US007196111B2

(12) **United States Patent**
Shipps et al.

(10) **Patent No.: US 7,196,111 B2**
(45) **Date of Patent: Mar. 27, 2007**

(54) **PYRAZOLO[1,5A]PYRIMIDINE COMPOUNDS AS ANTIVIRAL AGENTS**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 243 days.

(21) Appl. No.: **10/452,400**

(22) Filed: **Jun. 2, 2003**

(65) **Prior Publication Data**

US 2004/0038993 A1 Feb. 26, 2004

Related U.S. Application Data

(60) Provisional application No. 60/385,837, filed on Jun. 4, 2002.

(51) **Int. Cl.**

C07D 231/00	(2006.01)
C07D 231/54	(2006.01)
A61K 31/415	(2006.01)
A01N 43/56	(2006.01)

(52) **U.S. Cl.** **514/405**; 514/403; 514/406; 546/1; 546/26; 546/112; 546/134; 548/356.1; 548/358.1; 548/360.1

(58) **Field of Classification Search** 548/356.1, 548/358.1, 360.1; 514/403, 405, 406, 1, 514/26, 112, 134

See application file for complete search history.

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(57) **ABSTRACT**

The invention relates to the inhibition of hepatitis C virus (HCV) replication. In particular, embodiments of the invention provide compounds and methods for inhibiting HCV RNA-dependent RNA polymerase enzymatic activity. The invention also provides compositions and methods for the prophylaxis and treatment of HCV infection.

2 Claims, No Drawings

PYRAZOLO[1,5A]PYRIMIDINE COMPOUNDS AS ANTIVIRAL AGENTS

CROSS REFERENCE TO RELATED APPLICATION

This application claims the benefit of U.S. Provisional Patent Application Ser. No. 60/385,837, filed on Jun. 4, 2002.

FIELD OF THE INVENTION

This invention relates to the inhibition of hepatitis C virus (HCV) replication. In particular, the invention relates to compounds and methods for inhibiting HCV RNA-dependent RNA polymerase.

BACKGROUND OF THE INVENTION

Hepatitis C virus (HCV) is a positive strand RNA virus in the Flaviviridae family. Its 9.6 kb genome encodes for approximately 10 proteins, including the structural capsid and envelope proteins, as well as the nonstructural proteins NS3 (protease and helicase) and NS5B (polymerase). Ishii et al., Hepatology, 1227 (1999), teaches that the viral RNA-dependent RNA polymerase (RdRp) is responsible both for generating the intermediate minus-strand RNA template and for the synthesis of progeny positive-strand genomic RNA. The authors point out that RdRp is used only in the replication of RNA viruses and has very strict template specificities. The authors conclude that RNA-dependent RNA polymerase enzymes, including HCV RdRp, are ideal targets for antiviral drugs.

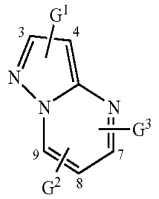
HCV is a major human pathogen and is believed to have infected approximately 3% of the worldwide population. Bressanelli et al., Proc. Natl. Acad. Sci. USA, 96: 13034–13039 (1999), teaches that HCV is capable of establishing a persistent infection that can cause chronic hepatitis leading to cirrhosis and hepatocellular carcinoma.

Existing therapies for HCV are limited, and only a few inhibitors of HCV RNA-dependent RNA polymerase are known. There is thus a need to identify additional HCV RdRp inhibitors and to identify the structural features required for potent HCV RdRp inhibitory activity.

SUMMARY OF THE INVENTION

The present invention provides compounds and methods useful for the prophylaxis or treatment of HCV infection. In particular, embodiments of the invention provide compounds and methods for inhibiting HCV RNA-dependent RNA polymerase (RdRp) enzymatic activity.

In one aspect, embodiments of the invention provide novel HCV RdRp inhibitors of formula (I):



or a pharmaceutically acceptable salt thereof, wherein:

G^1 is selected from the group consisting of —OH, cyano, —C(O)—OH, —C(O)—OR^8, —C(O)—NR^2R^3, —N(R)—C(O)R^8, —S(O)$_2$$NR^2R^3$, —N(R)—S(O)$_2$$R^8$, heteroaryl, aryl, halo, amino, formyl heterocyclenalkenyl, heterocyclylalkyl, CH(N)OH, CH(N)OR^8, hydroxyalkyl, and saturated or partially unsaturated heterocyclic radical, where

R^8, at each occurrence, is independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, aralkyl, heteroaryl, heteroarylalkyl, carboalkoxyalkyl, carboalkoxy, acyloxyalkyl, acyloxyalkyl, and saturated or partially unsaturated heterocyclic radical;

R^2 and R^3 are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, aralkyl, heteroaryl, heteroarylalkyl, and saturated or partially unsaturated heterocyclic radical; or

R^2 and R^3 taken together form a 5- or 6-membered heteroaromatic or saturated or partially unsaturated heterocyclic ring; or

—NR^2R^3 together forms an alpha-, beta-, or gamma-amino acid, wherein R^2 is hydrogen or C1-C6 alkyl, and R^3 has a formula selected from the group consisting of acylaminoalkyl, dialkylaminoalkyl, alkoxyalkyl, hydroxyalkyl, cyano, arylsulfonyl, alkylsulfonyl, hydroxy, alkoxy, —C(R^6)(R^6)CO_2H, —CH_2CH_2CH(R^6)CO_2H, —CH_2CH(R^6)CO_2H, —CH(R^6)CO_2alkyl, —SO_2aralkyl, —SO_2fluoroalkyl, —CH(R^6)$CONH_2$, —CH(R^6)CH_2CO_2H, —CH(R^6)CO_2H, —CH(R^6)$CH_2CH_2CO_2H$, —CH_2CH(R^6)CH_2CO_2H, and —CH_2CH_2CH(R^6)CO_2H;

wherein R^6 is independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, heteroaryl, saturated or partially unsaturated heterocyclic radical, aminoalkyl, alkylthioalkyl, carbamoyl, hydroxy, and —CH_2R^7, where R^7 is selected from the group consisting of aryl, aralkyl, cycloalkyl, heteroaryl, saturated or partially unsaturated heterocyclic radical, hydroxy, alkoxy, aryloxy, aralkoxy, thio, alkylthio, arylthio, and aralkylthio;

G^1 is attached to either of positions C3 or C4 of the pyrazole ring, the other position being optionally substituted with alkyl, alkenyl, alkynyl, halo, fluoroalkyl, hydroxy, alkoxy, or cyano; and

G^2 is independently are selected from the group consisting of alkyl, cycloalkyl, aryl, heteroaryl, saturated or partially unsaturated heterocyclic radical, trifluoromethyl, carboxyalkylamino, alkylamino, carboxy, alkenyl, alkoxyalkyl, heterocyclylalkyl, cycloalkylalkyl, arylalkyl, and —W—Cy, where

W is selected from the group consisting of O, N(R), S, C(O), CH(R), —O—CH(R)—, —N(R)—CH(R)—, —S—CH(R)—, —C(O)—N(R)—, —N(R)—C(O)—, —S(O)$_2$—N(R), —N(R)—S(O)$_2$—, and —N(R)—C(O)—N(R)—, where R, at each occurrence, is independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, aralkyl, heteroaryl, heteroarylalkyl, and saturated or partially unsaturated heterocyclic radical,

