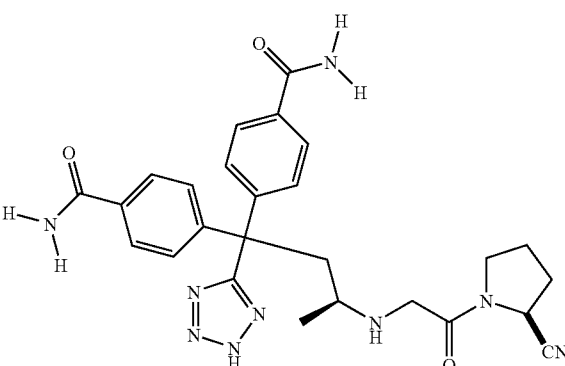
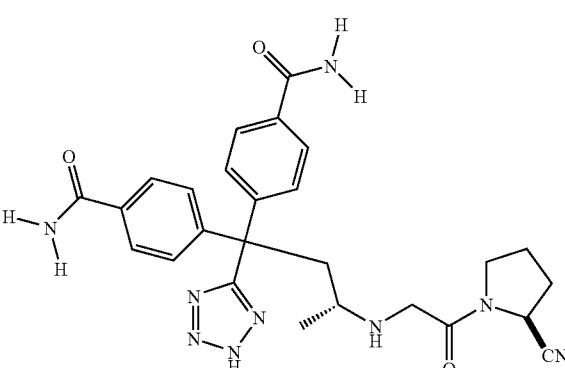
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Example	Preparative Example	Preparative Example	Product
1100	1352	2	
1101	1353	2	
1102	1354	2	

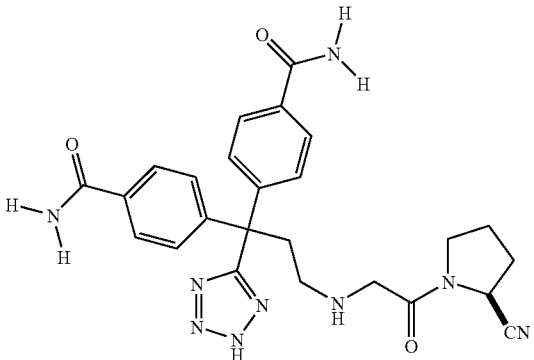
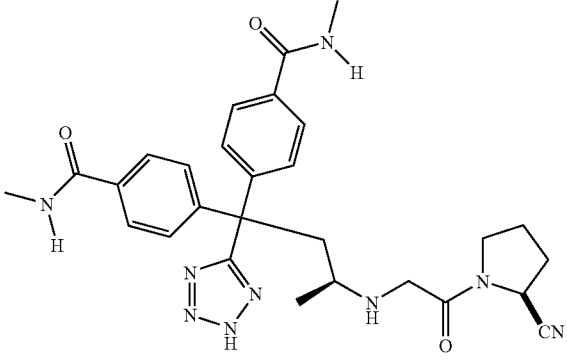
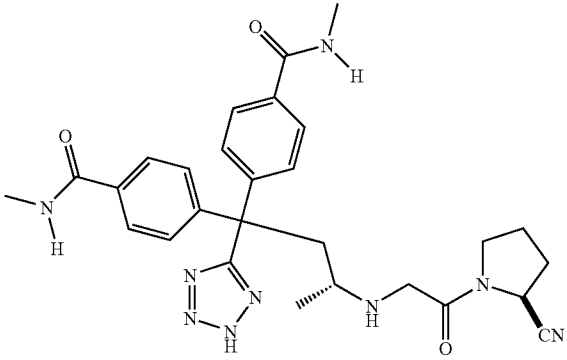
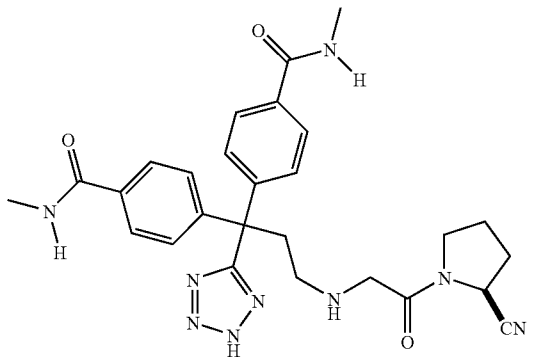
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Example	Preparative Example	Preparative Example	Product
1103	1355	2	
1104	1356	2	
1105	1357	2	
1106	1358	2	

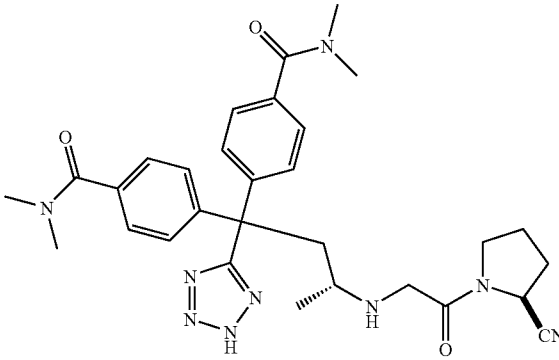
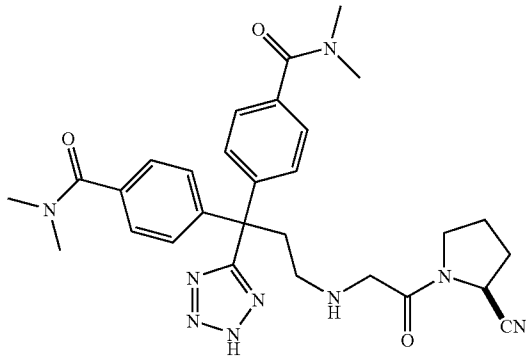
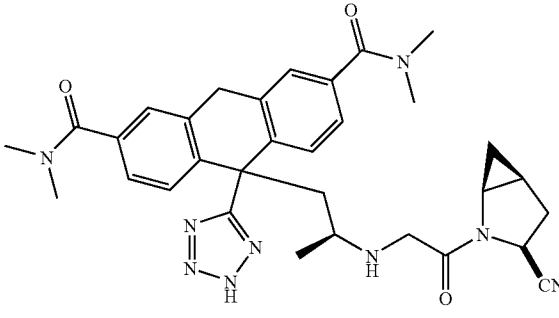
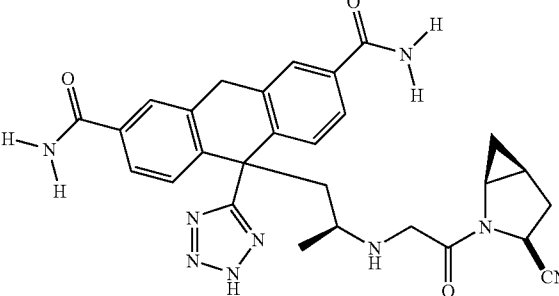
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Example	Preparative Example	Preparative Example	Product
1107	1359	2	
1108	1401	2	
1109	1402	2	
1110	1403	2	

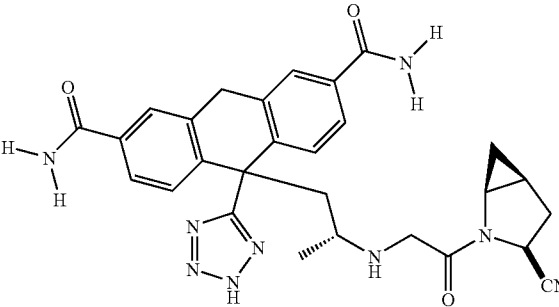
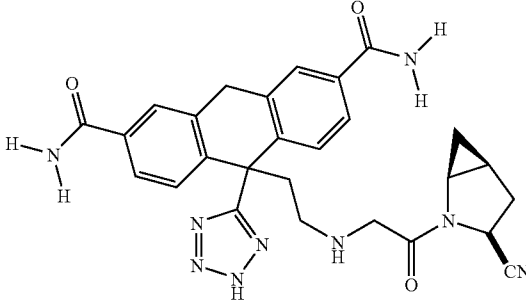
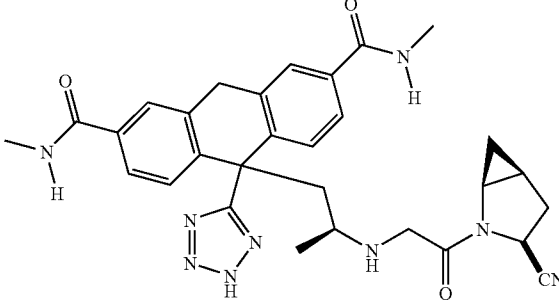
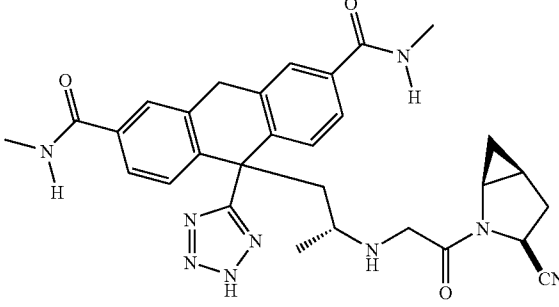
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Example	Preparative Example	Preparative Example	Product
1111	1404	2	
1112	1405	2	
1113	1406	2	
1114	1407	2	

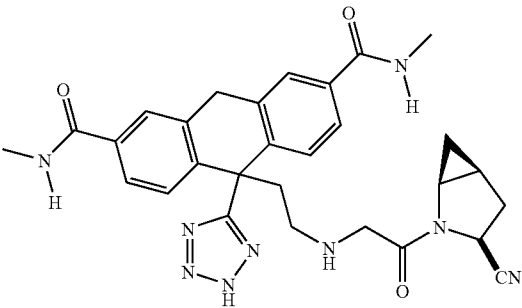
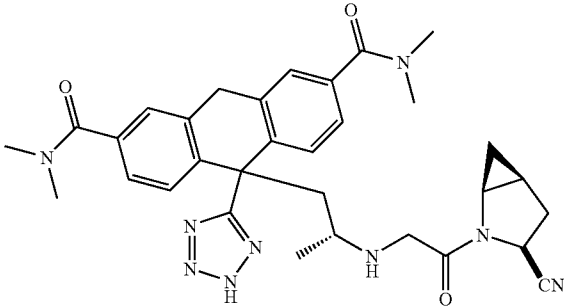
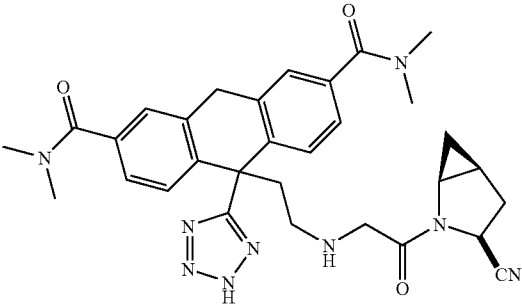
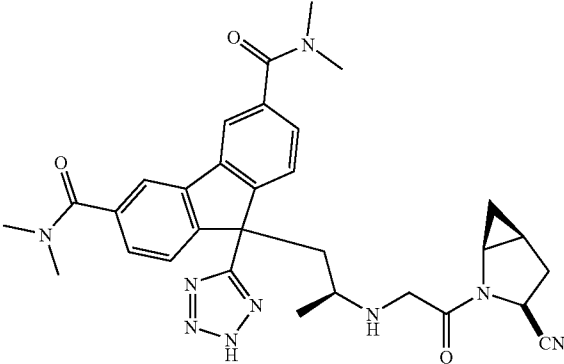
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Example	Preparative Example	Preparative Example	Product
1115	1408	2	
1116	1409	2	
1117	1301	89	
1118	1302	89	

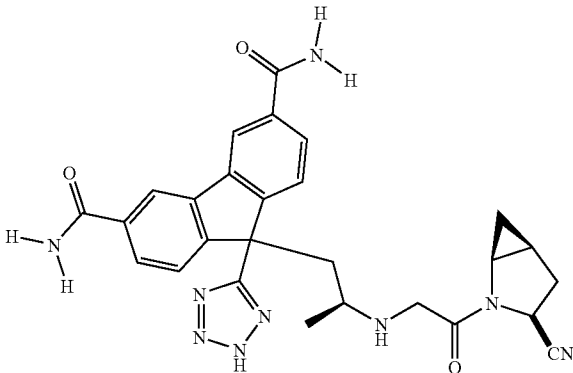
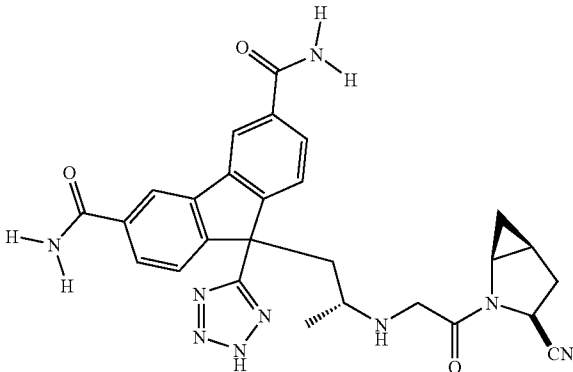
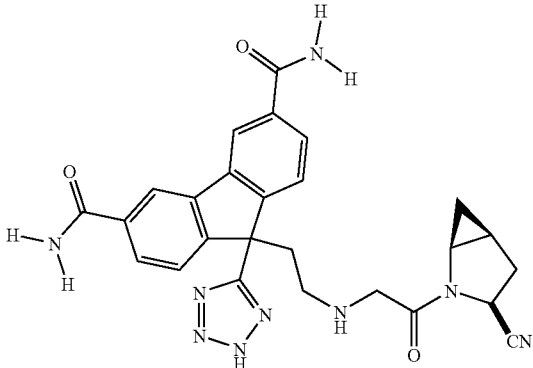
-continued

Example	Preparative Example	Preparative Example	Product
1119	1303	89	
1120	1304	89	
1121	1305	89	
1122	1306	89	

-continued

Example	Preparative Example	Preparative Example	Product
1123	1307	89	
1124	1308	89	
1125	1309	89	
1126	1351	89	

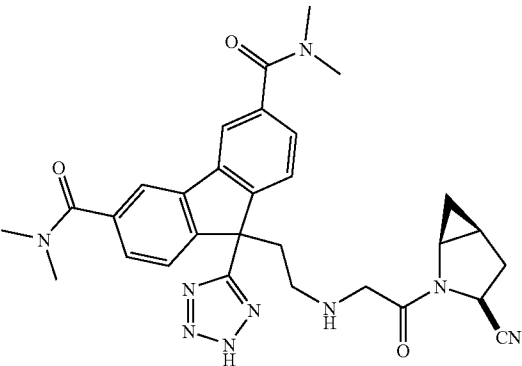
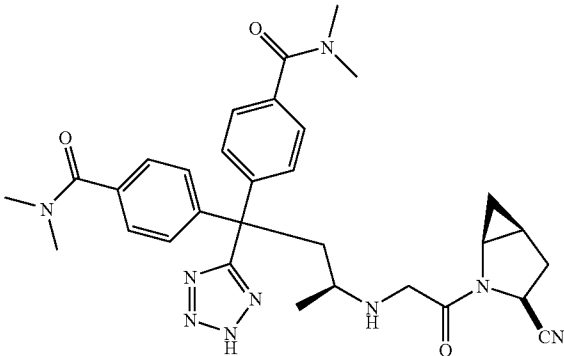
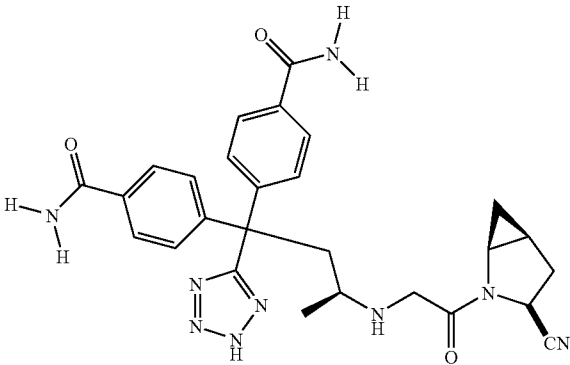
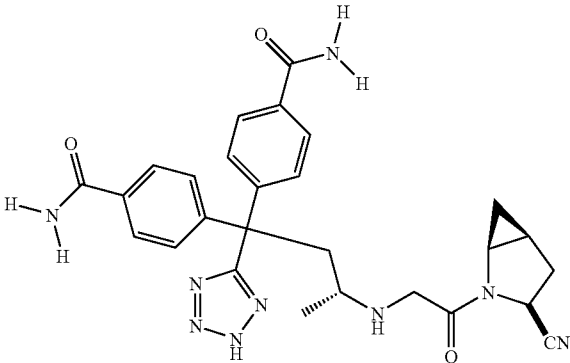
-continued

Example	Preparative Example	Preparative Example	Product
1127	1352	89	
1128	1353	89	
1129	1354	89	

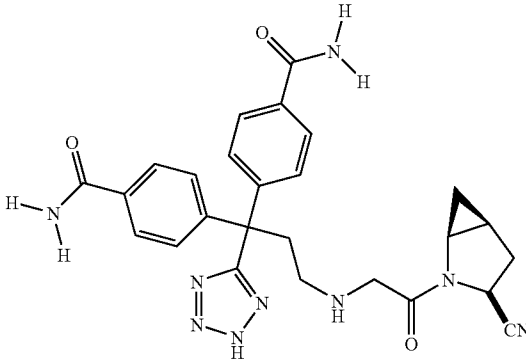
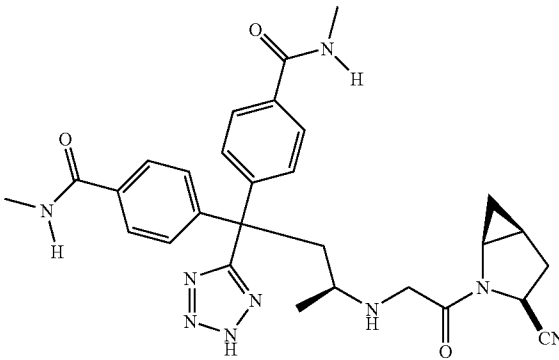
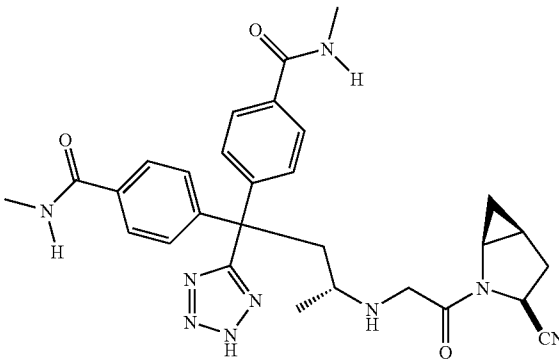
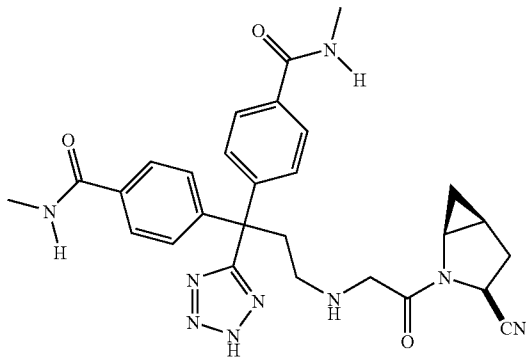
-continued

Example	Preparative Example	Preparative Example	Product
1130	1355	89	
1131	1356	89	
1132	1357	89	
1133	1358	89	