Cy is selected from the group consisting of cycloalkyl, aryl, aralkyl, heteroaryl, heteroarylalkyl, and saturated or partially unsaturated heterocyclic radical;

G^3 can be absent or is independently selected from the group consisting of alkyl, cycloalkyl, aryl, heteroaryl, saturated or partially unsaturated heterocyclic radical, and —W—Cy, where

W is selected from the group consisting of O, N(R), S, C(O), CH(R), —O—CH(R)—, —N(R)—CH(R)—, —S—CH(R)—, —C(O)—N(R)—, —N(R)—C(O)—, —S(O)$_2$—N(R), —N(R)—S(O)$_2$—, and —N(R)—C(O)—N(R)—, where R, at each occurrence, is independently selected from the group consisting of hydrogen, alkyl,

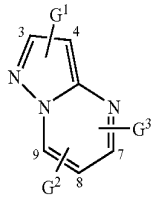
cycloalkyl, aryl, aralkyl, heteroaryl, heteroarylalkyl, and saturated or partially unsaturated heterocyclic radical,

Cy is selected from the group consisting of cycloalkyl, aryl, aralkyl, heteroaryl, heteroarylalkyl, and saturated or partially unsaturated heterocyclic radical, and

G^2 and G^3, collectively, are attached at any two of positions C7, C8, and C9 of the pyrimidine ring, the remaining position being optionally substituted with alkyl, alkenyl, alkynyl, halo, fluoroalkyl, hydroxy, alkoxy, or cyano;

wherein the ring portion of any of said cycloalkyl, aryl, aralkyl, heteroaryl, heteroarylalkyl, or heterocyclic radical in G^1, G^2, or G^3 can be optionally substituted.

In one aspect, embodiments of the invention provide novel HCV RdRp inhibitors of formula (I):



or a pharmaceutically acceptable salt thereof, wherein:

G^1 is selected from the group consisting of —OH, cyano, —C(O)—OH, —C(O)—OR, —C(O)—NR^2R^3, —N(R)—C(O)R, —$S(O)_2NR^2R^3$, —N(R)—$S(O)_2R$, heteroaryl, and saturated or partially unsaturated heterocyclic radical, where

R, at each occurrence, is independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, aralkyl, heteroaryl, heteroarylalkyl, and saturated or partially unsaturated heterocyclic radical;

R^2 and R^3 are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, aralkyl, heteroaryl, heteroarylalkyl, and saturated or partially unsaturated heterocyclic radical; or

R^2 and R^3 taken together form a 5- or 6-membered heteroaromatic or saturated or partially unsaturated heterocyclic ring; or

—NR^2R^3 together forms an alpha-, beta-, or gamma-amino acid, wherein R^2 is hydrogen or C1–C6 alkyl, and R^3 has a formula selected from the group consisting of —$CH_2CH(R^6)CO_2H$, —$CH(R^6)CH_2CO_2H$, —$CH(R^6)CO_2H$, —$CH(R^6)CH_2CH_2CO_2H$, —$CH_2CH(R^6)CH_2CO_2H$, and —$CH_2CH_2CH(R^6)CO_2H$;

wherein R^6 is selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, heteroaryl, saturated or partially unsaturated heterocyclic radical, and —CH_2R^7, where R^7 is selected from the group consisting of aryl, aralkyl, cycloalkyl, heteroaryl, saturated or partially unsaturated heterocyclic radical, hydroxy, alkoxy, aryloxy, aralkoxy, thio, alkylthio, arylthio, and aralkylthio;

G^1 is attached to either of positions C3 or C4 of the pyrazole ring, the other position being optionally substituted with alkyl, alkenyl, alkynyl, halo, fluoroalkyl, hydroxy, alkoxy, or cyano; and

G^2 and G^3 independently are selected from the group consisting of alkyl, cycloalkyl, aryl, heteroaryl, saturated or partially unsaturated heterocyclic radical, and —W—Cy, where

W is selected from the group consisting of O, N(R), S, C(O), CH(R), —O—CH(R)—, —N(R)—CH(R)—, —S—CH(R)—, —C(O)—N(R)—, —N(R)—C(O)—, —$S(O)_2$—N(R), —N(R)—$S(O)_2$—, and —N(R)—C(O)—N(R)—, where R, at each occurrence, is independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, aralkyl, heteroaryl, heteroarylalkyl, and saturated or partially unsaturated heterocyclic radical,

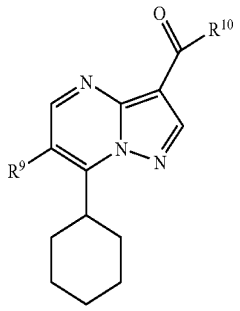
Cy is selected from the group consisting of cycloalkyl, aryl, aralkyl, heteroaryl, heteroarylalkyl, and saturated or partially unsaturated heterocyclic radical, and

G^2 and G^3, collectively, are attached at any two of positions C7, C8, and C9 of the pyrimidine ring, the remaining position being optionally substituted with alkyl, alkenyl, alkynyl, halo, fluoroalkyl, hydroxy, alkoxy, or cyano;

wherein the ring portion of any of said cycloalkyl, aryl, aralkyl, heteroaryl, heteroarylalkyl, or heterocyclic radical in G^1, G^2, or G^3 can be optionally substituted.

In one aspect, the invention features a compound of formula (V)

(V)



or a pharmaceutically acceptable salt thereof, wherein;

R^9 is aryl or heteroaryl, each of which is independently optionally substituted;

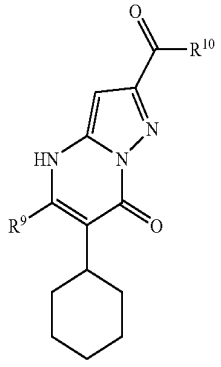
R^{10} is OH, heteroaryl, NHR, or NR^2R^3;

R, at each occurrence, is independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, aralkyl, heteroaryl, heteroarylalkyl, and saturated or partially unsaturated heterocyclic radical; and

—NR^2R^3 together forms an alpha- or beta-amino acid, wherein R^2 is hydrogen or C_1–C_6 alkyl, and R^3 has a formula selected from the group consisting of —$CH_2CH(R^6)CO_2H$, —$CH(R^6)CH_2CO_2H$, and —$CH(R^6)CO_2H$.

In another aspect, the invention features a compound of formula (VI):

(VI)



or a pharmaceutically acceptable salt thereof, wherein;

R^9 is aryl or heteroaryl, each of which is independently optionally substituted;

R^{10} is OH, heteroaryl, NHR, or NR^2R^3;

R, at each occurrence, is independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, aralkyl, heteroaryl, heteroarylalkyl, and saturated or partially unsaturated heterocyclic radical; and

—NR^2R^3 together forms an alpha- or beta-amino acid, wherein R^2 is hydrogen or C_1–C_6 alkyl, and R^3 has a formula selected from the group consisting of —$CH_2CH(R^6)CO_2H$, —$CH(R^6)CH_2CO_2H$, and —$CH(R^6)CO_2H$.

In another aspect, NR2R3 together forms an alpha- or beta-amino acid.