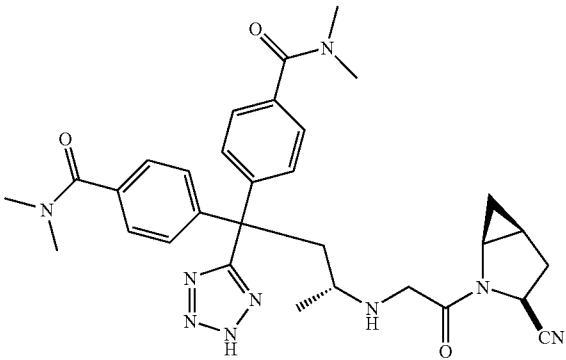
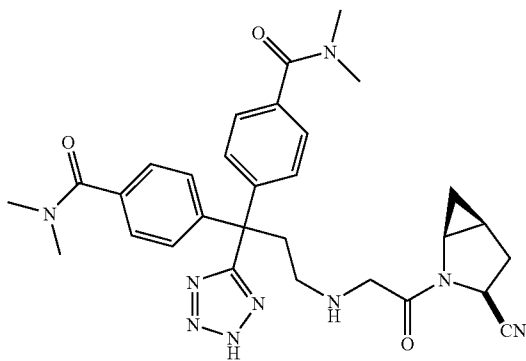
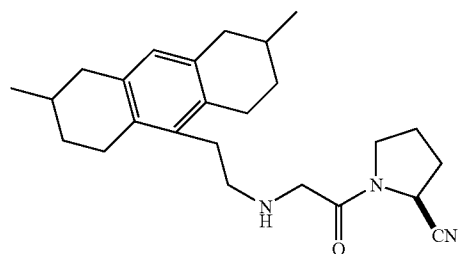
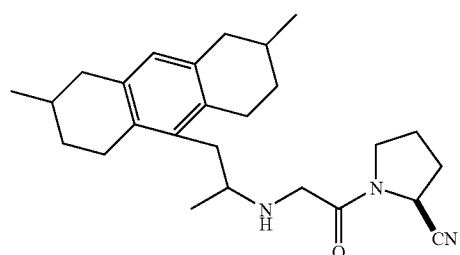
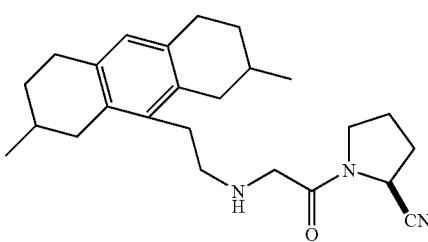
-continued

Example	Preparative Example	Preparative Example	Product
1134	1359	89	
1135	1401	89	
1136	1402	89	
1137	1403	89	

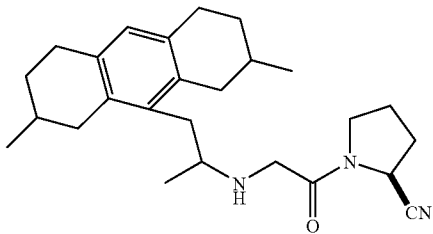
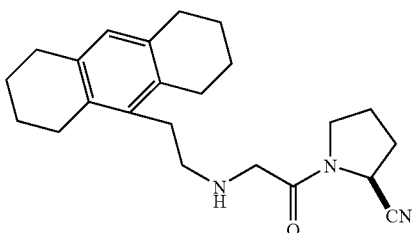
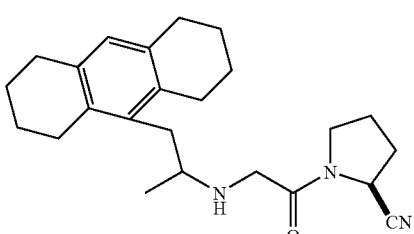
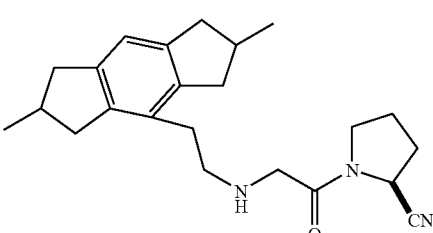
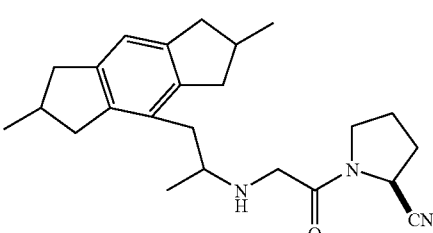
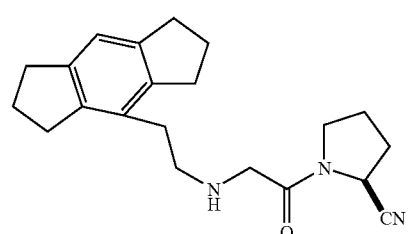
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Example	Preparative Example	Preparative Example	Product
1138	1404	89	
1139	1405	89	
1140	1406	89	
1141	1407	89	

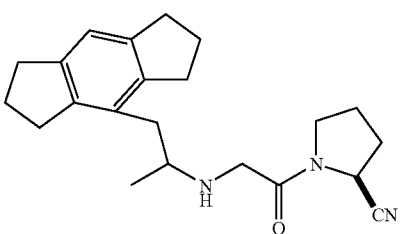
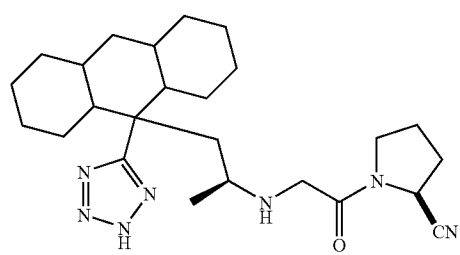
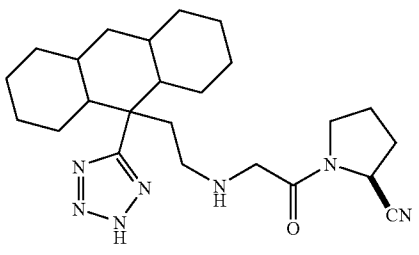
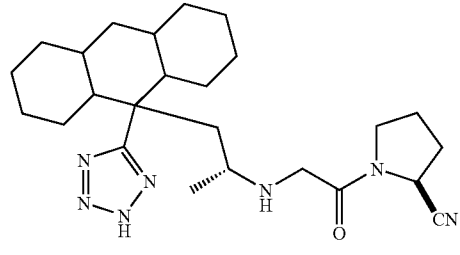
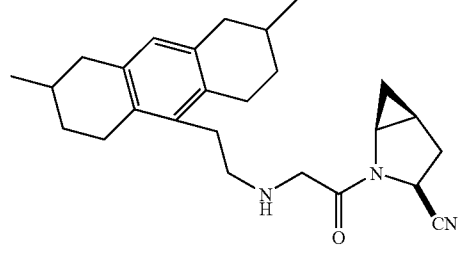
-continued

Example	Preparative Example	Preparative Example	Product
1142	1408	89	
1143	1409	89	
1144	1450 Step K	2	
1145	1450 Step O	2	
1146	1451 Step F	2	

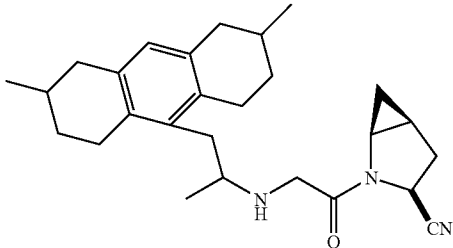
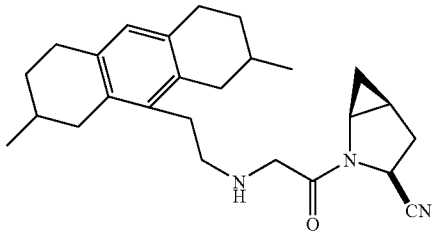
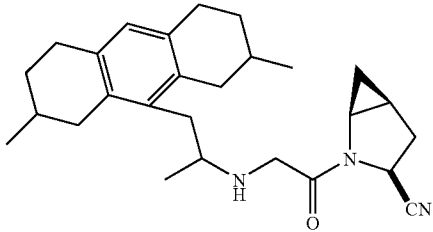
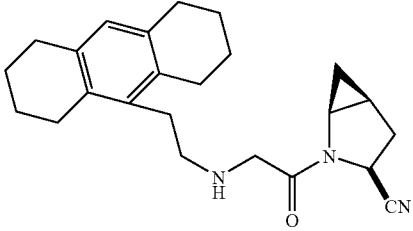
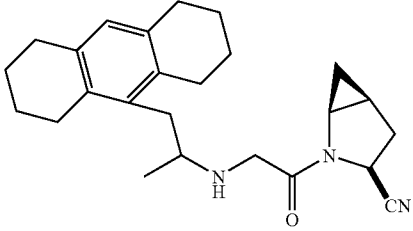
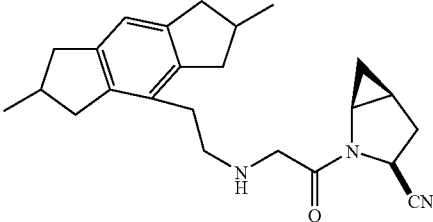
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Example	Preparative Example	Preparative Example	Product
1147	1451 Step J	2	
1148	1452 Step F	2	
1149	1452 Step J	2	
1150	1453 Step J	2	
1151	1453 Step M	2	
1152	1454 Step I	2	

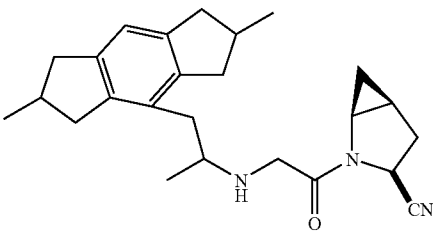
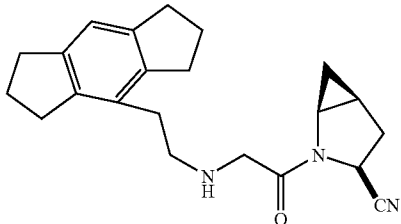
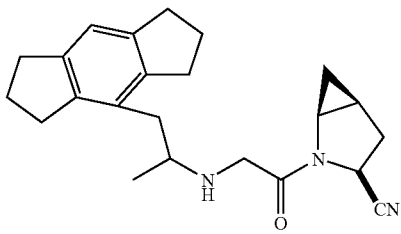
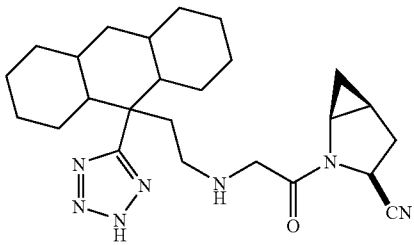
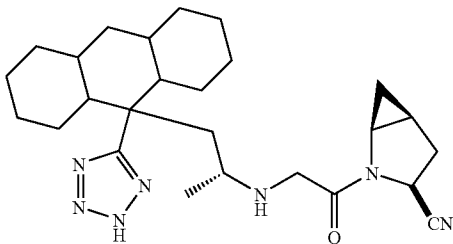
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Example	Preparative Example	Preparative Example	Product
1153	1454 Step L	2	
1154	1500	2	
1155	1501	2	
1156	1502	2	
1157	1450 Step K	89	

-continued

Example	Preparative Example	Preparative Example	Product
1158	1450 Step O	89	
1159	1451 Step F	89	
1160	1451 Step J	89	
1161	1452 Step F	89	
1162	1452 Step J	89	
1163	1453 Step J	89	

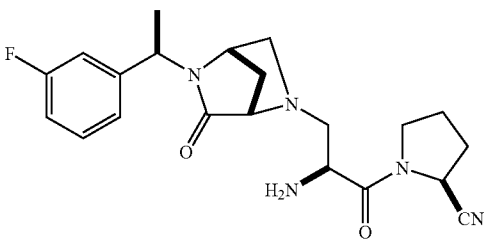
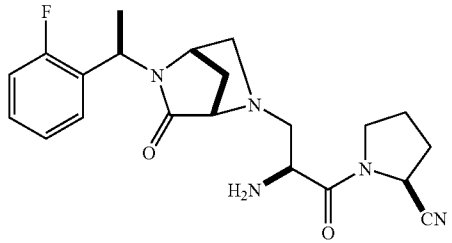
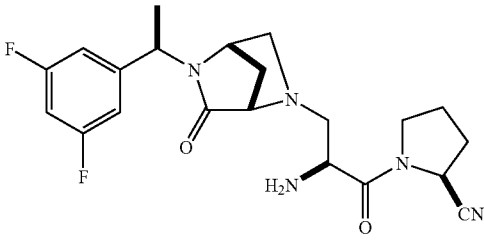
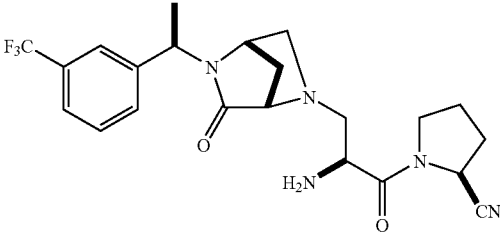
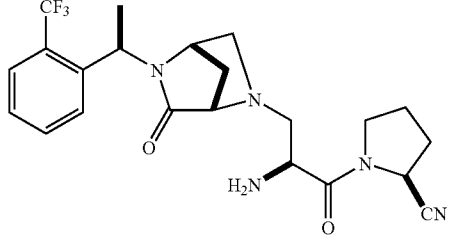
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Example	Preparative Example	Preparative Example	Product
1164	1453 Step M	89	
1165	1454 Step I	89	
1166	1454 Step L	89	
1167	1500	89	
1168	1501	89	

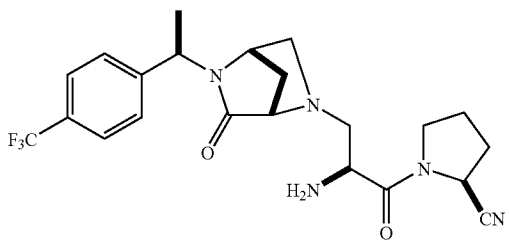
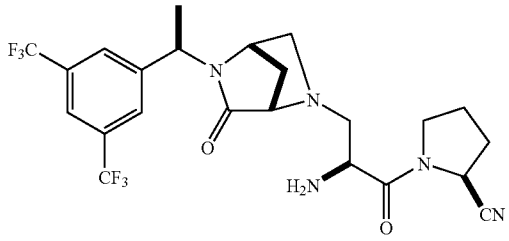
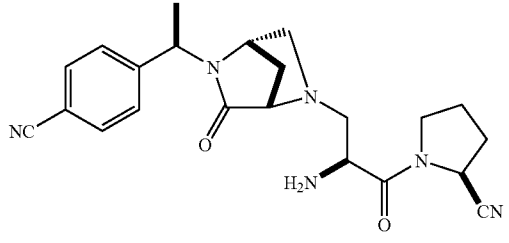
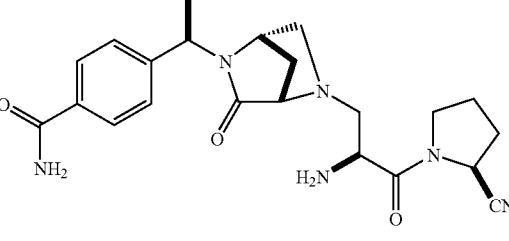
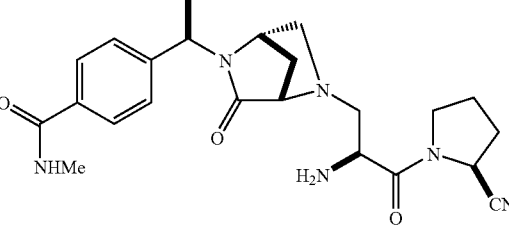
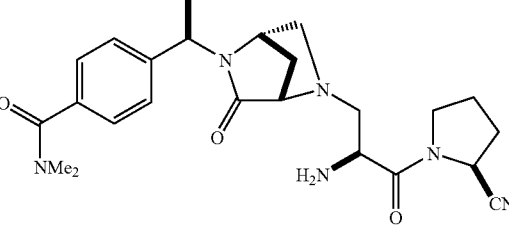
[0862] Examples 1169-1499 have been intentionally excluded.

Example 1500-1709

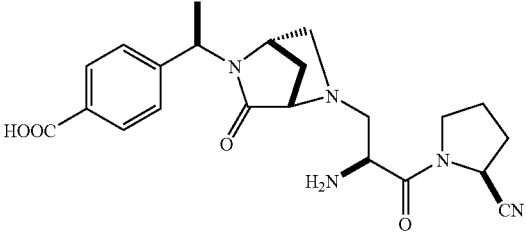
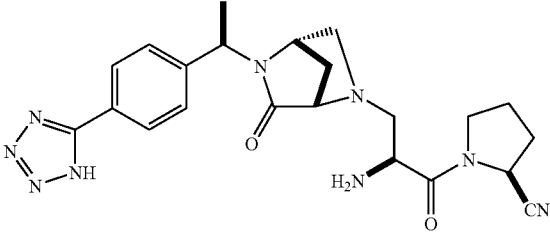
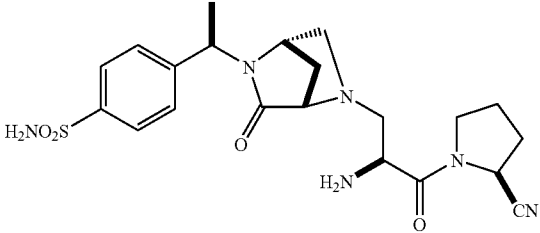
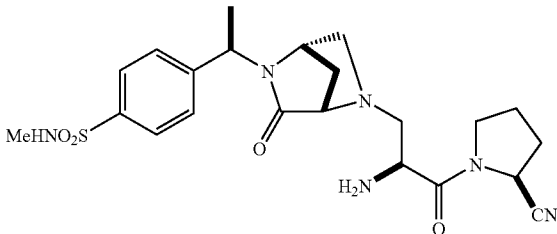
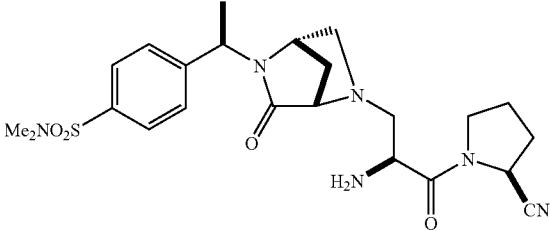
[0863] If one were to follow a similar procedure as that described in Preparative Example 48, except using the compounds from the Preparative Examples as indicated in the Table below, one would obtain the desired amine product.