In another aspect, embodiments of the invention provide pharmaceutical compositions comprising At least one compound of formula (I), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, excipient, or diluent.

In a further aspect, embodiments of the invention provide a method for inhibiting HCV replication in a cell, comprising contacting a cell that is infected by HCV with at least one compound of formula (I) or a pharmaceutically acceptable salt thereof.

In a further aspect, embodiments of the invention provide a use of at least one compound of formula (I) for preparation of a medicament for the prophylaxis or treatment of HCV infection.

In a further aspect, embodiments of the invention provide a method for the prophylaxis or treatment of HCV infection, comprising administering to a human or animal subject a therapeutically effective amount of at least one compound of formula (I), or a pharmaceutically acceptable salt thereof.

DESCRIPTION OF THE INVENTION

Embodiments of the invention provide compounds and methods for inhibiting HCV RNA-dependent RNA polymerase enzymatic activity. The invention also provides compositions and methods for the prophylaxis or treatment of HCV infection. The patent and scientific literature referred to herein establishes knowledge that is available to those with skill in the art. The issued patents, applications, and references that are cited herein are hereby incorporated by reference to the same extent as if each was specifically and individually indicated to be incorporated by reference. In the case of inconsistencies, the present disclosure will prevail.

For purposes of the present invention, the following definitions will be used:

The terms "HCV RNA-dependent RNA polymerase inhibitor", "HCV RdRp inhibitor", "inhibitor of HCV RNA-dependent RNA polymerase", and "inhibitor of HCV RdRp" are used to identify a compound having a structure as defined herein, which is capable of interacting with HCV RNA-dependent RNA polymerase and inhibiting its enzymatic activity. Inhibiting HCV RNA-dependent RNA polymerase enzymatic activity means reducing the ability of HCV RdRp to incorporate ribonucleotides into a growing HCV RNA strand. In some preferred embodiments, such reduction of HCV RdRp activity is at least 50%, more preferably at least 75%, and still more preferably at least 90%. In other preferred embodiments, HCV RdRp activity is reduced by at least 95% and more preferably by at least 99%.

Preferably, such inhibition is specific, i.e., the HCV RdRp inhibitor reduces the ability of HCV RdRp to incorporate ribonucleotides into a growing HCV RNA strand at a concentration that is lower than the concentration of the inhibitor that is required to produce another, unrelated biological effect. Preferably, the concentration of the inhibitor required for HCV RdRp inhibitory activity is at least 2-fold lower, more preferably at least 5-fold lower, even more preferably at least 10-fold lower, and most preferably at least 20-fold lower than the concentration required to produce an unrelated biological effect.

The terms "alkyl", "alkenyl", and "alkynyl", as employed herein, refer to straight and branched chain aliphatic groups having from 1 to 12 carbon atoms, preferably 1–8 carbon atoms, and more preferably 1–6 carbon atoms, which may be optionally substituted with one, two or three substituents. For purposes of the present invention, the term "alkyl" will be used when the carbon atom attaching the aliphatic group to the rest of the molecule is a saturated carbon atom. However, an alkyl group may include unsaturation at other carbon atoms. Thus, alkyl groups include, without limitation, methyl, ethyl, propyl, allyl, propargyl, butyl, pentyl, hexyl, 2-propynyl, 2-butynyl, 3-butenyl, and 3-methylbuten-2-yl.

For purposes of the present invention, the term "alkenyl" will be used when the carbon atom attaching the aliphatic group to the rest of the molecule forms part of a carbon-carbon double bond. Alkenyl groups include, without limitation, vinyl, 1-propenyl, 1-butenyl, 1-pentenyl, and 1-hexenyl. For purposes of the present invention, the term "alkynyl" will be used when the carbon atom attaching the aliphatic group to the rest of the molecule forms part of a carbon-carbon triple bond. Alkynyl groups include, without limitation, ethynyl, 1-propynyl, 1-butynyl, 1-pentynyl, and 1-hexynyl.

The term "cycloalkyl" as employed herein includes saturated and partially unsaturated cyclic hydrocarbon groups having from 3 to about 12 carbons, preferably from 3 to about 8 carbons, and more preferably from 3 to about 6 carbons, wherein the cycloalkyl group additionally may be optionally substituted. Cycloalkyl groups include, without limitation, cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptyl, and cyclooctyl.

An "aryl" group is a C_6–C_{14} aromatic moiety comprising one to three aromatic rings, which may be optionally substituted. Preferably, the aryl group is a C6–C10 aryl group. Aryl groups include, without limitation, phenyl, naphthyl, anthracenyl, and fluorenyl. An "aralkyl" or "arylalkyl" group comprises an aryl group covalently linked to an alkyl group, either of which may independently be optionally substituted or unsubstituted. Preferably, the aralkyl group is C_6–C10 aryl(C_1–C_6)alkyl, including, without limitation, benzyl, phenethyl, and naphthylmethyl.

As used herein, the term "heteroaryl" refers to groups having 5 to 14 ring atoms, preferably 5, 6, 9, or 10 ring atoms; having 6, 10, or 14 p electrons shared in a cyclic array; and having, in addition to carbon atoms, from one to four heteroatoms selected from the group consisting of N, O, and S. Heteroaryl groups include, without limitation, thienyl, benzothienyl, furanyl, benzofuranyl, dibenzofuranyl, pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl, indolyl, quinolyl, isoquinolyl, quinoxalinyl, tetrazolyl, oxazolyl, thiazolyl, and isoxazolyl. A "heteroaralkyl" or "heteroarylalkyl" group comprises a heteroaryl group covalently linked to an alkyl group, either of which may independently be optionally substituted or unsubstituted. Preferably, the heteroaralkyl group is C_6–C14 heteroaryl (C_1–C_6)alkyl, including, without limitation, pyridylmethyl, thiazolylmethyl and the like.

As used herein, the terms "heterocyclic radical" and "heterocyclyl" refer to a stable 5- to 7-membered monocyclic or 7- to 10-membered bicyclic heterocyclic moiety that

is either saturated or partially unsaturated, and having, in addition to carbon atoms, from one to three heteroatoms selected from the group consisting of N, O, and S, wherein the nitrogen and sulfur heteroatoms optionally can be oxidized and the nitrogen atoms optionally can be quaternized, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The heterocyclic ring can be attached to its pendant group at any heteroatom or carbon atom that results in a stable structure. Examples of such saturated or partially unsaturated heterocyclic radicals include, without limitation, tetrahydrofuranyl, tetrahydrothienyl, pyrrolidinyl, pyrrolidonyl, piperidinyl, pyrrolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, decahydroquinolinyl, oxazolidinyl, piperazinyl, dioxanyl, dioxolanyl, diazepinyl, oxazepinyl, thiazepinyl, and morpholinyl.

As used herein, the term "partially unsaturated" refers to a ring moiety that includes at least one double or triple bond between ring atoms. The term "partially unsaturated" is intended to encompass rings having multiple sites of unsaturation, but is not intended to include aryl or heteroaryl moieties, as herein defined.

The term "partially unsaturated heterocyclic radical" refers to a stable 5- to 7-membered monocyclic or 7- to 10-membered bicyclic heterocyclic ring moiety that includes at least one double bond between ring atoms. The term is intended to encompass rings having multiple sites of unsaturation, but is not intended to include aryl or heteroaryl moieties as herein defined. In addition to carbon atoms, the heterocyclic ring moiety has from one to three heteroatoms selected from the group consisting of N, O, and S, wherein the nitrogen and sulfur heteroatoms optionally can be oxidized and the nitrogen atoms optionally can be quaternized, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The heterocyclic ring can be attached to its pendant group at any heteroatom or carbon atom that results in a stable structure. Examples of such partially unsaturated heterocyclic radicals include, without limitation, tetrahydroquinolinyl, tetrahydroisoquinolinyl, tetrahydrobenzothiophene, tetrahydroindole, and tetrahydrobenzofuran.

The term "heterocyclenalkenyl" refers to a heterocyclyl group wherein a ring carbon and an exo carbon form a carbon-carbon double bond (e.g., as exemplified in compound 449 in the compound table herein), which is in turn attached to the core scaffold of interest. The designations —CH(N)OH and —CH(N)OR refer to groups wherein the carbon and nitrogen atoms are connected by a double bond, thereby forming an oxime or oxime alkyl ether, respectively.

As employed herein, a "substituted" cycloalkyl aryl, aralkyl, heteroaryl, heteroarylalkyl, or heterocyclyl group is one having from one to four, preferably from one to three, more preferably one or two, non-hydrogen substituents. Suitable substituents include, without limitation, halo, hydroxy, oxo, nitro, fluoroalkyl, alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, aryl, (aryl)alkyl, heteroaryl, (heteroaryl)alkyl, (heteroaryl)alkyloxy, (heteroaryl)alkylamino, (heteroaryl)alkylthio, heteroaryloxy, heteroarylamino, heteroarylthio, saturated or partially unsaturated heterocyclic radical, (heterocyclyl)alkyl, (heterocyclyl)oxy, (heterocyclyl)amino, (heterocyclyl)thio, (heterocyclyl)alkyloxy, (heterocyclyl)alkylthio, fluoroalkyloxy, cycloalkylalkoxy, cycloalkoxy, alkoxyalkyl, alkoxy, (aryl)alkoxy, aryloxy, amino, acylamino, carbamoyl, aminoalkyl, hydroxyalkyl, carboalkoxy, carboaryloxy, carboxy, alkylthio, arylthio, aralkylthio, alkylsulfinyl, arylsulfinyl, aralkylsulfinyl, alkylsulfonyl, arylsulfonyl, aralkylsulfonyl, alkylsulfonamido, arylsulfonamido, aralkylsulfonamido, acyl, acyloxy, cyano, and ureido groups.

The term "substituted", as used herein, means that one or more hydrogens of the designated moiety are replaced, provided that no atom's normal valency is exceeded, and provided that the substitution results in a stable compound.

The terms "stable compound" and "stable structure" refer to a compound that is sufficiently robust to survive isolation to a useful degree of purity and formulation into an efficacious therapeutic agent.

The term "halogen" or "halo" as employed herein refers to chlorine, bromine, fluorine, or iodine.

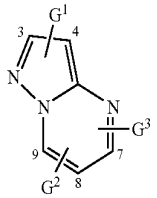
As herein employed, the term "acyl" refers to an alkylcarbonyl or arylcarbonyl substituent.

The terms "acylamino" and "amido" refer to an amide group attached at the nitrogen atom. The term "carbamoyl" refers to an amide group attached at the carbonyl carbon atom. The nitrogen atom of an acylamino or carbamoyl substituent may be additionally substituted. The term "sulfonamido" refers to a sulfonamide substituent attached by either the sulfur or the nitrogen atom. Unless otherwise explicitly limited, the term "amino" is meant to include NH_2, alkylamino, dialkylamino, arylamino, aralkylamino, and cyclic amino groups.

The term "ureido" as employed herein refers to a substituted or unsubstituted urea moiety.

The term, "pharmaceutically acceptable" is used herein to mean a non-toxic material that is compatible with a biological system such as a cell, cell culture, tissue, or organism.

In one aspect, embodiments of the invention provide novel inhibitors of HCV RNA-dependent RNA polymerase of formula (I):



or a pharmaceutically acceptable salt thereof, wherein:

G^1 is selected from the group consisting of —OH, cyano, —C(O)—OH, —C(O)—OR, —C(O)—NR^2R^3, —N(R)—C(O)R, —$S(O)_2NR^2R^3$, —N(R)—$S(O)_2R$, heteroaryl, and saturated or partially unsaturated heterocyclic radical, where

R, at each occurrence, is independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, aralkyl, heteroaryl, heteroarylalkyl, and saturated or partially unsaturated heterocyclic radical;

R^2 and R^3 are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, aralkyl, heteroaryl, heteroarylalkyl, and saturated or partially unsaturated heterocyclic radical; or

R^2 and R^3 taken together form a 5- or 6-membered heteroaromatic or saturated or partially unsaturated heterocyclic ring; or

—NR^2R^3 together forms an alpha-, beta-, or gamma-amino acid, wherein R^2 is hydrogen or C_1–C_6 alkyl, and R^3 has a formula selected from the group consisting of —$CH_2CH(R^6)CO_2H$, —$CH(R^6)CH_2CO_2H$, —$CH(R^6)CO_2H$, —$CH(R^6)CH_2CH_2CO_2H$, —$CH_2CH(R^6)CH_2CO_2H$, and —$CH_2CH_2CH(R^6)CO_2H$;

wherein R^6 is selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, heteroaryl, saturated or

partially unsaturated heterocyclic radical, and —CH_2R^7, where R^7 is selected from the group consisting of aryl, aralkyl, cycloalkyl, heteroaryl, saturated or partially unsaturated heterocyclic radical, hydroxy, alkoxy, aryloxy, aralkoxy, thio, alkylthio, arylthio, and aralkylthio;

G^1 is attached to either of positions C3 or C4 of the pyrazole ring, the other position being optionally substituted with alkyl, alkenyl, alkynyl, halo, fluoroalkyl, hydroxy, alkoxy, or cyano; and

G^2 and G^3 independently are selected from the group consisting of alkyl, cycloalkyl, aryl, heteroaryl, saturated or partially unsaturated heterocyclic radical, and —W—Cy, where

W is selected from the group consisting of O, N(R), S, C(O), CH(R), —O—CH(R), —N(R)—CH(R)—, —S—CH(R)—, —C(O)—N(R)—, —N(R)—C(O)—, —$S(O)_2$—N(R)—, —N(R)—$S(O)_2$—, and —N(R)—C(O)—N(R)—, where R, at each occurrence, is independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, aralkyl, heteroaryl, heteroarylalkyl, and saturated or partially unsaturated heterocyclic radical,

Cy is selected from the group consisting of cycloalkyl, aryl, aralkyl, heteroaryl, heteroarylalkyl, and saturated or partially unsaturated heterocyclic radical, and

G^2 and G^3, collectively, are attached at any two of positions C7, C8, and C9 of the pyrimidine ring, the remaining position being optionally substituted with alkyl, alkenyl, alkynyl, halo, fluoroalkyl, hydroxy, alkoxy, or cyano;

wherein the ring portion of any of said cycloalkyl, aryl, aralkyl, heteroaryl, heteroarylalkyl, or heterocyclic radical in G^1, G^2, or G^3 can be optionally substituted.