Example	Compound Preparative Example	Product
1500	1000	
1501	1001	
1502	1002	
1503	1003	
1504	1004	

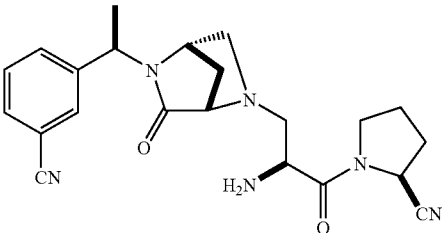
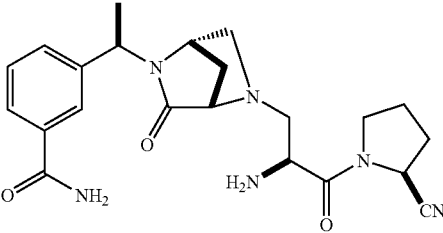
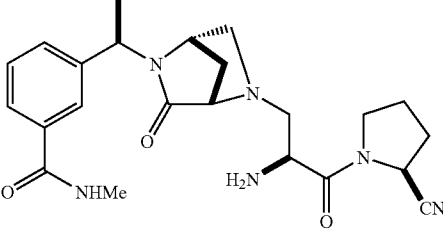
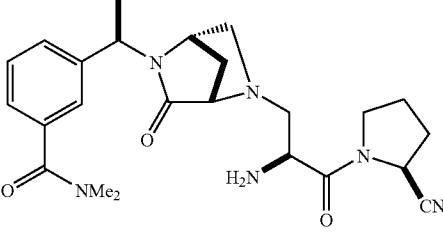
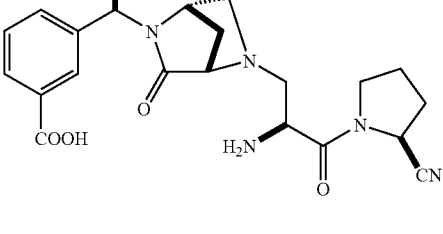
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Example	Compound Preparative Example	Product
1505	1005	
1506	1006	
1507	1007	
1508	1008	
1509	1009	
1510	1010	

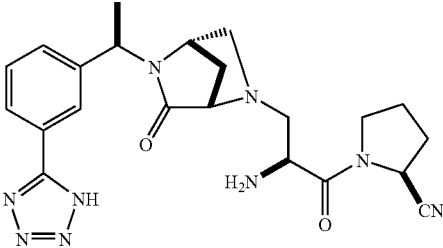
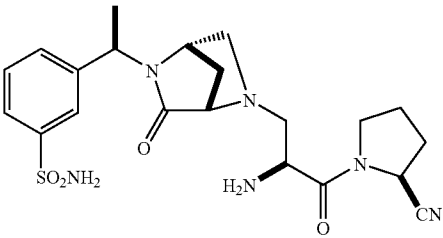
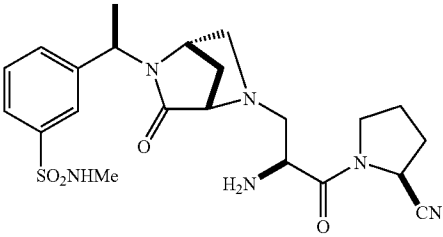
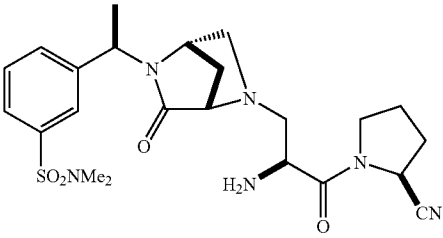
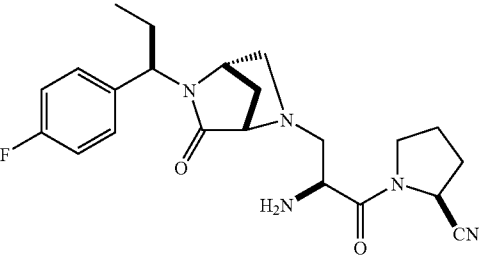
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Example	Compound Preparative Example	Product
1511	1011	
1512	1012	
1513	1013	
1514	1014	
1515	1015	

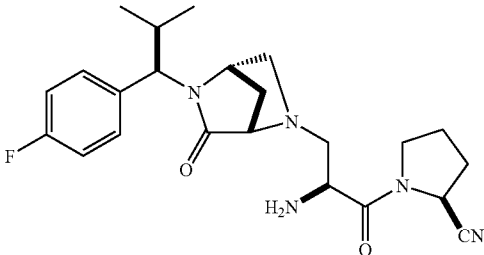
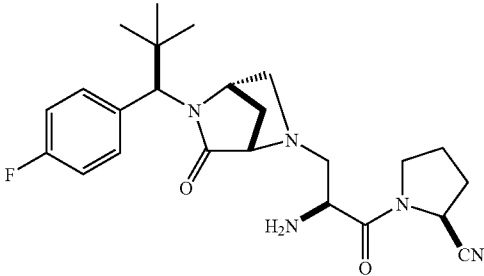
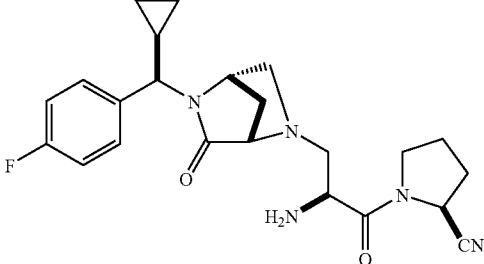
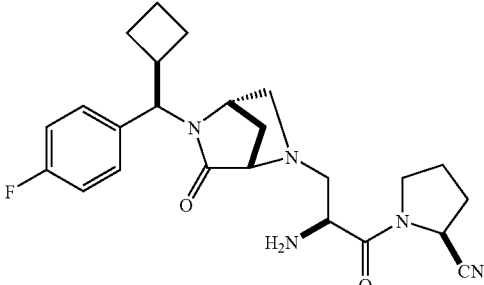
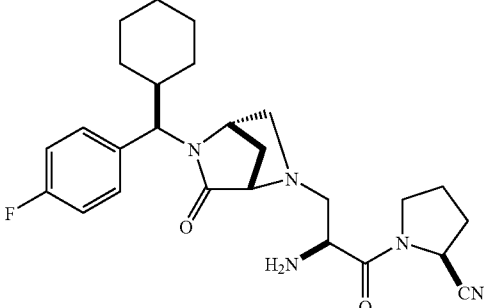
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Compound Preparative		Product
Example	Example	
1516	1016	
1517	1017	
1518	1018	
1519	1019	
1520	1020	

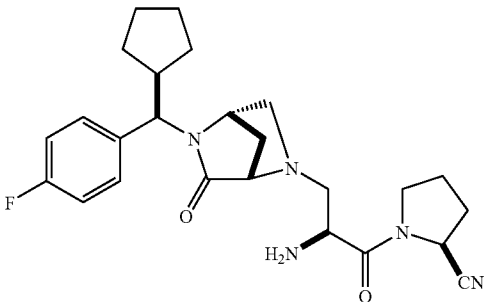
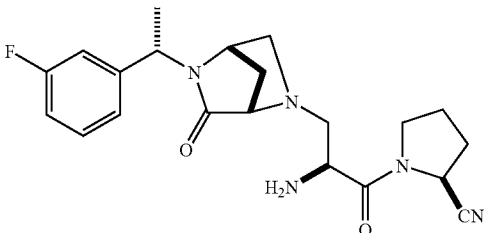
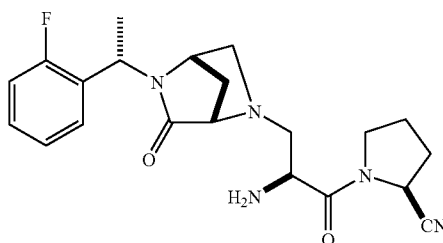
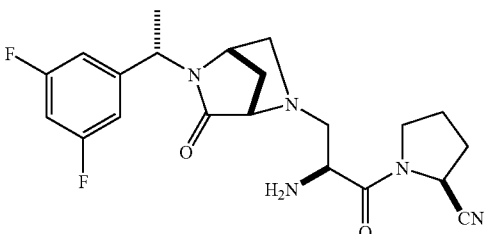
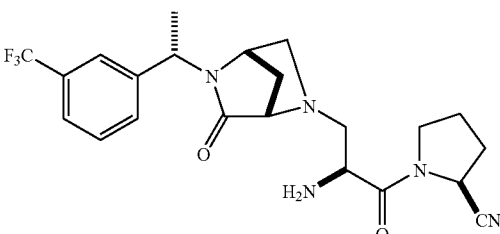
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Example	Compound Preparative Example	Product
1521	1021	
1522	1022	
1523	1023	
1524	1024	
1525	1025	

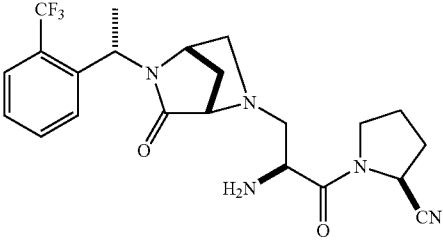
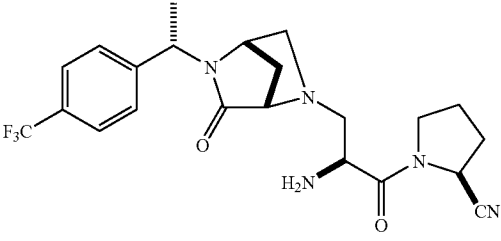
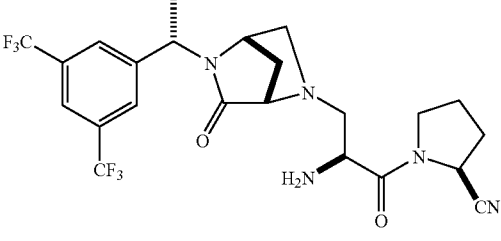
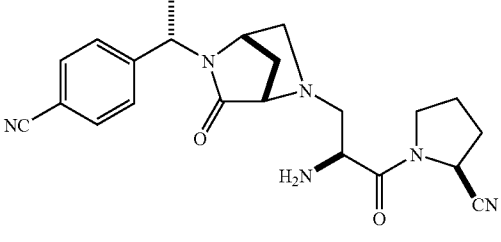
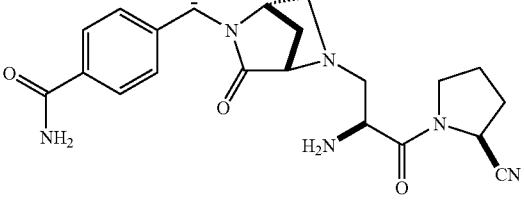
-continued

Example	Compound Preparative Example	Product
1526	1026	
1527	1027	
1528	1028	
1529	1029	
1530	1030	

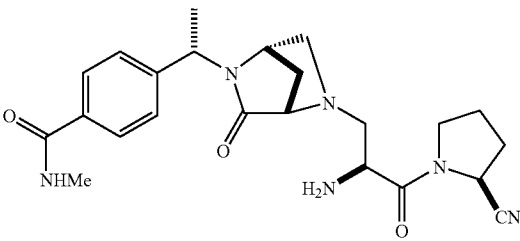
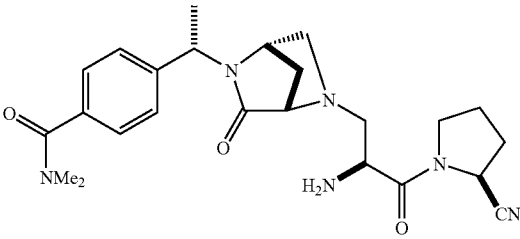
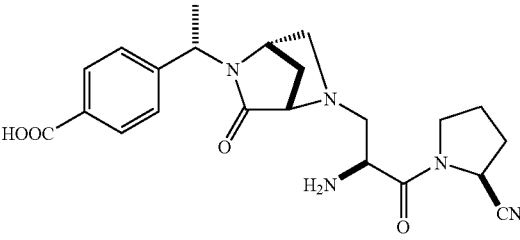
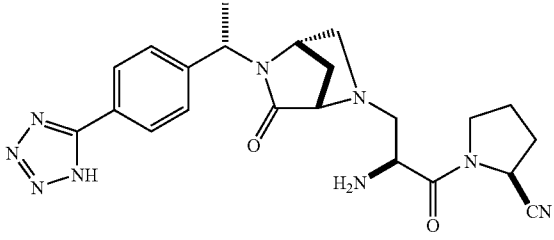
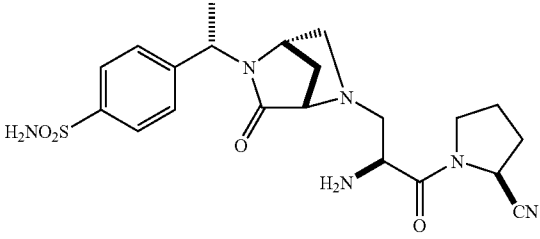
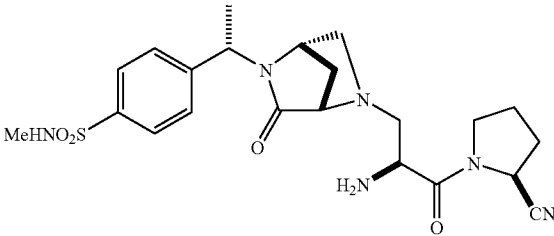
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Example	Compound Preparative Example	Product
1531	1031	
1532	1032	
1533	1033	
1534	1034	
1535	1035	

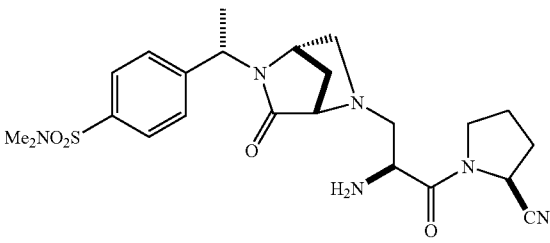
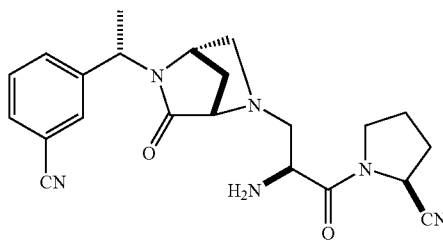
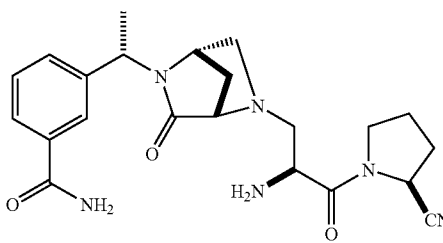
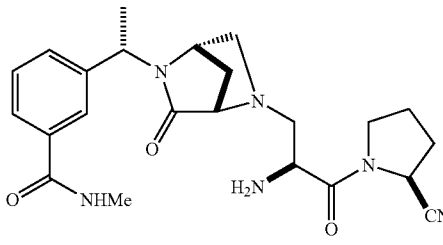
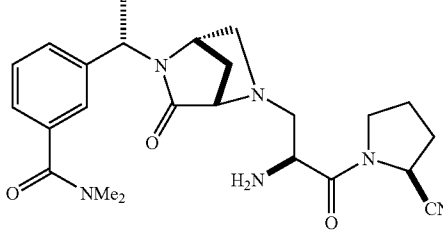
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Example	Compound Preparative Example	Product
1536	1036	
1537	1037	
1538	1038	
1539	1039	
1540	1040	

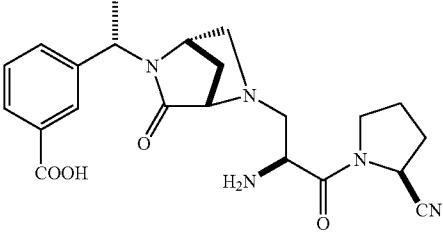
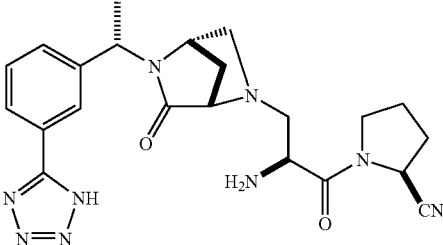
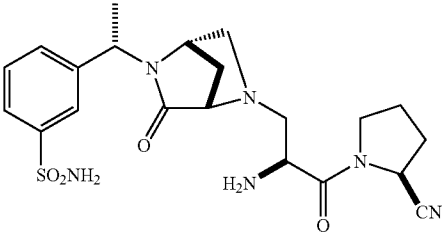
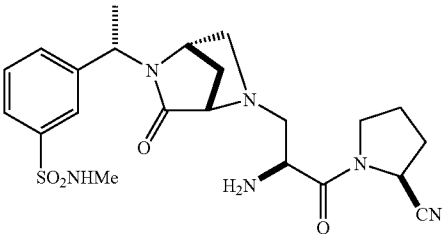
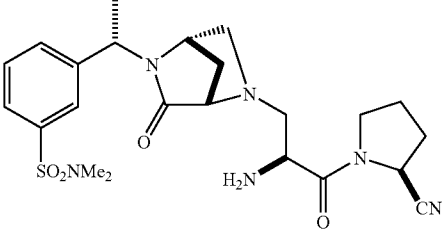
-continued

Example	Compound Preparative Example	Product
1541	1041	
1542	1042	
1543	1043	
1544	1044	
1545	1045	
1546	1046	

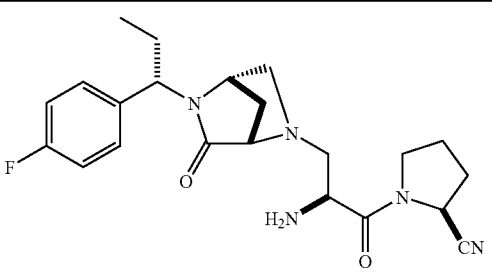
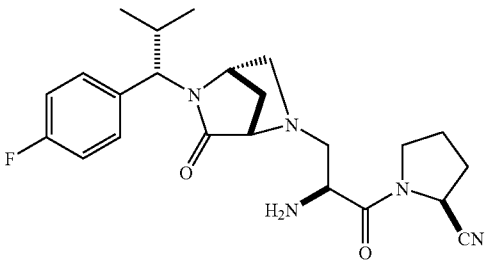
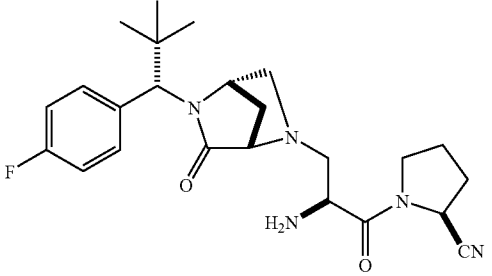
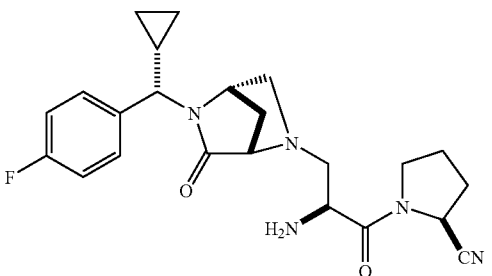
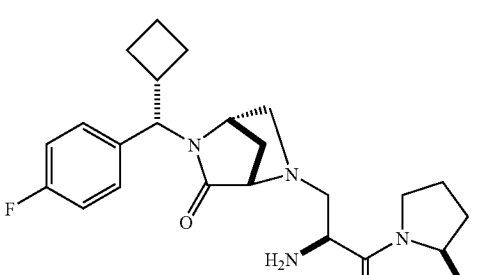
-continued

Example	Compound Preparative Example	Product
1547	1047	
1548	1048	
1549	1049	
1550	1050	
1551	1051	