Substituted cycloalkyl, aryl, heteroaryl, or heterocyclic groups are preferably substituted with one or more substituents selected from the group consisting of halo, preferably Cl, Br, or F; hydroxy; nitro; fluoroalkyl, preferably $(fluoro)_{1-5}(C_1–C_6)$alkyl, more preferably $(fluoro)_{1-5}(C_1–C_6)$alkyl, including, e.g., CH_2F, CF_3, CH_2CH_2F, and CF_2CF_3; alkyl, preferably $C_1–C_6$ alkyl, more preferably $C_1–C_4$ alkyl; alkenyl, preferably $C_2–C_8$ alkenyl, more preferably $C_2–C_6$ alkenyl; alkynyl, preferably $C_2–C_8$ alkynyl, more preferably $C_2–C_6$ alkynyl; cycloalkyl, preferably $C_3–C_8$ cycloalkyl, more preferably $C_3–C_6$ cycloalkyl; (cycloalkyl)alkyl, preferably $C_3–C_8$ cycloalkyl$(C_1–C_6)$alkyl, more preferably $C_3–C_6$ cycloalkyl$(C_1–C_6)$alkyl; aryl, preferably $C_6–C_{14}$ aryl, more preferably $C_6–C_{10}$ aryl, including, e.g., phenyl and naphthyl; (aryl)alkyl, preferably $C_6–C_{10}$ aryl$(C_1–C_6)$alkyl, more preferably $C_6–C_{10}$ aryl$(C_1–C_4)$alkyl, including, e.g., benzyl and phenethyl; heteroaryl; (heteroaryl)alkyl, preferably heteroaryl$(C_1–C_6)$alkyl, more preferably heteroaryl$(C_1–C_4)$alkyl; (heteroaryl)alkyloxy, (e.g., (furyl)alkoxy, (thiophenyl)alkoxy, (pyridyl)alkoxy, etc); (heteroaryl)alkylamino, (e.g., (furyl)alkylamino, (thiophenyl)alkylamino, (pyridyl)alkylamino, etc); (heteroaryl)alkylthio, (e.g., (furyl)alkylthio, (thiophenyl)alkylthio, (pyridyl)alkylthio, etc); alkylamino (e.g., $(C_1–C_6)$alkylamino); heteroaryloxy (e.g., furyloxy, thiophenyloxy, pyridyloxy, etc); heteroarylamino (e.g., furylamino, thiophenylamino, pyridylamino, etc); heteroarylthio (e.g., furylthio, thiophenylthio, pyridylthio, etc); saturated or partially unsaturated heterocyclic radical; (heterocyclyl)alkyl; (heterocyclyl)oxy; (heterocyclyl)amino; (heterocyclyl)thio; (heterocyclyl)alkyloxy; (heterocyclyl)alkylthio; alkoxy, preferably $C_1–C_6$ alkoxy, including, e.g., methoxy and ethoxy; (aryl)alkoxy, preferably $C_6–C_{10}$ aryl$(C_1–C_6)$alkoxy, more preferably $C_6–C_{10}$ aryl$(C_1–C_4)$alkoxy, including, e.g., benzyloxy; aryloxy, preferably $C_6–C_{10}$aryloxy, including, e.g., phenoxy; amino, including: NH_2; alkylamino, preferably $C_1–C_6$ alkylamino, more preferably $C_1–C_4$ alkylamino, including, e.g., methylamino, ethylamino, and propylamino; dialkylamino, preferably di$(C_1–C_6)$alkylamino, more preferably di$(C_1–C_4)$alkylamino, including, e.g., dimethylamino and diethylamino; arylamino, preferably $C_6–C_{14}$ arylamino, more preferably $C_6–C_{10}$ arylamino, including, e.g., phenylamino; diarylamino, preferably di$(C_6–C_{14})$arylamino, more preferably di$(C_6–C_{10})$arylamino, including, e.g., diphenylamino; (aryl)alkylamino, preferably $C_6–C_{10}$ aryl$(C_1–C_6)$alkylamino, more preferably $C_6–C_{10}$ aryl$(C_1–C_4)$alkylamino, including, e.g., benzylamino; and di(aryl)alkylamino, preferably di$(C_6–C_{10})$aryl$(C_1–C_6)$alkylamino, more preferably di$(C_6–C_{10})$aryl$(C_1–C_4)$alkylamino, including, e.g., dibenzylamino; acylamino, including: alkaneacylamino, preferably $C_1–C_6$ alkaneacylamino, more preferably $C_1–C_4$ alkaneacylamino, including, e.g., acetamido and propionamido; areneacylamino, preferably $C_6–C_{14}$ areneacylamino, more preferably $C_6–C_{10}$ areneacylamino, including, e.g., benzamido; and arylalkaneacylamino, preferably $C_6–C_{10}$ aryl$(C_1–C_6)$alkaneacylamino, more preferably $C_6–C_{10}$ aryl$(C_1–C_4)$alkaneacylamino, including, e.g., phenylacetamido; carbamoyl, including: —C(O)NH_2; alkylcarbamoyl, preferably $C_1–C_6$ alkylcarbamoyl or di$(C_1–C_6)$alkylcarbamoyl, including, e.g., methylcarbamoyl and dimethylcarbamoyl; arylcarbamoyl, preferably $(C_6–C_{10})$arylcarbamoyl or di$(C_6–C_{10})$arylcarbamoyl, including, e.g., phenylcarbamoyl and diphenylcarbamoyl; and arylalkylcarbamoyl, preferably $C_6–C_{10}$ aryl$(C_1–C_6)$alkylcarbamoyl or di$(C_6–C_{10})$aryl$(C_1–C_6)$alkylcarbamoyl, including, e.g., benzylcarbamoyl and dibenzylcarbamoyl; aminoalkyl, preferably amino$(C_1–C_6)$alkyl; hydroxyalkyl, preferably hydroxy$(C_1–C_6)$alkyl; carboalkoxy, preferably carbo$(C_1–C_6)$alkoxy, including, e.g., carbomethoxy and carboethoxy; carboaryloxy, preferably carbo$(C_6–C_{10})$aryloxy, including, e.g., carbophenoxy; carboaralkoxy, preferably carbo$(C_6–C_{10})$ar$(C_1–C_6)$alkoxy, including, e.g., carbobenzyloxy; carboxy; alkylthio, preferably $C_1–C_6$ alkylthio, more preferably $C_1–C_4$ alkylthio, including, e.g., methylthio; arylthio, preferably $C_6–C_{10}$ arylthio, including, e.g., phenylthio and tolylthio; aralkylthio, preferably $C_6–C_{10}$ ar$(C_1–C_6)$alkylthio, including, e.g., benzylthio; alkylsulfinyl, preferably $C_1–C_6$ alkylsulfinyl, more preferably $C_1–C_4$ alkylsulfinyl, including, e.g., methylsulfinyl; arylsulfinyl, preferably $C_6–C_{10}$ arylsulfinyl, including, e.g., phenylsulfinyl and tolylsulfinyl; aralkylsulfinyl, preferably $C_6–C_{10}$ ar$(C_1–C_6)$alkylsulfinyl, including, e.g., benzylsulfinyl; alkylsulfonyl, preferably $C_1–C_6$ alkylsulfonyl, more preferably $C_1–C_4$ alkylsulfonyl, including, e.g., methylsulfonyl; arylsulfonyl, preferably $C_6–C_{10}$ arylsulfonyl, including, e.g., phenylsulfonyl and tolylsulfonyl; aralkylsulfonyl, preferably $C_6–C_{10}$ ar$(C_1–C_6)$alkylsulfonyl, including, e.g., benzylsulfonyl; alkylsulfonamido, preferably $C_1–C_6$ alkylsulfonamido, more preferably $C_1–C_4$ alkylsulfonamido, including, e.g., methylsulfonamido; arylsulfonamido, preferably $C_6–C_{10}$ arylsulfonamido, including, e.g., phenylsulfonamido and tolylsulfonamido; aralkylsulfonamido, preferably $C_6–C_{10}$ ar$(C_1–C_6)$alkylsulfonamido, including, e.g., benzylsulfonamido; acyl, including: alkanoyl, preferably $C_1–C_6$ alkanoyl, including, e.g., acetyl; aroyl, preferably $C_6–C_{10}$ aroyl, including, e.g., benzoyl; and aralkanoyl, preferably $C_6–C_{10}$ ar$(C_1–C_6)$alkanoyl, including, e.g., phenylacetyl; acyloxy, including, e.g., acetoxy; cyano; and ureido groups. One or more carbon atoms of a cycloalkyl group and one or more carbon atoms or heteroatoms of a heterocyclic radical also may be optionally substituted with an oxo group. The prefix or suffix "ar" refers to aryl.