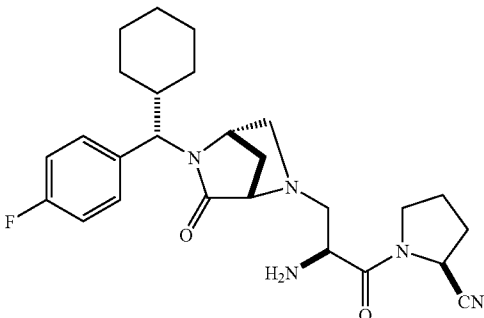
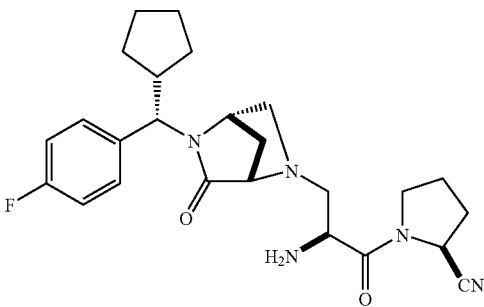
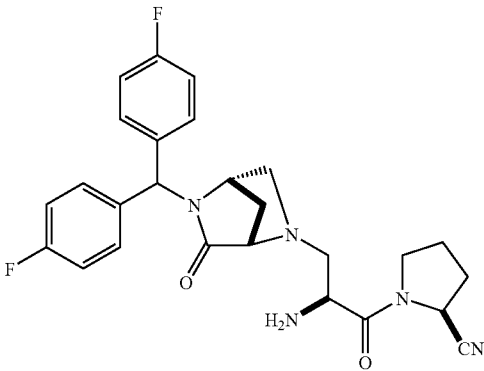
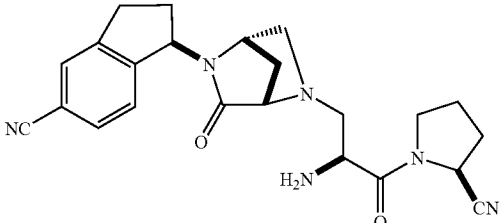
-continued

Example	Compound Preparative Example	Product
1552	1052	
1553	1053	
1554	1054	
1555	1055	
1556	1056	

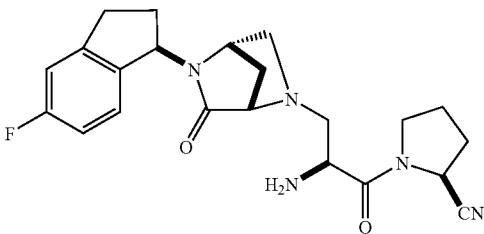
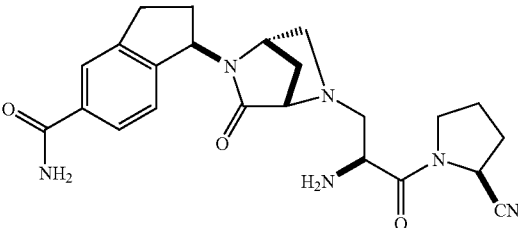
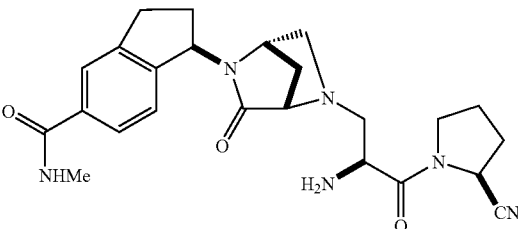
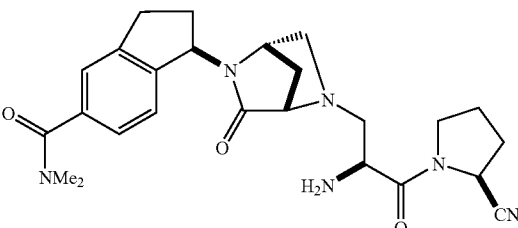
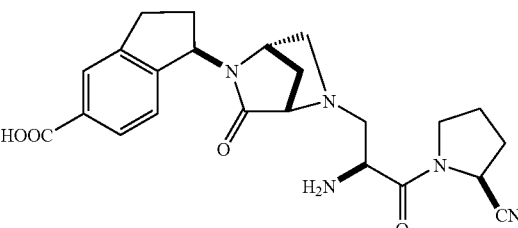
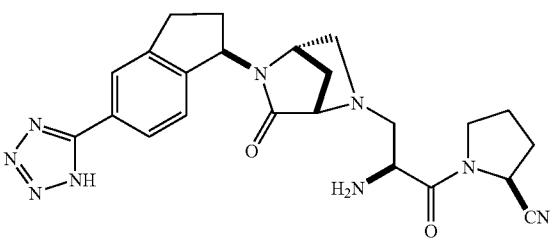
-continued

Example	Compound Preparative Example	Product
1557	1057	
1558	1058	
1559	1059	
1560	1060	
1561	1061	

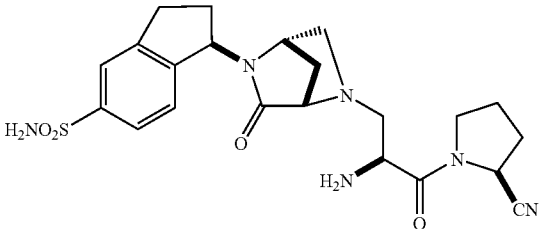
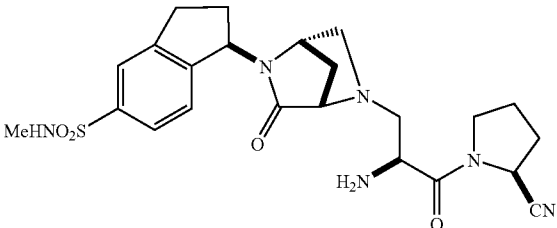
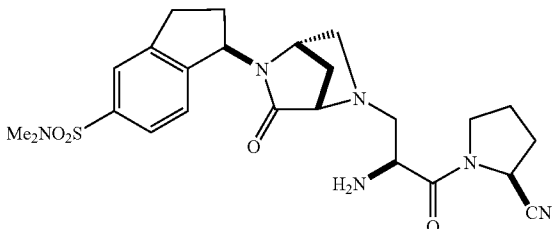
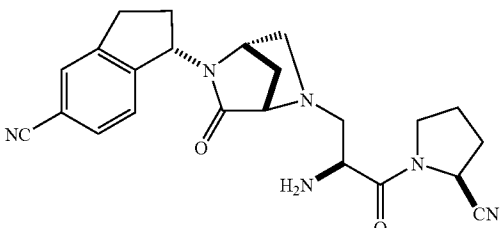
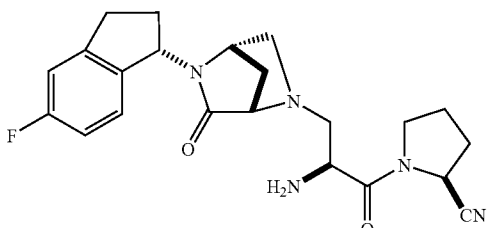
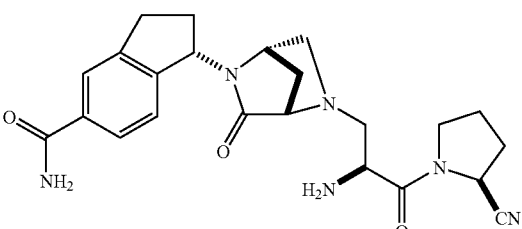
-continued

Example	Compound Preparative Example	Product
1562	1062	
1563	1063	
1564	1064	
1565	1065	

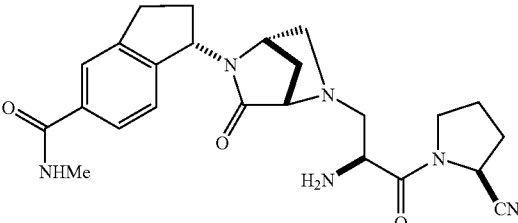
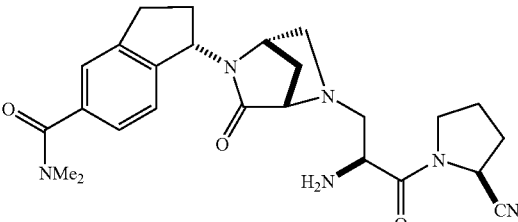
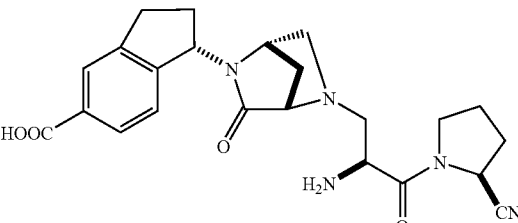
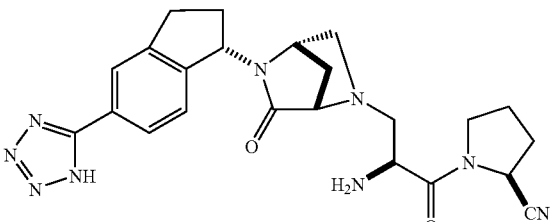
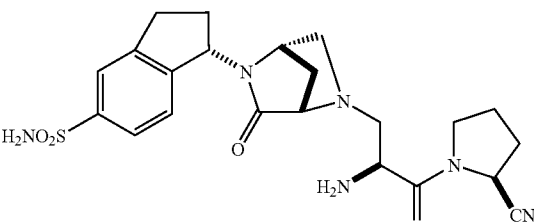
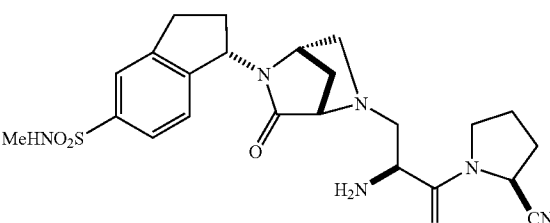
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Example	Compound Preparative Example	Product
1566	1066	
1567	1067	
1568	1068	
1569	1069	
1570	1070	
1571	1071	

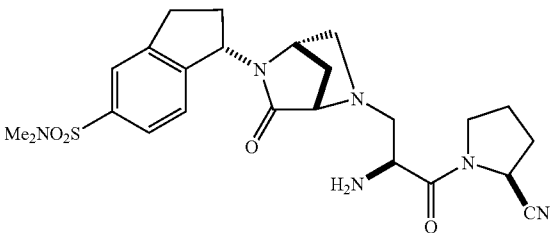
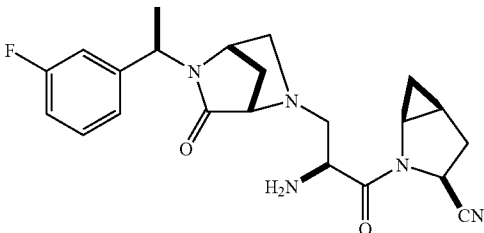
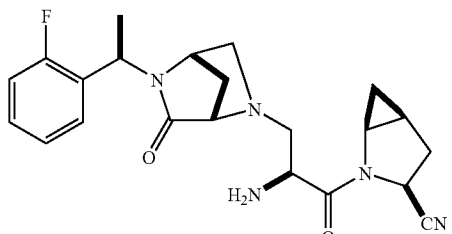
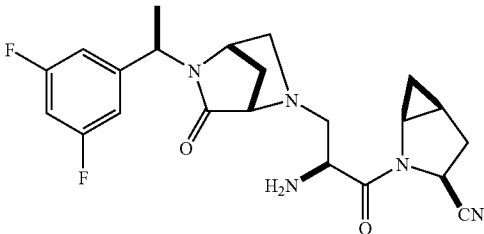
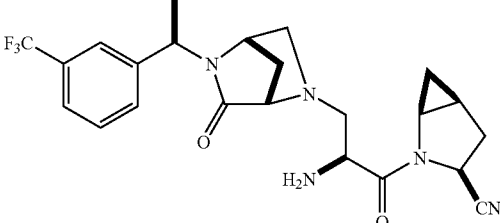
-continued

Example	Compound Preparative Example	Product
1572	1072	
1573	1073	
1574	1074	
1575	1075	
1576	1076	
1577	1077	

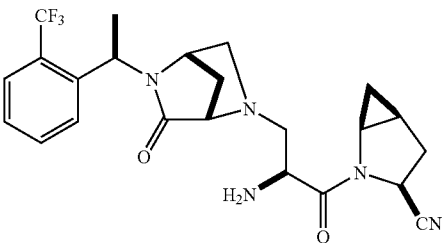
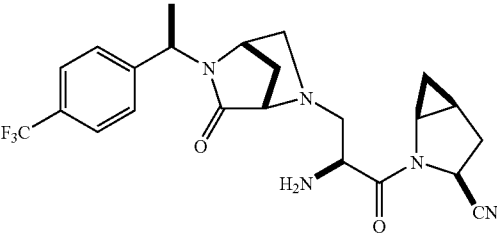
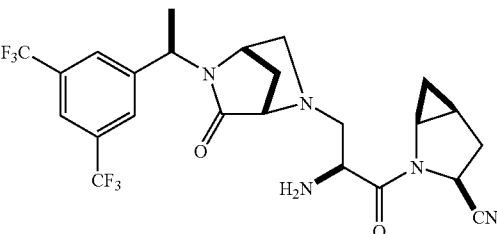
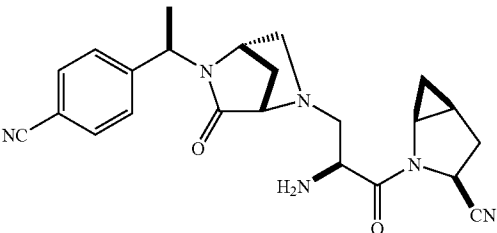
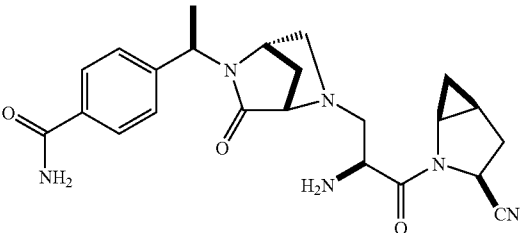
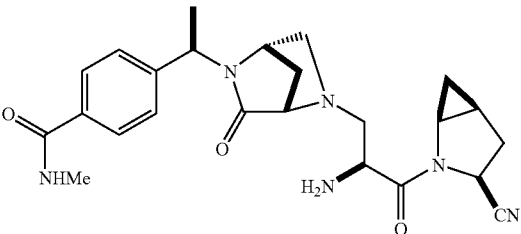
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Example	Compound Preparative Example	Product
1578	1078	
1579	1079	
1580	1080	
1581	1081	
1582	1082	
1583	1083	

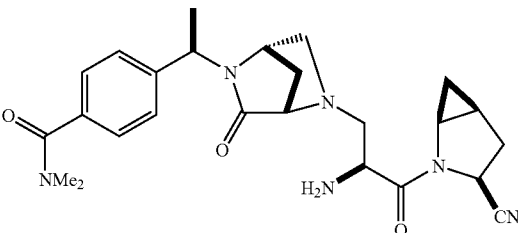
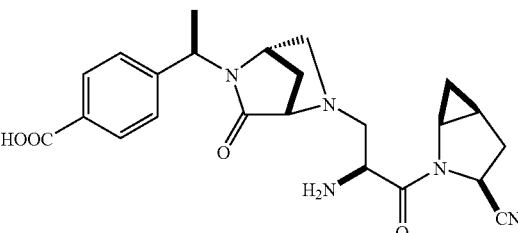
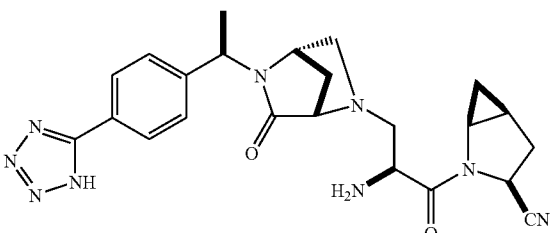
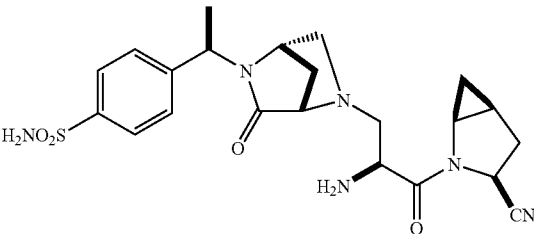
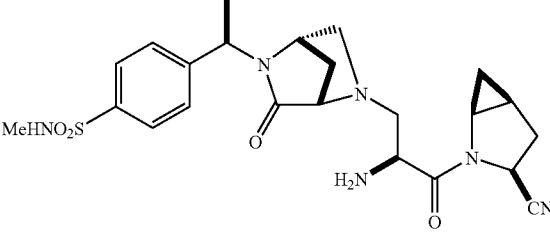
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Example	Compound Preparative Example	Product
1584	1084	
1585	1085	
1586	1086	
1587	1087	
1588	1088	

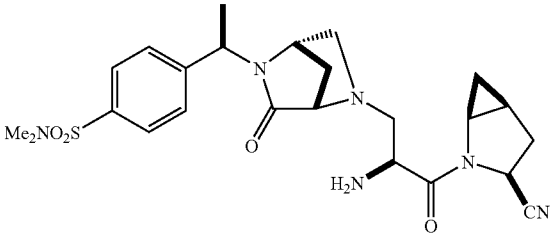
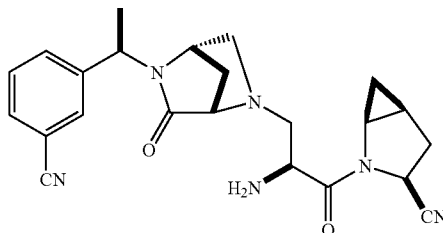
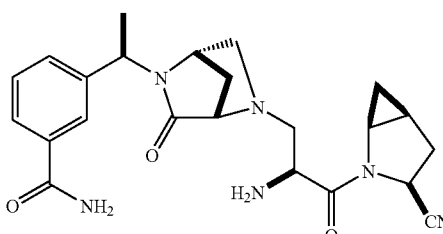
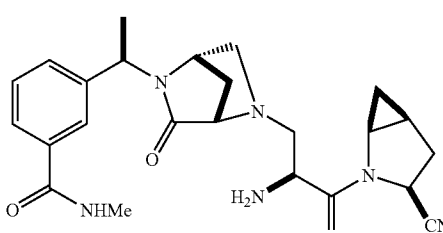
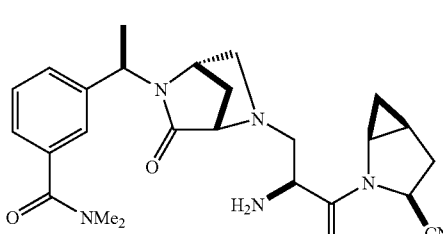
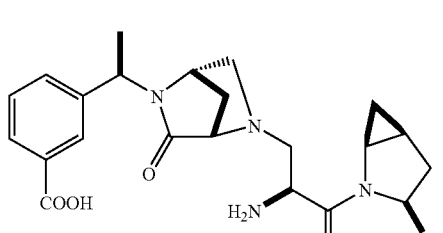
-continued

Example	Compound Preparative Example	Product
1589	1089	
1590	1090	
1591	1091	
1592	1092	
1593	1093	
1594	1094	

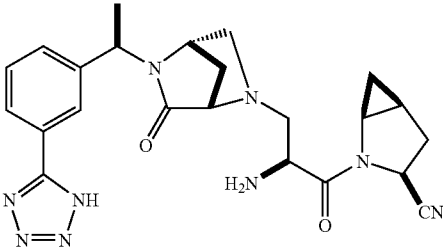
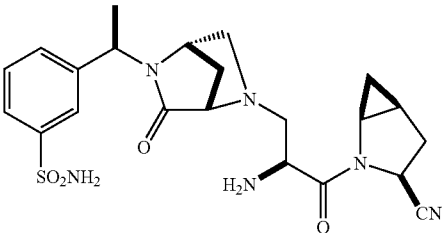
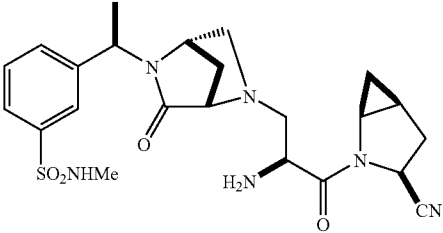
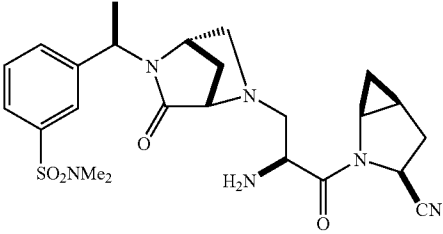
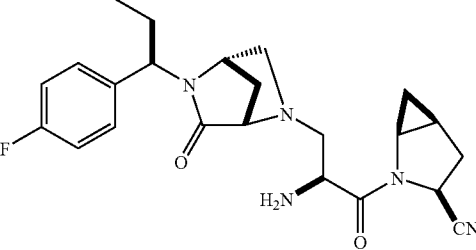
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Example	Compound Preparative Example	Product
1595	1095	
1596	1096	
1597	1097	
1598	1098	
1599	1099	

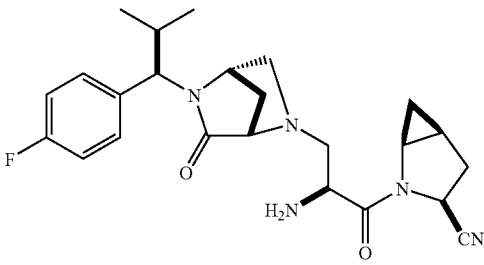
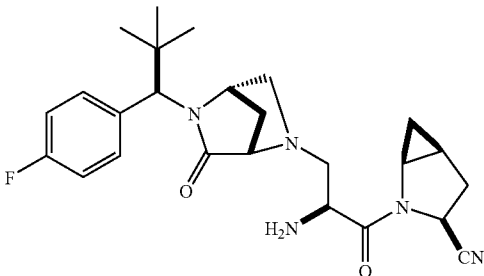
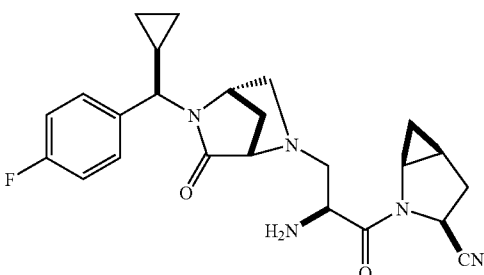
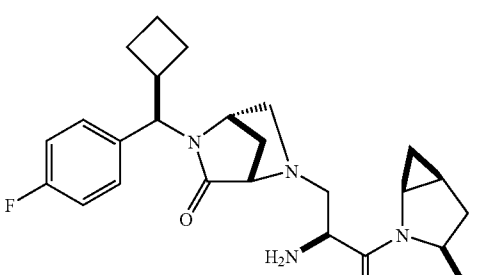
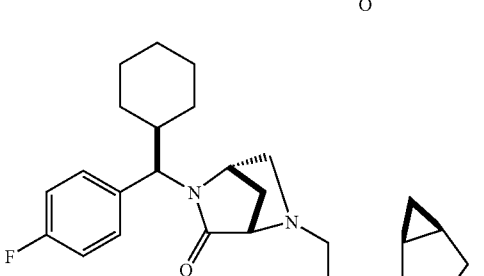
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Example	Compound Preparative Example	Product
1600	1100	
1601	1101	
1602	1102	
1603	1103	
1604	1104	
1605	1105	

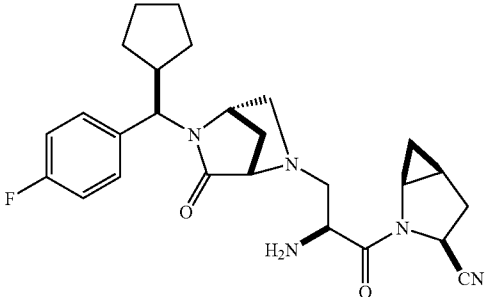
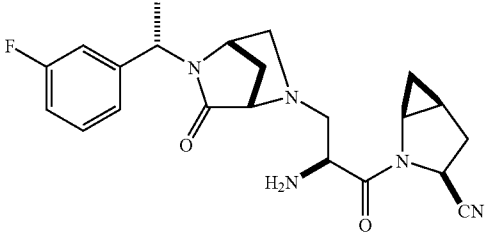
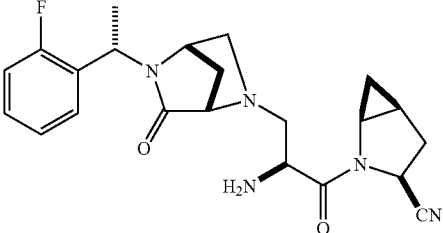
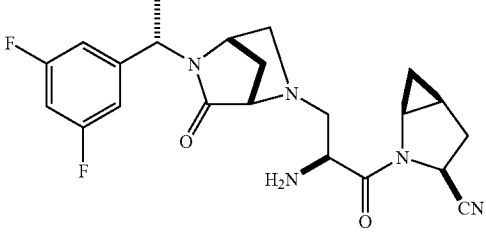
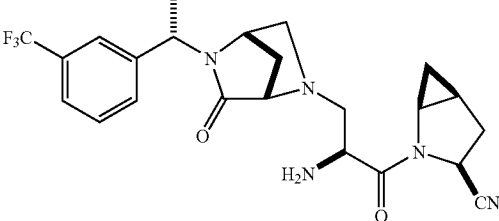
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Example	Compound Preparative Example	Product
1606	1106	
1607	1107	
1608	1108	
1609	1109	
1610	1110	

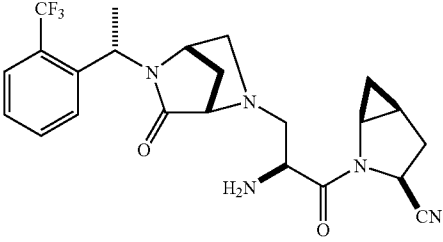
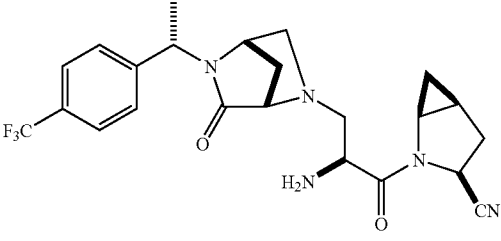
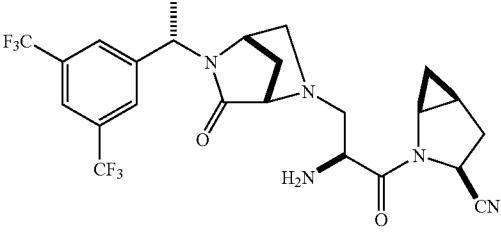
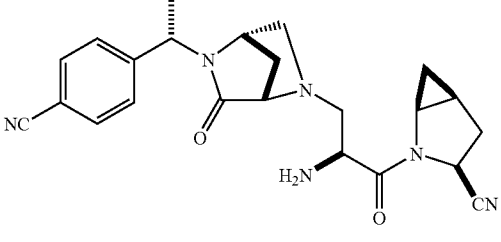
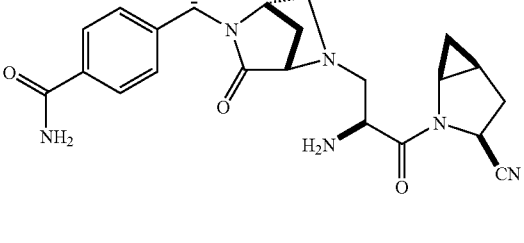
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Example	Compound Preparative Example	Product
1611	1111	
1612	1112	
1613	1113	
1614	1114	
1615	1115	

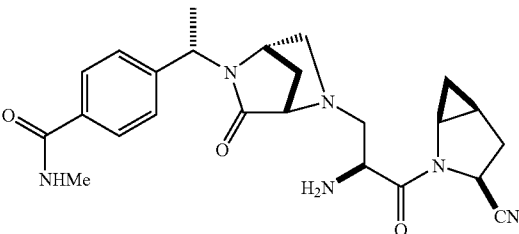
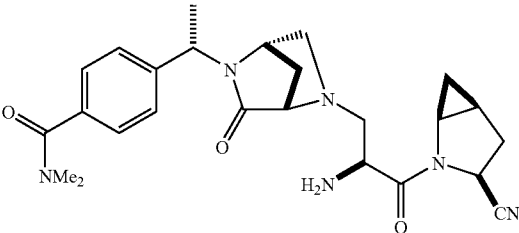
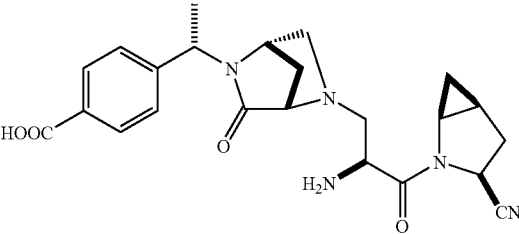
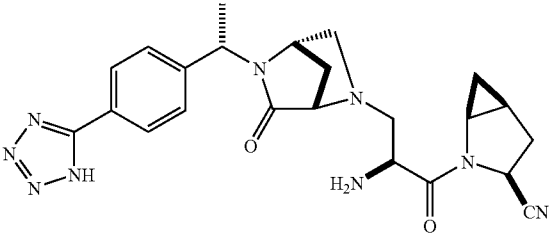
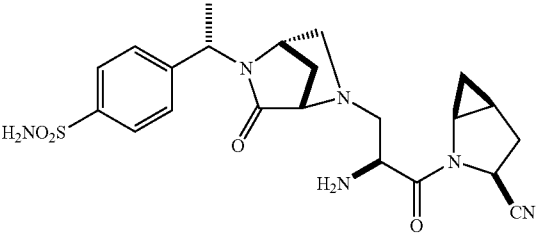
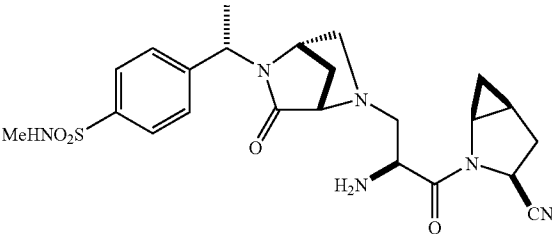
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Example	Compound Preparative Example	Product
1616	1116	
1617	1117	
1618	1118	
1619	1119	
1620	1120	

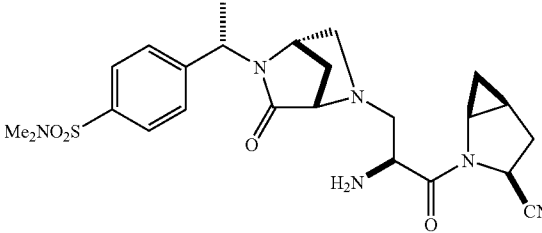
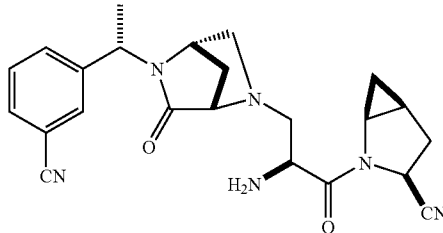
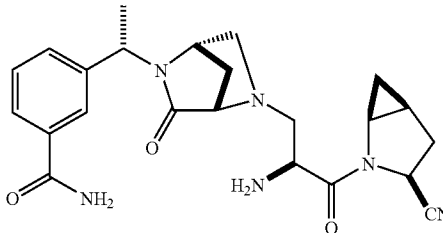
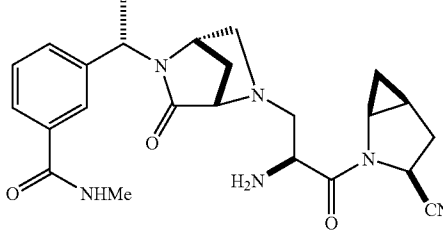
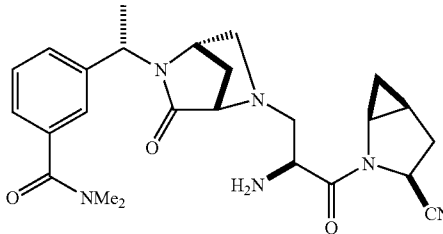
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Example	Compound Preparative Example	Product
1621	1121	
1622	1122	
1623	1123	
1624	1124	
1625	1125	

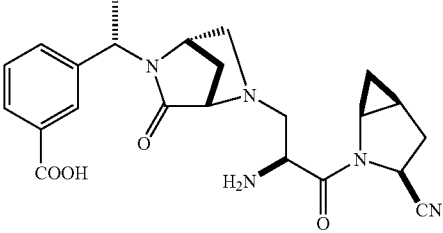
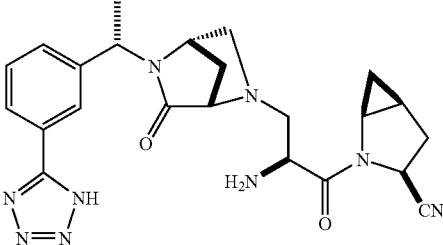
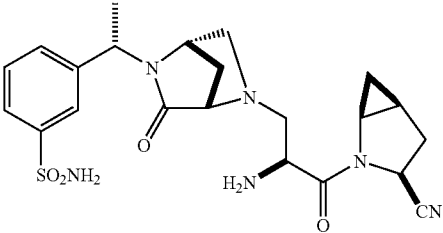
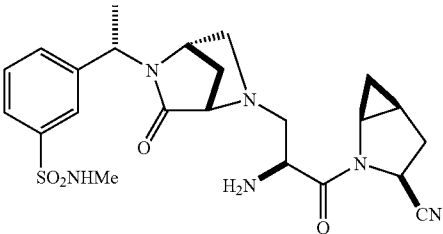
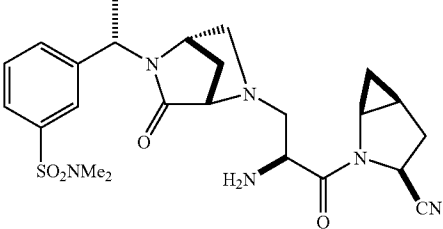
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Example	Compound Preparative Example	Product
1626	1126	
1627	1127	
1628	1128	
1629	1129	
1630	1130	
1631	1131	

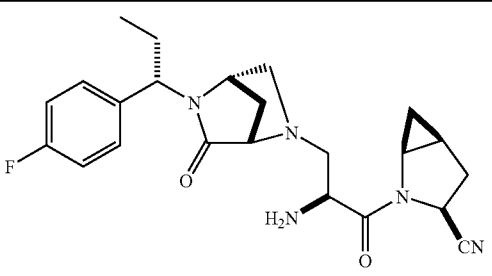
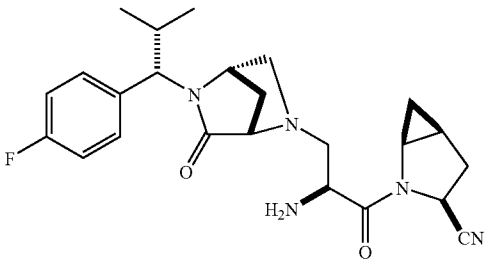
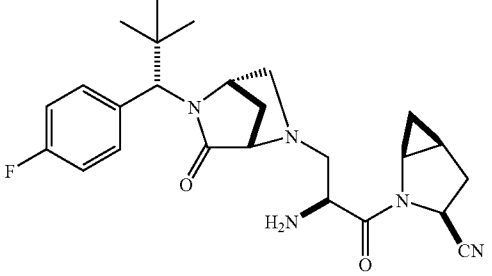
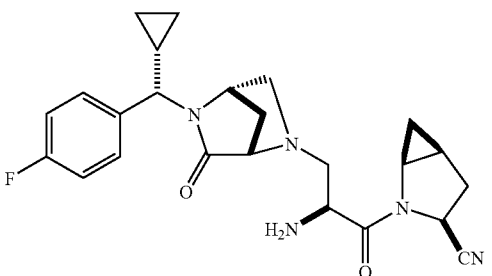
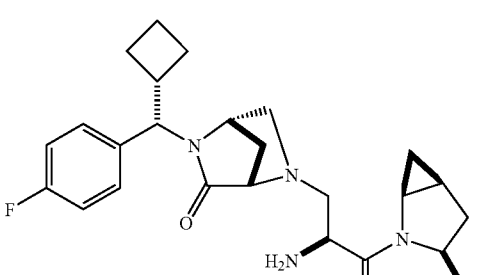
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Example	Compound Preparative Example	Product
1632	1132	
1633	1133	
1634	1134	
1635	1135	
1636	1136	

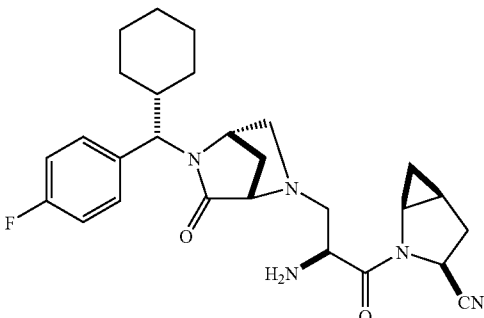
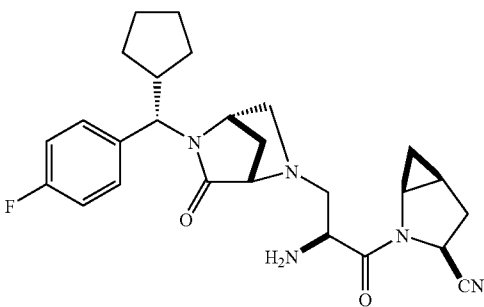
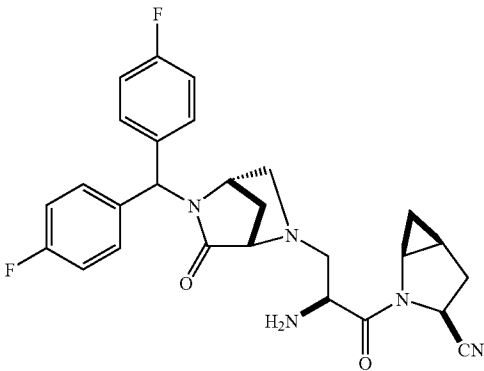
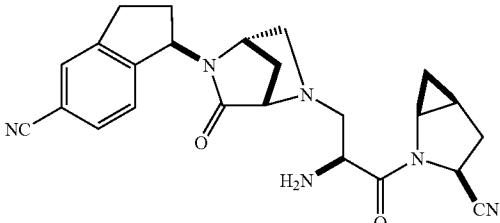
-continued

Example	Compound Preparative Example	Product
1637	1137	
1638	1138	
1639	1139	
1640	1140	
1641	1141	