In some embodiments, at least one of G^2 and G^3 is aryl or heteroaryl, optionally substituted as described above. In some embodiments, at least one of G^2 and G^3 is substituted phenyl. In some embodiments, at least one of G^2 and G^3 is phenyl substituted with one or two substituents selected from the group consisting of C_1–C_6 alkyl, C_6–C_{10} aryl, C_6–C_{10} ar(C_1–C_6)alkyl, heterocyclic radical, halo, (fluoro)$_{1-5}$(C_1–C_6)alkyl, C_1–C_6 alkoxy, C_6–C_{10} aryloxy, and C_6–C_{10} ar(C_1–C_6)alkoxy. In certain preferred embodiments, each of G^2 and G^3 is aryl or heteroaryl, optionally substituted as described above. In some embodiments, G^2 and G^3 preferably are not both unsubstituted phenyl when G^2 and G^3 are at positions C7 and C9. In other embodiments, one of G^2 or G^3 is substituted phenyl when G^2 and G^3 are at positions C7 and C9. In other embodiments, both G^2 and G^3 are independently substituted phenyl when G^2 and G^3 are at positions C7 and C9.

In some embodiments, at least one of G^2 and G^3 is —W—Cy, where Cy is selected from the group consisting of cycloalkyl, aryl, aralkyl, heteroaryl, heteroarylalkyl, and saturated or partially unsaturated heterocyclic radical, any of which optionally can be substituted as described above. In certain embodiments, Cy is aryl, preferably C_6–C_{10} aryl, which can be unsubstituted or optionally substituted. In some preferred embodiments, Cy is unsubstituted phenyl or phenyl substituted with one or two substituents selected from the group consisting of C_1–C_6 alkyl, C_6–C_{10} aryl, C_6–C_{10} ar(C_1–C_6)alkyl, heterocyclic radical, halo, (fluoro)$_{1-5}$(C_1–C_6)alkyl, C_1–C_6 alkoxy, C_6–C_{10} aryloxy, and C_6–C_{10} ar(C_1–C_6)alkoxy.

In certain other embodiments, Cy is cycloalkyl, preferably C_5–C_6 cycloalkyl, where the cycloalkyl can be unsubstituted or optionally substituted. In some preferred embodiments, Cy is unsubstituted C_5–C_6 cycloalkyl, or C_5–C_6 cycloalkyl substituted with one or two substituents selected from the group consisting of C_1–C_6 alkyl, C_6–C_{10} aryl, C_6–C_{10} ar(C_1–C_6)alkyl, heterocyclic radical, halo, (fluoro)$_{1-5}$(C_1–C_6)alkyl, C_1–C_6 alkoxy, C_6–C_{10} aryloxy, and C_6–C_{10} ar(C_1–C_6)alkoxy.

In some embodiments, the heterocyclyl in G^1 is optionally substituted as described above. In some embodiments, the heterocyclyl in G^2 or G^3 is optionally substituted as described above.

In yet other embodiments, Cy is aralkyl, preferably C_6–C_{10} ar(C_1–C_6)alkyl, wherein the aryl portion of the aralkyl can be optionally substituted as described above. In some preferred embodiments, Cy is benzyl or phenethyl, or a substituted benzyl or phenethyl, wherein the phenyl ring is substituted with one or two substituents selected from the group consisting of C_1–C_6 alkyl, C_6–C_{10} aryl, C_6–C_{10} ar(C_1–C_6)alkyl, heterocyclic radical, halo, (fluoro)$_{1-5}$(C_1–C_6)alkyl, C_1–C_6 alkoxy, C_6–C_{10} aryloxy, and C_6–C_{10} ar(C_1–C_6)alkoxy.

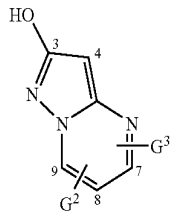
In each of the embodiments described above for Cy, W is selected from the group consisting of O, N(R), S, C(O), CH(R), —O—CH(R)—, —N(R)—CH(R)—, —S—CH(R)—, —C(O)—N(R)—, —N(R)—C(O)—, —S(O)$_2$—N(R)—, —N(R)—S(O)$_2$—, and —N(R)—C(O)—N(R)—, where R, at each occurrence, is independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, aralkyl, heteroaryl, heteroarylalkyl, and saturated or partially unsaturated heterocyclic radical. In some preferred embodiments, W is N(R), wherein R is hydrogen or C_1–C_6 alkyl. In some preferred embodiments, W is NH or NCH_3.

In some embodiments, G^1 is selected from the group consisting of OH, —C(O)OH, and heteroaryl. The heteroaryl preferably is an acidic heteroaryl, including, e.g., tetrazolyl.

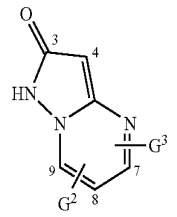
In some other embodiments, G^1 is —C(O)NR^2R^3, wherein —NR^2R^3 together forms an alpha-, beta-, or gamma-amino acid. In these embodiments, R^2 is hydrogen or C_1–C_6 alkyl, and R^3 has a formula selected from the group consisting of —$CH_2CH(R^6)CO_2H$, —$CH(R^6)CH_2CO_2H$, —$CH(R^6)CO_2H$, —$CH(R^6)CH_2CH_2CO_2H$, —$CH_2CH(R^6)CH_2CO_2H$, and —$CH_2CH_2CH(R^6)CO_2H$ wherein R^6 is selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, heteroaryl, saturated or partially unsaturated heterocyclic radical, and —CH_2R^7, and R^7 is selected from the group consisting of aryl, aralkyl, cycloalkyl, heteroaryl, saturated or partially unsaturated heterocyclic radical, hydroxy, alkoxy, aryloxy, aralkoxy, thio, alkylthio, arylthio, and aralkylthio. The substituent R^6 can be in either the (R) or (S) configuration. In some embodiments, —NR^2R^3 together forms a naturally occurring amino acid. In some other embodiments, —NR^2R^3 together forms a non-naturally occurring amino acid.

It will be appreciated that heteroaromatic rings bearing a hydroxy substituent at a position adjacent to a ring nitrogen atom may exist in either the hydroxy or the keto tautomeric form, or may exist as a mixture of the two. For example, compounds of formula (I) having a hydroxy substituent at C3 may exist as the hydroxy tautomer (1) or as the keto tautomer (2):

1

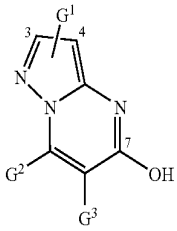


2



Similarly, compounds of formula (I) having a hydroxy substituent at C7 may exist as the hydroxy tautomer (3) or the keto tautomer (4):

3



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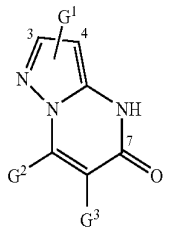
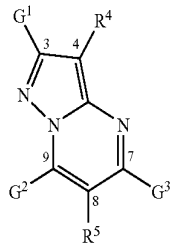


It is to be understood that all tautomeric forms of the compounds of formula (I), as well as all possible mixtures thereof in any proportion, are included within the scope of the invention, as also stated later.

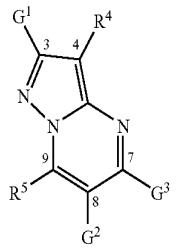
Additionally, it is to be understood that the invention also encompasses all hydrated, dehydrated, and solvated forms of the compounds of formula (I).

In some embodiments, G^1 is attached at C3, and G^2 and G^3 are attached at C9 and C7, respectively. Thus, the compounds of these embodiments have the formula (II):



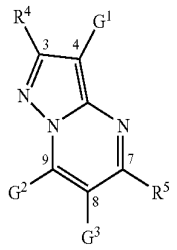
wherein G^1, G^2 and G^3 are as described above, and R^4 and R^5 independently are selected from the group consisting of hydrogen, alkyl, halo, fluoroalkyl, hydroxy, alkoxy, and cyano. In some preferred embodiments, R^4 and R^5 are both hydrogen.

In some other embodiments, G^1 is attached at C3, and G^2 and G^3 are attached at C8 and C7, respectively. Thus, the compounds of these embodiments have the formula (III):



wherein G^1, G^2 and G^3 are as described above, and R^4 and R^5 independently are selected from the group consisting of hydrogen, alkyl, halo, fluoroalkyl, hydroxy, alkoxy, and cyano. In some preferred embodiments, R^4 and R^5 are both hydrogen.

In yet other embodiments, G^1 is attached at C4, and G^2 and G^3 are attached at C9 and C8, respectively. Thus, the compounds of these embodiments have the formula (IV):



wherein G^1, G^2 and G^3 are as described above, and R^4 and R^5 independently are selected from the group consisting of hydrogen, alkyl, halo, fluoroalkyl, hydroxy, alkoxy, and cyano. In some preferred embodiments, R^4 and R^5 are both hydrogen.

Formulae (II)–(IV) illustrate certain preferred embodiments. However, other regioisomers are also possible and are included within the scope of the invention.

The term "optionally substituted" means optional substitution with the specified groups, radicals or moieties.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

Prodrugs and solvates of the compounds of the invention are also contemplated herein. The term "prodrug", as employed herein, denotes a compound that is a drug precursor which, upon administration to a subject, undergoes chemical conversion by metabolic or chemical processes to yield a compound of formula I or a salt and/or solvate thereof. A discussion of prodrugs is provided in T. Higuchi and V. Stella, *Pro-drugs as Novel Delivery Systems* (1987) Volume 14 of the A.C.S. Symposium Series, and in *Bioreversible Carriers in Drug Design,* (1987) Edward B. Roche, ed., American Pharmaceutical Association and Pergamon Press, both of which are incorporated herein by reference thereto.

"Solvate" means a physical association of a compound of this invention with one or more solvent molecules. This physical association involves varying degrees of ionic and covalent bonding, including hydrogen bonding. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. "Solvate" encompasses both solution-phase and isolatable solvates. Non-limiting examples of suitable solvates include ethanolates, methanolates, and the like. "Hydrate" is a solvate wherein the solvent molecule is H_2O.

The compounds of formula I form salts (e.g., pharmaceutically acceptable salts) which are also within the scope of this invention. Reference to a compound of formula I herein is understood to include reference to salts thereof, unless otherwise indicated. The term "salt(s)", as employed herein, denotes acidic salts formed with inorganic and/or organic acids, as well as basic salts formed with inorganic and/or organic bases. In addition, when a compound of formula I contains both a basic moiety, such as, but not limited to a pyridine or imidazole, and an acidic moiety, such as, but not limited to a carboxylic acid, zwitterions ("inner salts") may be formed and are included within the term "salt(s)" as used herein. Pharmaceutically acceptable (i.e., non-toxic, physiologically acceptable) salts are preferred, although other salts are also useful. Salts of the compounds of the formula

I may be formed, for example, by reacting a compound of formula I with an amount of acid or base, such as an equivalent amount, in a medium such as one in which the salt precipitates or in an aqueous medium followed by lyophilization.

Exemplary acid addition salts include acetates, adipates, alginates, ascorbates, aspartates, benzoates, benzenesulfonates, bisulfates, borates, butyrates, citrates, camphorates, camphorsulfonates, cyclopentanepropionates, digluconates, dodecylsulfates, ethanesulfonates, fumarates, glucoheptanoates, glycerophosphates, hemisulfates, heptanoates, hexanoates, hydrochlorides, hydrobromides, hydroiodides, 2-hydroxyethanesulfonates, lactates, maleates, methanesulfonates, 2-naphthalenesulfonates, nicotinates, nitrates, oxalates, pamoates (i.e., 1,1-methylene-bis-(2-hydroxy-3-naphthoates)), pectinates, persulfates, 3-phenylpropionates, phosphates, picrates, pivalates, propionates, salicylates, succinates, sulfates, sulfonates (such as those mentioned herein), tartarates, thiocyanates, toluenesulfonates (also known as tosylates,) undecanoates, and the like. Additionally, acids which are generally considered suitable for the formation of pharmaceutically useful salts from basic pharmaceutical compounds are discussed, for example, by S. Berge et al, *Journal of Pharmaceutical Sciences* (1977) 66(1) 1–19; P. Gould, *International J. of Pharmaceutics* (1986) 33 201–217; Anderson et al, *The Practice of Medicinal Chemistry* (1996), Academic Press, New York; in *The Orange Book* (Food & Drug Administration, Washington, D.C. on their website) and *Remington: The Science and Practice of Pharmacy,* 20th Ed., ed. A. Gennaro, Lippincott Williams & Wilkins, 2000. These disclosures are incorporated herein by reference thereto.