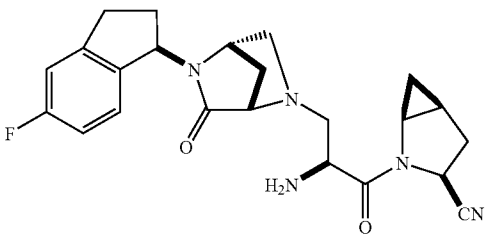
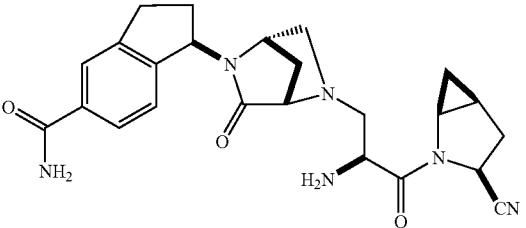
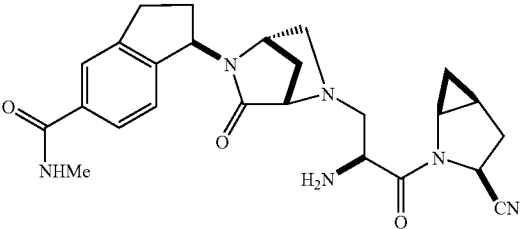
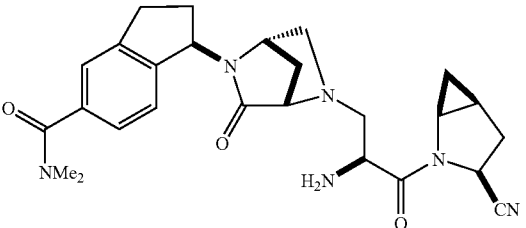
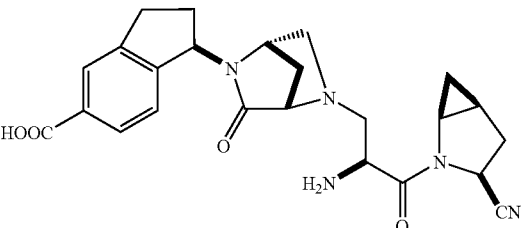
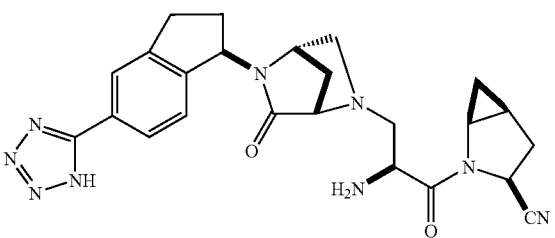
-continued

Example	Compound Preparative Example	Product
1642	1142	
1643	1143	
1644	1144	
1645	1145	
1646	1146	

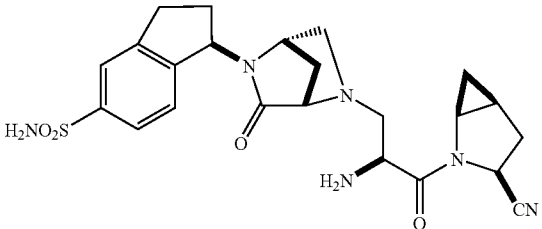
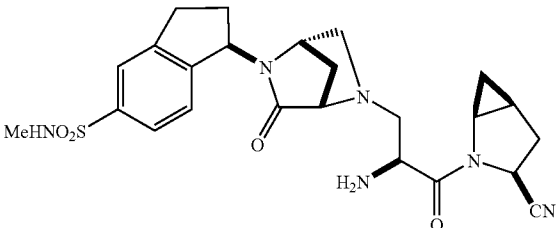
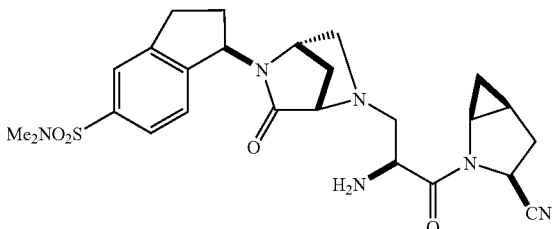
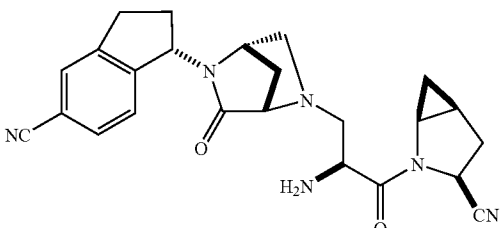
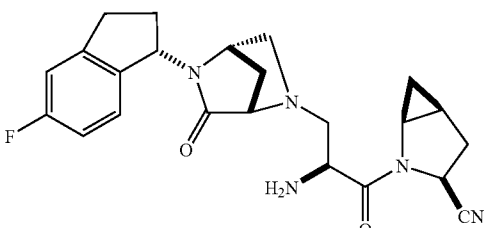
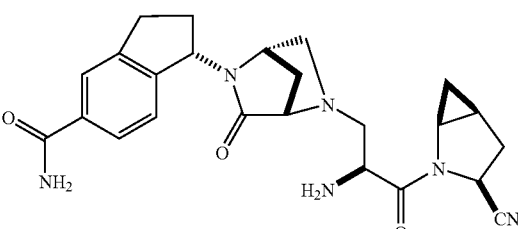
-continued

Example	Compound Preparative Example	Product
1647	1147	
1648	1148	
1649	1149	
1650	1150	

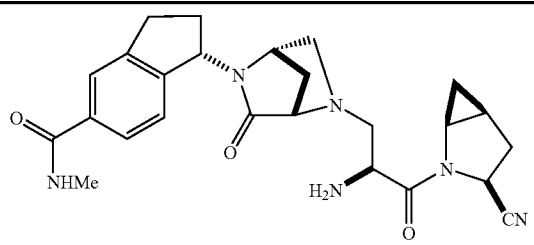
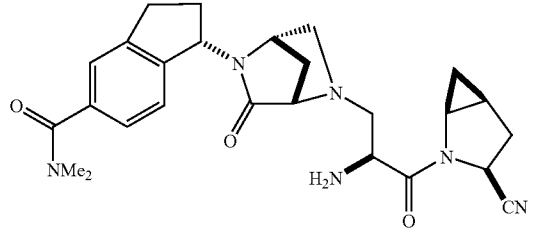
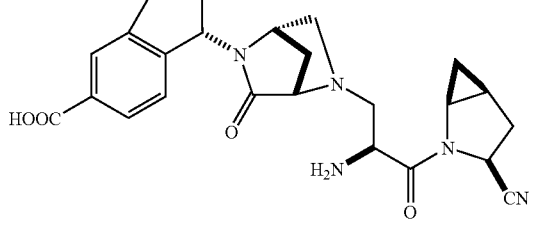
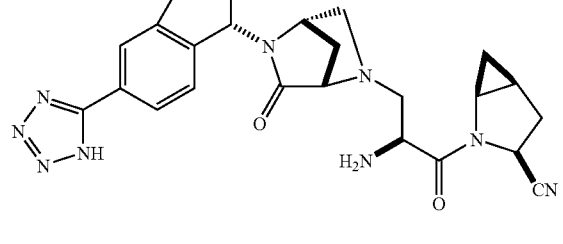
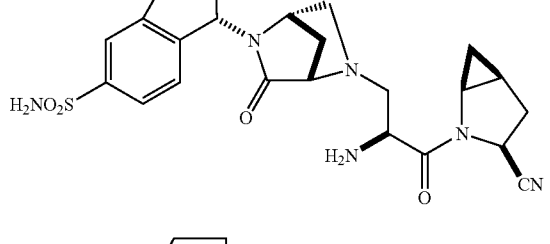
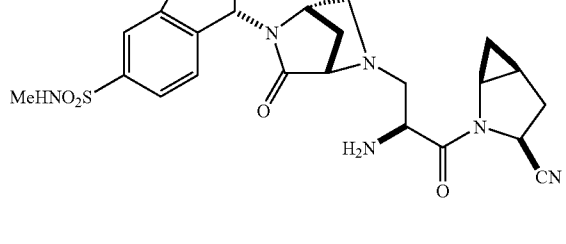
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Example	Compound Preparative Example	Product
1651	1151	
1652	1152	
1653	1153	
1654	1154	
1655	1155	
1656	1156	

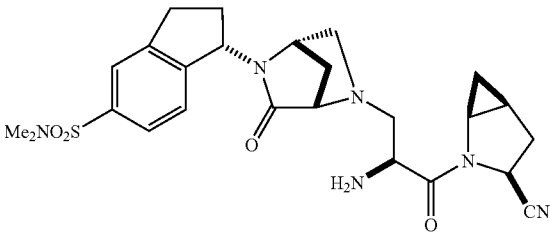
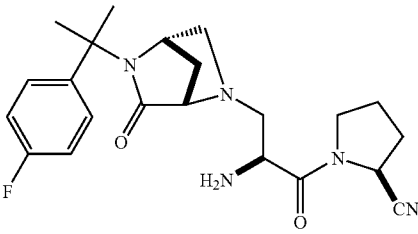
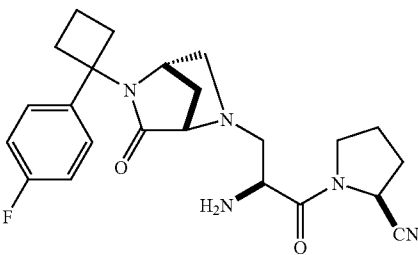
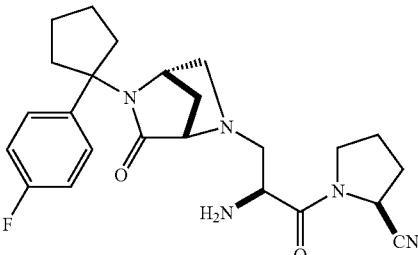
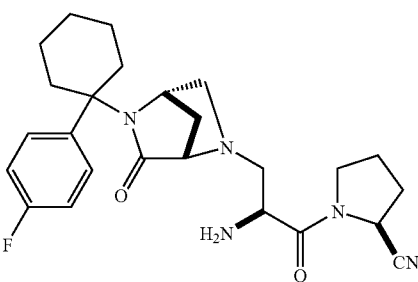
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Example	Compound Preparative Example	Product
1657	1157	
1658	1158	
1659	1159	
1660	1160	
1661	1161	
1662	1162	

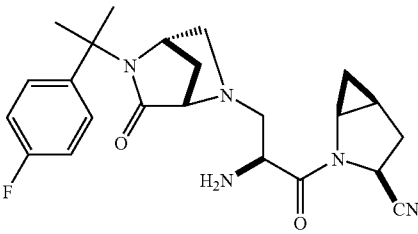
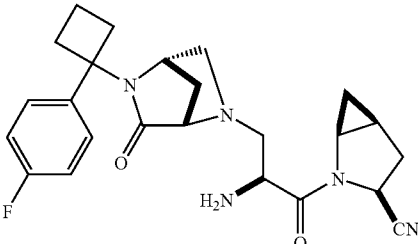
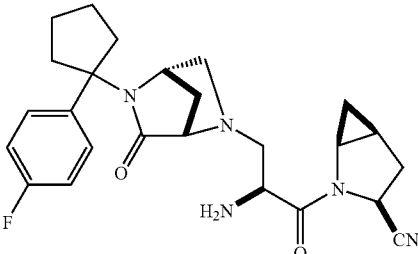
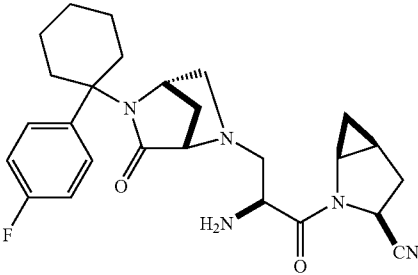
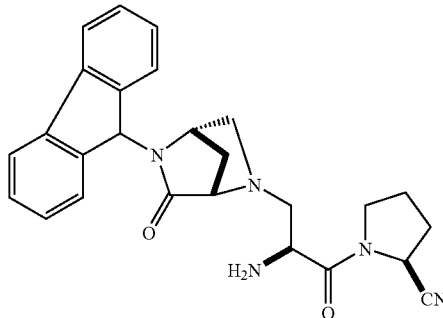
-continued

Example	Compound Preparative Example	Product
1663	1163	
1664	1164	
1665	1165	
1666	1166	
1667	1167	
1668	1168	

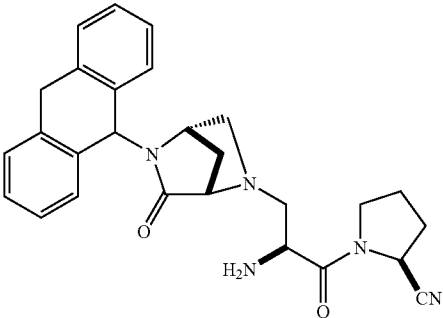
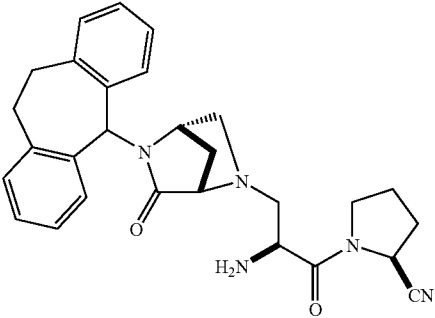
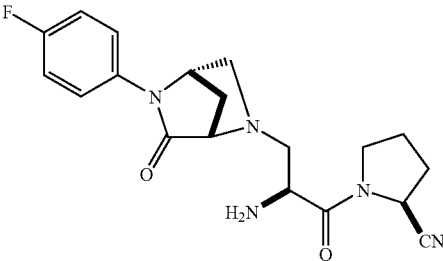
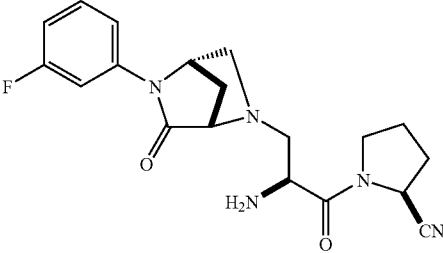
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Example	Compound Preparative Example	Product
1669	1169	
1670	1170	
1671	1171	
1672	1172	
1673	1173	

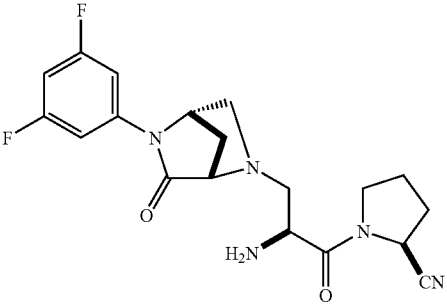
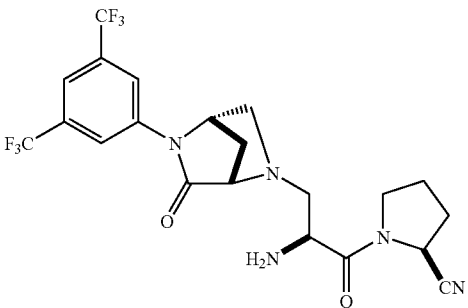
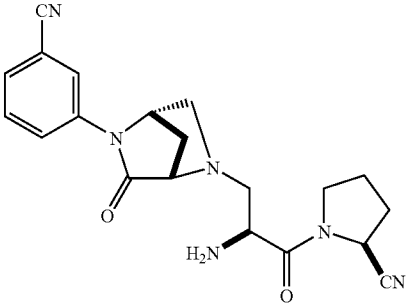
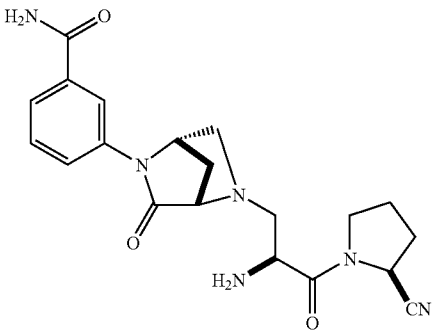
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Example	Compound Preparative Example	Product
1674	1174	
1675	1175	
1676	1176	
1677	1177	
1678	1178	

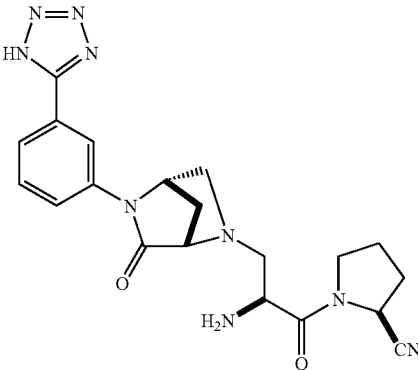
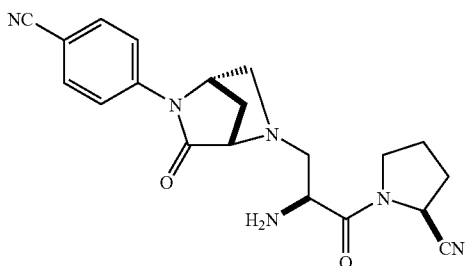
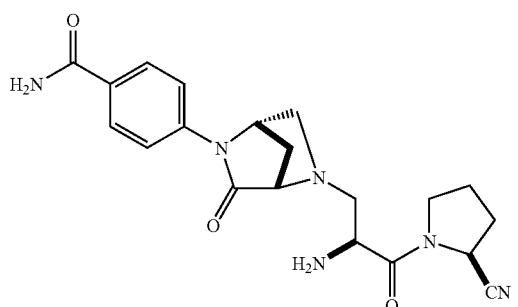
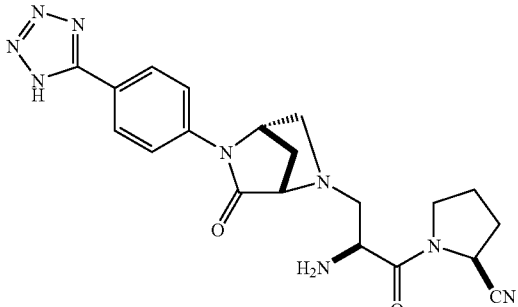
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Example	Compound Preparative Example	Product
1679	1179	
1680	1180	
1681	1181	
1682	1182	

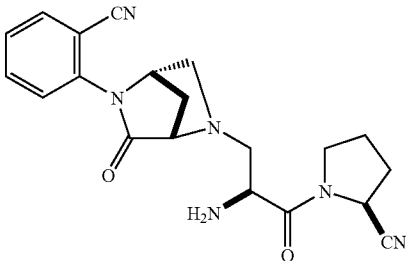
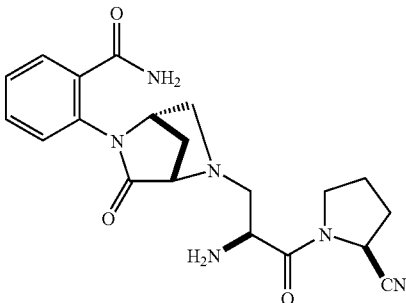
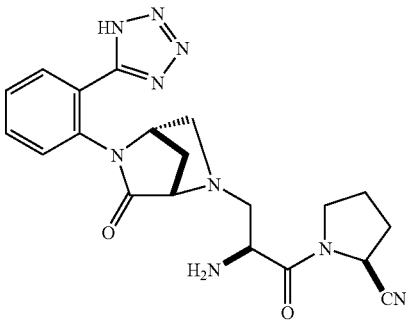
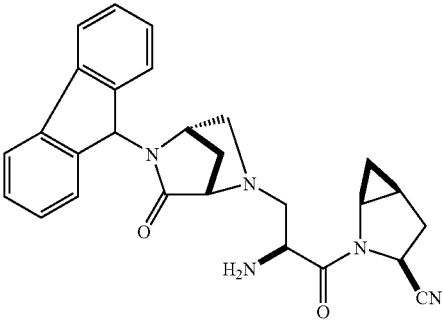
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Example	Compound Preparative Example	Product
1683	1183	
1684	1184	
1685	1185	
1686	1186	

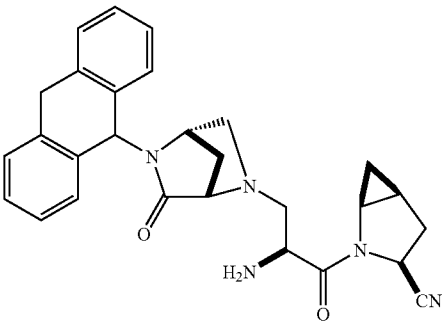
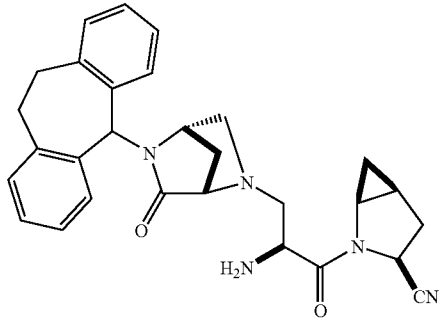
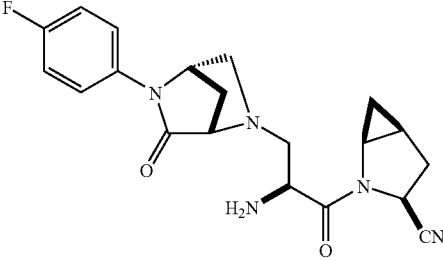
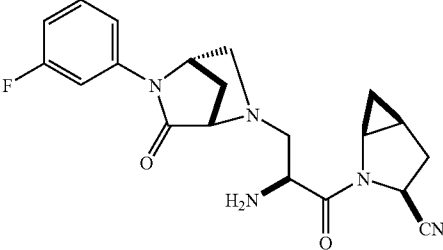
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Example	Compound Preparative Example	Product
1687	1187	
1688	1188	
1689	1189	
1690	1190	

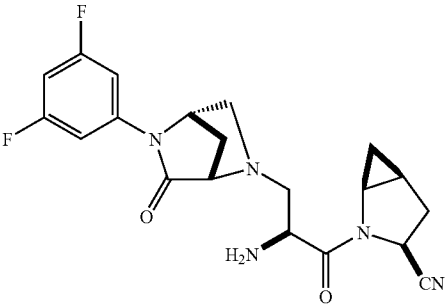
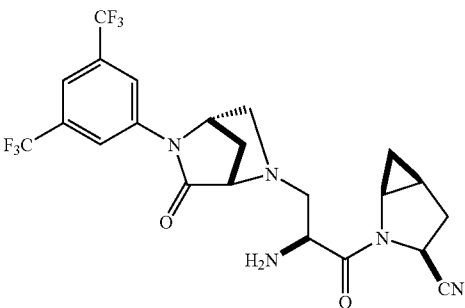
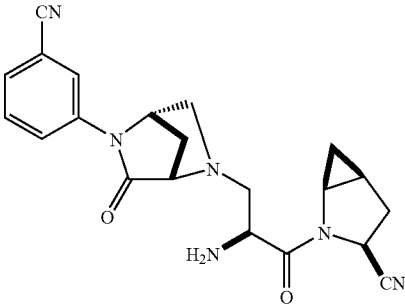
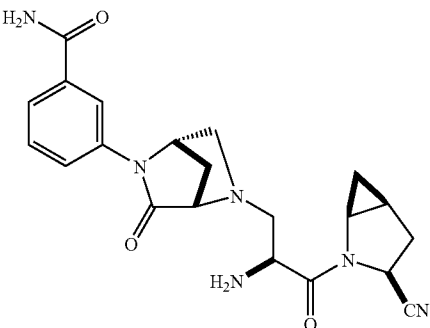
-continued

Example	Compound Preparative Example	Product
1691	1191	
1692	1192	
1693	1193	
1694	1194	

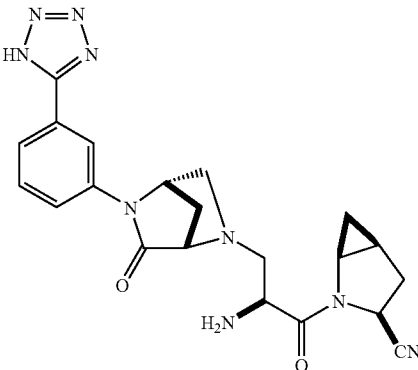
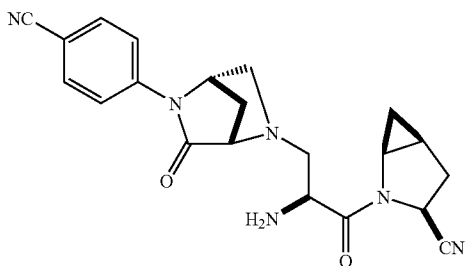
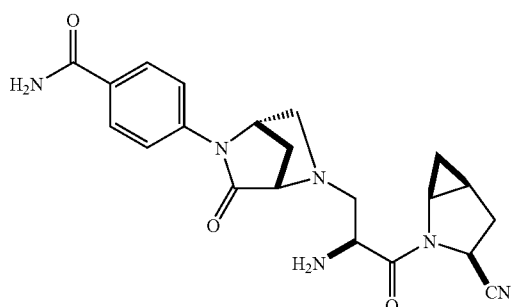
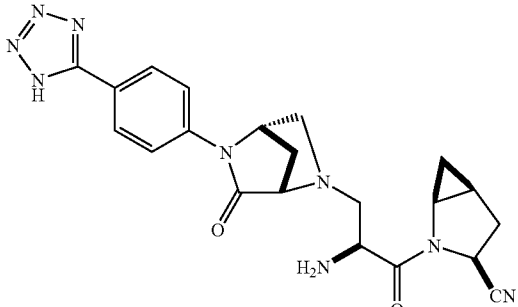
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Example	Compound Preparative Example	Product
1695	1195	
1696	1196	
1697	1197	
1698	1198	

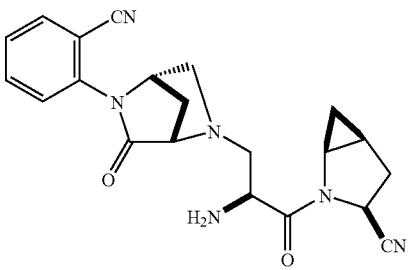
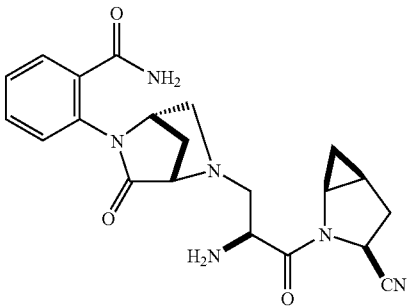
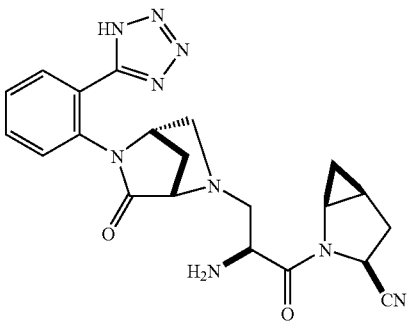
-continued

Example	Compound Preparative Example	Product
1699	1199	
1700	1200	
1701	1201	
1702	1202	

-continued

Example	Compound Preparative Example	Product
1703	1203	
1704	1204	
1705	1205	
1706	1206	

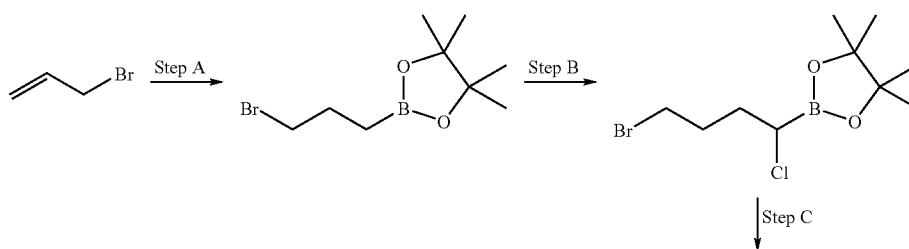
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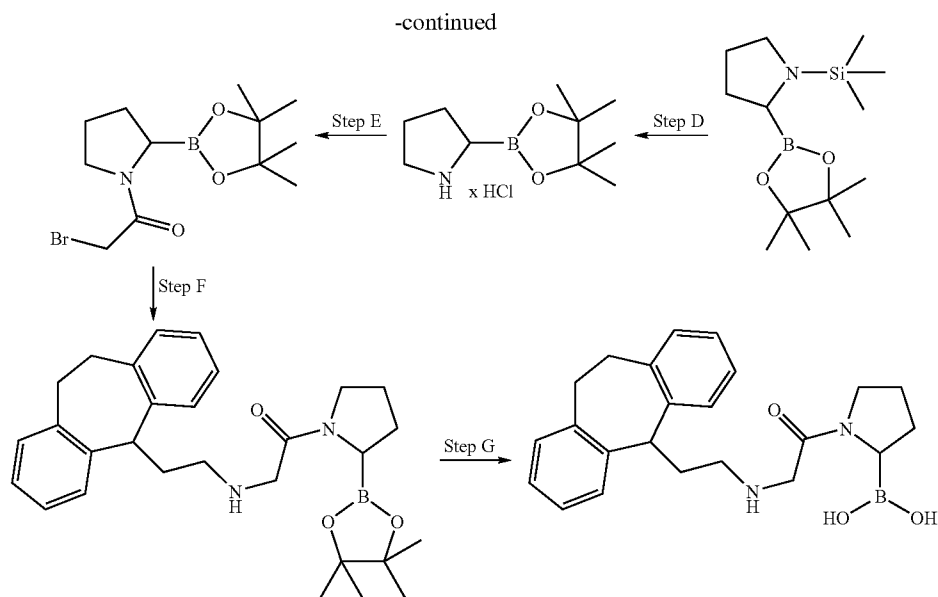
Example	Compound Preparative Example	Product
1707	1207	
1708	1208	
1709	1209	

[0864] Examples 1710-1799 have been intentionally excluded.

Example 1800

[0865]





Step A

[0866] If one were to treat allyl bromide with 1.0 eq. catechol borane, heat the mixture at 100° C., distillate at reduced pressure, treat the intermediate with 2.0 eq. pinacol in THF at 0° C. and room temperature, evaporate, dissolve in hexane and remove pinacol by filtration, distillate at reduced pressure, one would obtain the title compound.

Step B

[0867] If one were to dissolve methylene chloride (1.0 eq.) in THF and then slowly add 1.54 N ⁿBuLi in hexane (1.1 eq.) at -100° C., and would then add the title compound from Step A above (1.0 eq.), dissolved in THF, cooled to the freezing point of the solution, to the reaction mixture, followed by adding a suspension of zinc chloride (0.55 eq.) in THF, cooled to 0° C., in several portions to the reaction mixture, subsequently allowing the mixture to slowly warm to room temperature and to stir overnight, then, after evaporation of the solvent and redissolving the residue in hexane and washing with water, discarding insoluble material, drying (MgSO₄) and evaporation of the solvent, followed by distillation, one would obtain the title compound.

Step C

[0868] If one were to treat a fresh prepared LiHMDS solution in THF with 1 eq. of the title compound from Step B at -78° C., one would obtain after stirring overnight at rt, filtering of the precipitant and distillation of the filtrate the title compound as an oil.

Step D

[0869] If one were to treat the title compound from Step C above with 3 eq. of a 4 M HCl solution in dioxane at -78° C., one would obtain after stirring for 1 hour at rt and evaporation of the solvent the title compound as a HCl salt.

Step E

[0870] If one were to treat the title compound from Step D above with bromo acetyl bromide as described in Example 1, one would obtain the title compound.

Step F

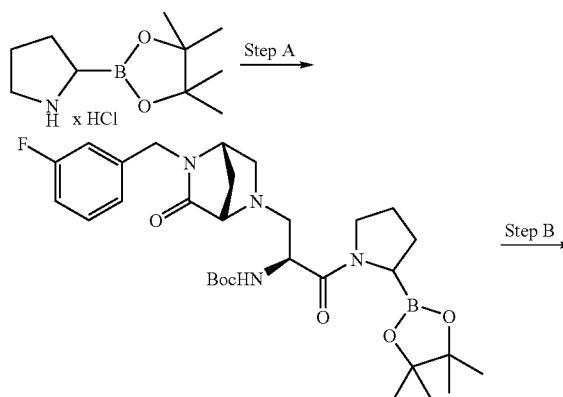
[0871] If one were to treat the title compound from Step E above with the title compound from Preparative Example 15 as described in Example 1, one would obtain the title compound.

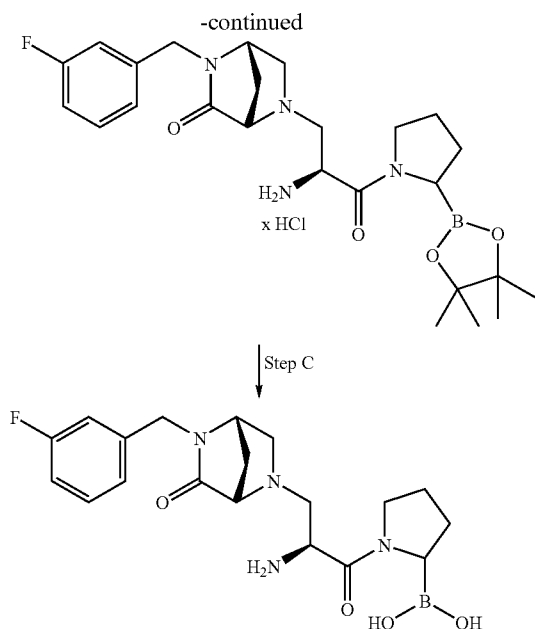
Step G

[0872] If one were to treat the title compound from Step F above with 6.0 eq. diethanolamine in THF at room temperature, add Et₂O to the mixture, separate the precipitate by filtration, dissolve the solid in an appropriate solvent and add Dowex AG 50-X8, filtrate and evaporate the filtrate, one would obtain the title compound.

[0873] Examples 1801-1849 have been intentionally excluded.

Example 1850

[0874]



Step A

[0875] If one were to treat the title compound from Preparative Example 92 with the title compound from Example 1800, Step D, as described in Preparative Example 93, one would obtain the title compound.

Step B

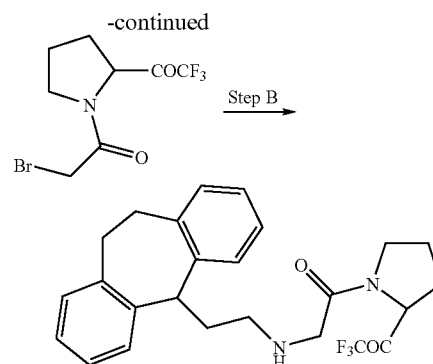
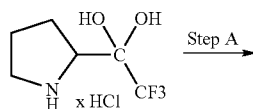
[0876] If one were to treat the title compound from Step A above as described in Example 48, one would obtain the title compound. If one were to use a reverse phase HPLC separation (5- μ m Nucleosil C18 HPLC column, acetonitrile:H₂O: 0.1% TFA), one could obtain the individual diastereomers.

Step C

[0877] If one were to treat the title compound from Step B above with 6.0 eq. diethanolamine in THF at room temperature, add Et₂O to the mixture, separate the precipitate by filtration, dissolve the solid in an appropriate solvent and add Dowex AG 50-X8, filtrate and evaporate the filtrate, one would obtain the title compound.

[0878] Examples 1851-1899 have been intentionally excluded.

Example 1900

[0879]

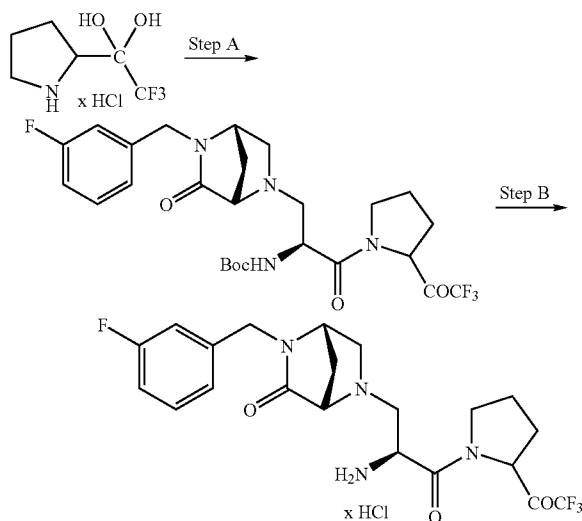
Step A

[0880] If one were to treat the title compound from Preparative Example 130 with bromoacetyl bromide as described in Preparative Example 1, one would obtain the title compound.

Step B

[0881] If one were to treat the title compound from Step A above with the title compound from Preparative Example 15 as described in Example 1, one would obtain the title compound. Examples 1901-1949 have been intentionally excluded.

Example 1950

[0882]

Step A

[0883] If one were to treat title compound from Preparative Example 130 with the title compound from Preparative Example 92 as described in Preparative Example 93, one would obtain the title compound.

Step B

[0884] If one were to treat the title compound from Step A above as described in Example 48, one would obtain the title compound.

Assay for Determining DP-IV Inhibition

[0885] The inhibitory activity of compounds against DPP-IV can be determined by in vitro assay systems, which are themselves well established in the art. The assay results given in Table 5 were obtained according to the following method, employing a modified version of the assay described by Leit-ing et al., in an article entitled "Catalytic properties and inhibition of proline-specific dipeptidyl peptidases II, IV and VII" in *Biochem. J.* Vol. 371, pages 525-532 (2003):

[0886] DPP-IV activity was determined fluorometrically with Gly-Pro-AMC (where AMC stands for 7-amido-4-methylcoumarin, Bachem AG, Switzerland) as substrate. The reaction mixture contained 10 μ l of 1 ng/ μ l DPP-IV (R&D Systems GmbH, Germany) and 80 μ l of 25 mM Tris/HCl buffer, pH 8.0. Compounds were supplied as DMSO stock solutions and diluted in assay buffer to a maximal DMSO concentration of 1% in the assay. Prior to start of the reaction, the mixture was incubated for 30 min at room temperature. The reaction was started by addition of 10 μ l of 100 μ M substrate solution.

[0887] The fluorescence intensity was measured at excitation and emission wavelengths of 355 and 460 nm, respectively, in a FluoStar Galaxy Multiwell Plate (BMG Labtech, Germany). Fluorescence was determined 3 and 4 minutes after start of reaction and increase in fluorescence was used for determination of enzymatic activity. IC(50) values of tested compounds were determined via plotting enzymatic activity versus concentration of test compound and determining the concentration of test compound which yields a 50% inhibition of enzymatic activity.

[0888] K(i) values were calculated using the Michaelis-Menten equation for competitive inhibition:

$$IC(50) = K(i)(1 + [S]/Km)$$

[0889] As set forth in Table A, K(i) for each compound corresponds to A is K(i) < 6 nM, B is K(i) 6-50 nM, C is K(i) from 51-500 nM and D is K(i) from 0.5-30 μ M.

TABLE A

Activity Data for Inhibition of DPP-IV	
Example	Activity (K(i))
1	C
2	D
3	D
4	D
5	D
6	C
7	C
8	C
9	C
10	C
11	C
12	C
13	C
14	D
15	D
16	C
17	B
18	A
19	B
20	C
21	C
22	A

TABLE A-continued

Activity Data for Inhibition of DPP-IV	
Example	Activity (K(i))
23	B
24	A
25	B
26	C
27	A
28	A
29	A
30	A
31	B
32	A
33	A
34	A
35	A
36	B
37	B
38	B
39	B
40	D
41	B
42	C
43	A
44	A
45	B
46	D
47	A
48	A
49	A
50	B
51	A
52	A
53	A
54	A
55	A
56	A
57	A
58	A
59	A
60	A
61	A
62	A
63	A
64	A
65	B
66	B
67	A
68	B
69	B
70	B
71	B
72	A
73	B
74	C
75	C
76	B
77	A
78	B

[0890] All patents, patent applications, and published references cited herein are hereby incorporated by reference in their entirety. While this invention has been particularly shown and described with references to preferred embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the scope of the invention encompassed by the appended claims.

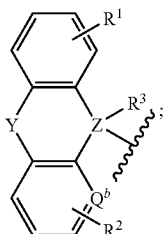
What claimed is:

1. A compound of formula (I):

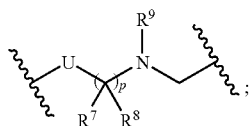
A-B-D

(I)

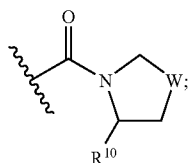
or a pharmaceutically acceptable salt thereof,
wherein A is:



B is:



Dis:



Y is divalent and is: a bond, CR^4R^5 , O, NR^4 , S, $\text{S}=\text{O}$, $\text{S}(\text{=O})_2$, $\text{C}(\text{=O})$, $(\text{C}=\text{O})\text{N}(\text{R}^4)$, $\text{S}(\text{=O})_2\text{N}(\text{R}^4)$, $\text{C}=\text{N}-\text{OR}^4$, $-\text{C}(\text{R}^4\text{R}^5)\text{C}(\text{R}^4\text{R}^5)-$, $-\text{C}(\text{R}^4\text{R}^5)\text{C}(\text{R}^4\text{R}^5)\text{C}(\text{R}^4\text{R}^5)-$, $-\text{C}(\text{R}^4\text{R}^5)\text{C}(\text{R}^4\text{R}^5)\text{C}(\text{R}^4\text{R}^5)\text{C}(\text{R}^4\text{R}^5)-$, $-\text{C}(\text{R}^4)=\text{C}(\text{R}^5)-$, $-\text{C}(\text{R}^4\text{R}^5)\text{NR}^4-$, $-\text{C}(\text{R}^4\text{R}^5)\text{O}-$, $-\text{C}(\text{R}^4\text{R}^5)\text{S}(\text{=O})-$, $-(\text{C}=\text{O})\text{O}-$, $-(\text{C}=\text{NR}^4)\text{N}(\text{R}^4)-$, $-(\text{C}=\text{NR}^4)-$, $\text{N}(\text{C}=\text{O})\text{NR}^4\text{NR}^5$, $\text{N}(\text{C}=\text{O})\text{R}^4$, $\text{N}(\text{C}=\text{O})\text{OR}^4$, $\text{NS}(\text{=O})_2\text{NR}^4\text{NR}^5$, or $\text{NS}(\text{=O})_2\text{R}^4$;

R¹ and R² are independently: hydrogen, —F, —Cl, —CONR⁴R⁵, or —CO₂R⁴;

R³ is CONR⁴R⁵, tetrazolyl or oxadiazolonyl;

R^a is hydrogen, CN, NO_2 , alkyl, haloalkyl, $\text{S(O)}_t\text{NR}^4\text{R}^5$, $\text{S(O)}_t\text{R}^4$, C(O)OR^4 , C(O)R^4 , or $\text{C(O)NR}^4\text{R}^5$;

each occurrence of R⁴ and R⁵ are each independently: hydrogen or alkyl, or R⁴ and R⁵ when taken together with a nitrogen to which they are attached form a 3- to 8-membered ring containing carbon atoms and may optionally contain a heteroatom selected from O, S, or NR⁵⁰.

R^{50} is, in each occurrence, R^{20} , CN, NO_2 , $S(O)_rNR^{20}R^{21}$, $S(O)_rR^{20}$, $C(O)OR^{20}$, $C(O)R^{20}C(=NR^a)NR^{20}R^{21}$, $C(=NR^{20})NR^{21}R^a$, $C(=NOR^{20})R^{21}$ or $C(O)NR^{20}R^{21}$.

each occurrence of R²⁰ and R²¹ are each independently:
hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, heterocy-

cloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl or aminoalkyl;

each occurrence of R^7 and R^8 are each independently: halogen, CF_3 , COR^4 , OR^4 , NR^4R^5 , NO_2 , CN , SO_2OR^4 , CO_2R^4 , $CONR^4R^5$, CO_2H , $SO_2NR^4R^5$, $S(O)_tR^4$, SO_3H , $OC(O)R^4$, $OC(O)NR^4R^5$, $NR^4C(O)R^5$, $NR^4CO_2R^5$, (C_0-C_6) -alkyl-C($=NR^4$) NHR^a , (C_0-C_6) -alkyl-C($=NR^4$) NHR^a , (C_0-C_6) -alkyl- $NR^4C(=NR^4)NR^4R^5$, (C_0-C_6) -alkyl-C(O) OR^4 , (C_0-C_6) -alkyl-C(O) NR^4R^5 , (C_0-C_6) -alkyl-C(O)—NH—CN, O— (C_0-C_6) -alkyl-C(O) NR^4R^5 , $S(O)_t$ — (C_1-C_6) -alkyl-C(O) OR^4 , $S(O)_t$ — (C_0-C_6) -alkyl-C(O) NR^4R^5 , (C_0-C_6) -alkyl-C(O) NR^4 , (C_0-C_6) -alkyl- NR^4R^5 , (C_0-C_6) -alkyl- $NR^4—C(O)R^5$, (C_0-C_6) -alkyl- $NR^4—C(O)OR^4$, (C_0-C_6) -alkyl- $NR^4—C(O)—NR^4R^5$, (C_0-C_6) -alkyl- $NR^4—SO_2NR^4R^5$, (C_0-C_6) -alkyl- $NR^4—SO_2R^4$, hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, haloalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, alkoxyalkyl or aminoalkyl, wherein alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, alkoxyalkyl or aminoalkyl;

R⁹ is H or C₁₋₆ alkyl;

R¹⁰ is halogen, CF₃, COR⁴, OR⁴, NR⁴R⁵, NO₂, CN, SO₂OR⁴, CO₂R⁴, CONR⁴R⁵, CO₂H, SO₂NR⁴R⁵, S(O)_rR⁴, SO₃H, OC(O)R⁴, OC(O)NR⁴R⁵, NR⁴C(O)R⁵, NR⁴CO₂R⁵, (C₀-C₆)-alkyl-C(=NR^a)NHR⁴, (C₀-C₆)-alkyl-C(=NR⁴)NHR^a, (C₀-C₆)-alkyl-NR⁴C(=NR⁴)NR⁴R⁵, (C₀-C₆)-alkyl-C(O)OR⁴, (C₀-C₆)-alkyl-C(O)NR⁴R⁵, (C₀-C₆)-alkyl-C(O)—NH—CN, O—(C₀-C₆)-alkyl-C(O)NR⁴R⁵, S(O)_r—(C₀-C₆)-alkyl-C(O)OR⁴, S(O)_r—(C₀-C₆)-alkyl-C(O)NR⁴R⁵, (C₀-C₆)-alkyl-C(O)NR⁴—(C₀-C₆)-alkyl-NR⁴R⁵, (C₀-C₆)-alkyl-NR⁴C(O)R⁵, (C₀-C₆)-alkyl-NR⁴—C(O)R⁵, (C₀-C₆)-alkyl-NR⁴—C(O)OR⁴, (C₀-C₆)-alkyl-NR⁴—C(O)—NR⁴R⁵, (C₀-C₆)-alkyl-NR⁴—SO₂NR⁴R⁵, (C₀-C₆)-alkyl-NR⁴—SO₂R⁴, hydrogen, B(OH)₂, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, haloalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, alkoxyalkyl or aminoalkyl:

Q^b is CH or N;

$$\begin{aligned} \text{U is } & \text{—C(O)—, —C(=NR}^4\text{)—, —(CR}^4\text{R}^5\text{—)}_p, \text{NR}^{50}, \\ & \text{S(=O)}_2, \text{C(=O), (C=O)N(R}^4\text{), N(R}^4\text{)(C=O), S(=O)}_2\text{N(R}^4\text{),} \\ & \text{N(R}^4\text{)S(=O)}_2, \text{C=N—OR}^4, \text{—C(R}^4\text{)=C(R}^5\text{)—,} \\ & \text{—C(R}^4\text{R}^5\text{—)}_p\text{NR}^{50}, \text{N(R}^{50}\text{)C(R}^4\text{R}^5\text{—)}_p, \\ & \text{—O—C(R}^4\text{R}^5\text{—), —C(R}^4\text{R}^5\text{)S(=O)—, —(C=O)O—,} \\ & \text{—(C=NR}^a\text{)N(R}^4\text{)—, —(C=NR}^a\text{—), N(C=O)NR}^4\text{NR}^5, \\ & \text{N(C=O)R}^4, \text{N(C=O)OR}^4, \text{NS(=O)}_2\text{NR}^4\text{NR}^5, \text{ or NS(=O)}_2\text{R}^4; \end{aligned}$$

W is $\text{—CH}_2\text{—}$, —S— , —CHF— or $\text{—CF}_2\text{—}$;

Z is \mathbb{C} ;

p is 0 to 6; and

t is 0, 1, or 2.

2. A compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein:

Q^b is CH;

U is $(-\text{CH}_2-)_n$;

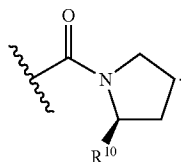
p is 1;

R⁷ and R⁸ are each independently H or alkyl; and

 R^9 is H.

3. A compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein:

D is:



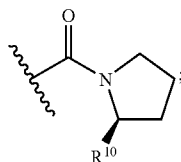
4. A compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein:

Y is $-\text{CH}_2-\text{CH}_2-$.

5. A compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein:

Y is $-\text{CH}_2-\text{CH}_2-$;

D is



Q^b is CH;

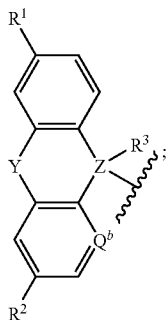
U is $(-\text{CH}_2-)_p$;

p is 1; and

R^9 is H.

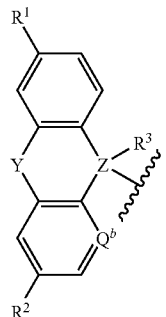
6. A compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein:

A is:



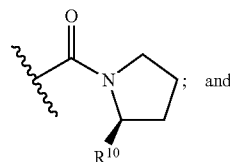
7. A compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein:

A is:



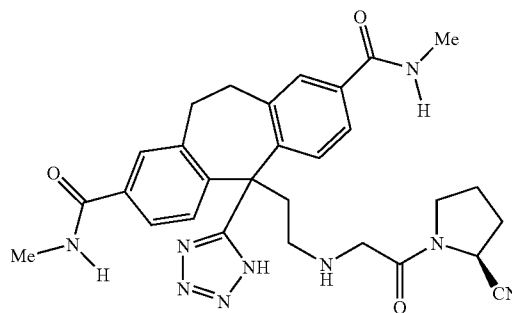
Y is $-\text{CH}_2-\text{CH}_2-$;

D is



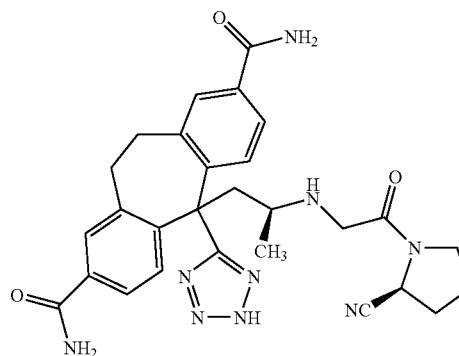
Q^b is CH.

8. A compound according to the following formula:



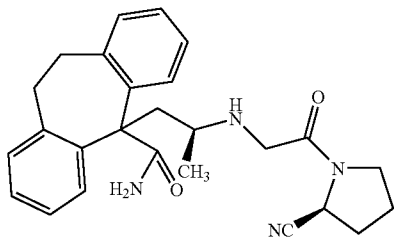
or a pharmaceutically acceptable salt thereof.

9. A compound according to the following formula:



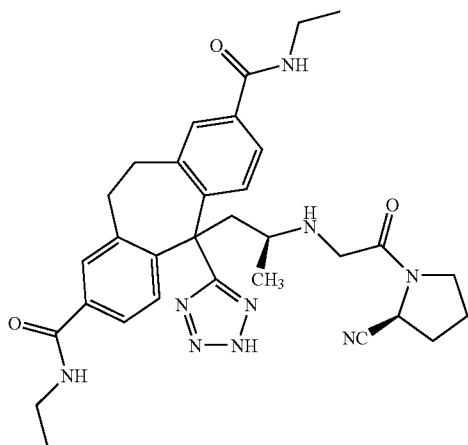
or a pharmaceutically acceptable salt thereof.

10. A compound according to the following formula:



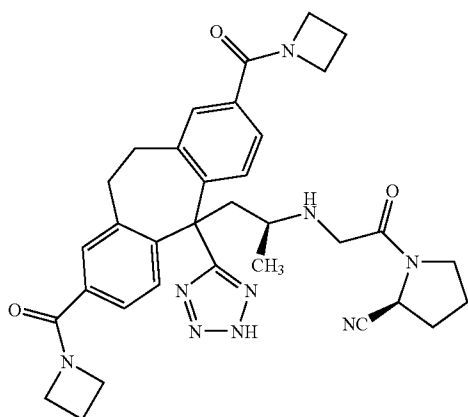
or a pharmaceutically acceptable salt thereof.

11. A compound according to the following formula:



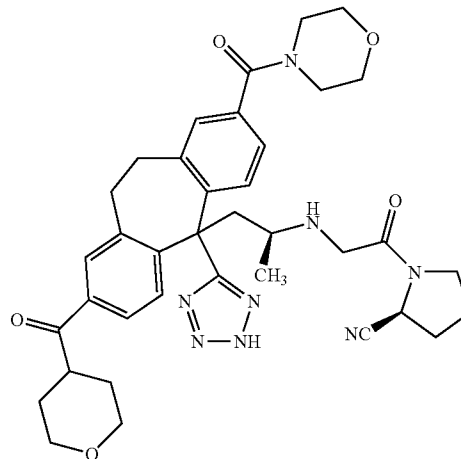
or a pharmaceutically acceptable salt thereof.

12. A compound according to the following formula:



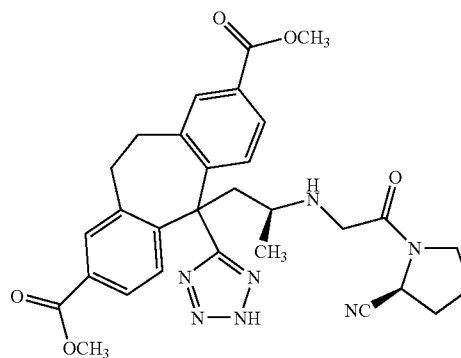
or a pharmaceutically acceptable salt thereof.

13. A compound according to the following formula:



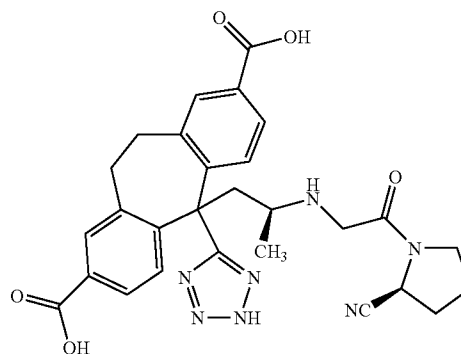
or a pharmaceutically acceptable salt thereof.

14. A compound according to the following formula:



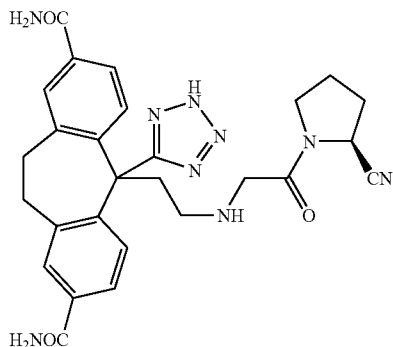
or a pharmaceutically acceptable salt thereof.

15. A compound according to the following formula:



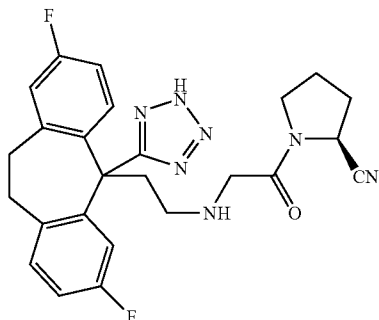
or a pharmaceutically acceptable salt thereof.

16. A compound according to the following formula:



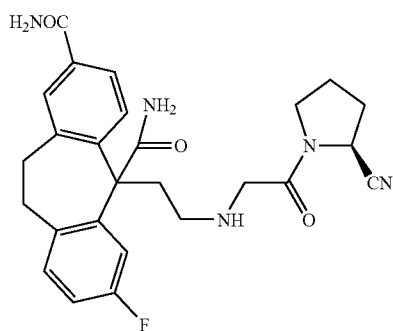
or a pharmaceutically acceptable salt thereof.

17. A compound according to the following formula:



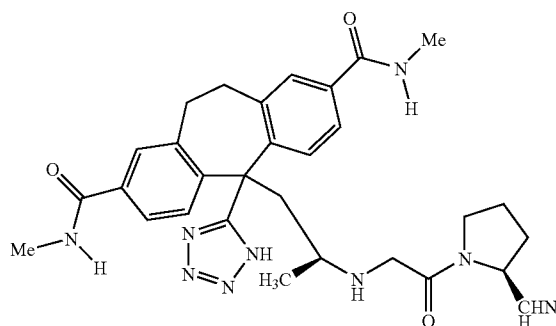
or a pharmaceutically acceptable salt thereof.

18. A compound according to the following formula:



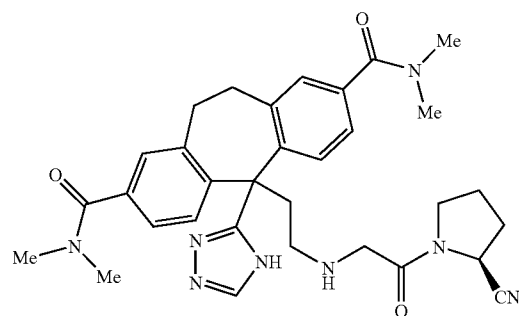
or a pharmaceutically acceptable salt thereof.

19. A compound according to the following formula:



or a pharmaceutically acceptable salt thereof.

20. A compound according to the following formula:



or a pharmaceutically acceptable salt thereof.

21. A pharmaceutical composition comprising a compound in accordance with claim 1, or a pharmaceutically acceptable salt thereof.

22. A method of treating type-2 diabetes comprising administering to a patient in need thereof an effective amount of a compound in accordance with claim 1, or a pharmaceutically acceptable salt thereof.

23. A pharmaceutical composition comprising a compound in accordance with claim 7, or a pharmaceutically acceptable salt thereof.

24. A method of treating type-2 diabetes comprising administering to a patient in need thereof an effective amount of a compound in accordance with claim 7, or a pharmaceutically acceptable salt thereof.

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