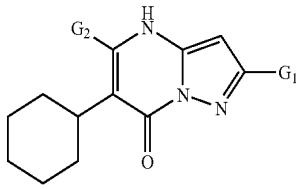
Exemplary basic salts include ammonium salts, alkali metal salts such as sodium, lithium, and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases (for example, organic amines) such as benzathines, dicyclohexylamines, hydrabamines (formed with N,N-bis(dehydroabietyl)ethylenediamine), N-methyl-D-glucamines, N-methyl-D-glucamides, t-butyl amines, and salts with amino acids such as arginine, lysine and the like. Basic nitrogen-containing groups may be quaternized with agents such as lower alkyl halides (e.g. methyl, ethyl, propyl, and butyl chlorides, bromides and iodides), dialkyl sulfates (e.g. dimethyl, diethyl, dibutyl, and diamyl sulfates), long chain halides (e.g. decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides), aralkyl halides (e.g. benzyl and phenethyl bromides), and others.

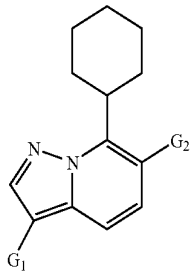
All such acid salts and base salts are intended to be pharmaceutically acceptable salts within the scope of the invention and all acid and base salts are considered equivalent to the free forms of the corresponding compounds for purposes of the invention.

Compounds of formula I, and salts, solvates and prodrugs thereof, may exist in their tautomeric form (for example, as an amide or imino ether). All such tautomeric forms are contemplated herein as part of the present invention.

All stereoisomers (for example, geometric isomers, optical isomers and the like) of the present compounds (including those of the salts, solvates and prodrugs of the compounds as well as the salts and solvates of the prodrugs), such as those which may exist due to asymmetric carbons on various substituents, including enantiomeric forms (which may exist even in the absence of asymmetric carbons), rotameric forms, atropisomers, and diastereomeric forms, are contemplated within the scope of this invention. Individual stereoisomers of the compounds of the invention may, for example, be substantially free of other isomers, or may be admixed, for example, as racemates or with all other, or other selected, stereoisomers. The chiral centers of the present invention can have the S or R configuration as defined by the *IUPAC* 1974 Recommendations. The use of the terms "salt", "solvate" "prodrug" and the like, is intended to equally apply to the salt, solvate and prodrug of enantiomers, stereoisomers, rotamers, tautomers, racemates or prodrugs of the inventive compounds.

In other embodiments the compounds (including salts, prodrugs, compositions and methods thereof) are of the following formulae, wherein the variables are as defined herein:





In another aspect, embodiments of the invention provide pharmaceutical compositions comprising an inhibitor of HCV RNA-dependent RNA polymerase according to any one of formulae (I)–(IV) and a pharmaceutically acceptable carrier, excipient, or diluent.

Preferred values for G^1, G^2, G^3, W, Cy, R, R^2, R^3, R^4, and R^5 are as set forth above for the first aspect of the invention. Compounds of the invention may be formulated by any method well known in the art and may be prepared for administration by any route, including, without limitation, parenteral, oral, sublingual, transdermal, topical, or intrarectal. In some embodiments, oral administration is preferred.

The characteristics of the carrier will depend on the route of administration. The compositions according to the invention may contain, in addition to the HCV RdRp inhibitor, diluents, fillers, salts buffers, stabilizers, solubilizers, and other materials well known in the art, provided that such materials do not interfere with the effectiveness of the biological activity of the active ingredient(s). The composition may be in any suitable form, depending on the intended route of administration, including, e.g., tablet, capsule, or liquid forms for oral administration, or solution or suspension forms for parenteral administration. The preparation of pharmaceutically acceptable formulations is described in, e.g., *Remington: The Science and Practice of Pharmacy,* 20*th Ed.,* ed. A. Gennaro, Lippincott Williams & Wilkins, 2000.

In some embodiments, the pharmaceutical compositions of the invention also include one or more other agents for the treatment of viral infections, including e.g., antiviral agents or immunomodulatory agents. In certain embodiments, the other agent is an inhibitor of HCV RdRp, HCV helicase, HCV protease, or another HCV target protein. In certain other embodiments, the other agent is a broad-spectrum antiviral or immunomodulatory agent, e.g., ribavirin, interferon, or a derivative thereof.

In a further aspect, embodiments of the invention provide methods for inhibiting HCV replication in a cell. The methods comprise contacting a cell that is infected by HCV with a compound or composition according to the invention.

In some embodiments, the cell is a hepatocyte. However, HCV is capable of replication in cell types other than hepatocytes, and the methods of the invention are also effective in such other cell types.

In certain embodiments, the cell is a cultured cell that is capable of supporting replication of HCV. Cell culture systems that support HCV replication can be prepared by infection of primary cell cultures or cell lines, or by cultivation of primary cells from a chronically infected mammal. Examples of such HCV replication systems can be found described, e.g., in Lohmann et al., *Science* 285: 110–113 (1999), Blight et al., *Science* 290: 1972 (2000), and Barenschlager and Lohmann, *J. Gen. Virology* 81: 8631–1648 (2000). In certain other embodiments, the cell is located in a human or animal subject. Preferably, the animal is a mammal. In some embodiments, the animal is a primate.

In a further aspect, embodiments of the invention provide a use of at least one compound of formula (I) for preparation of a medicament for use in prophylaxis or treatment of HCV infection.

In a further aspect, embodiments of the invention provide methods for treating or preventing an illness or condition associated with HCV infection, the methods comprising administering to a human or animal subject infected with HCV a therapeutically or prophylactically effective amount of at least one compound or composition according to the invention. By "illness or condition associated with HCV infection" is meant any illness or condition caused directly or indirectly by infection with HCV. Preferably, the animal is a mammal. In some embodiments, the animal is a primate.

HCV is characterized by pronounced genomic variability, and HCV replication leads to the rapid generation of virus variants. Holland et al., *Current Topics in Microbiology and Immunology* 176: 1–20 (1992) teaches that HCV exists, even within an individual patient, as a swarm of microvariants, a phenomenon the authors refer to as quasispecies. Therefore, the terms "hepatitis C virus" and "HCV", as used herein, are intended to refer to any of such virus variants, or mixtures thereof.

The term "therapeutically effective amount", as used herein, refers to an amount sufficient to cause a benefit to the subject or sufficient to cause any beneficial change in any symptom or marker associated with HCV infection. By "marker associated with HCV infection" is meant any biological measure that correlates with HCV infection and/or is predictive of clinical prognosis. Such markers include, without limitation, active virus and viral antigens.

The term "prophylactically effective amount", as used herein, refers to an amount sufficient to prevent or reduce the severity of HCV symptoms in a human or animal subject exposed to or infected by HCV. In some embodiments, prophylactic treatment includes administering a compound or composition according to the invention to a human or animal subject found to carry HCV, but which does not exhibit symptoms of hepatitis C disease. Prophylactic treatment also includes administering a compound or composition according to the invention to a human or animal subject which shows an improved disease state, but which still carries HCV and is at risk of recurrence of symptomatic disease.

The effective (e.g., therapeutically or prophylactically) amount of the HCV RdRp inhibitor administered will be determined empirically, and will be based on such considerations as the particular inhibitor used, the age, body weight, and condition of the individual, the treatment effect desired, administration route, and the like. It is expected that the typical dose range will be from about 0.1 mg/kg to about 100 mg/kg per dose, which can be given one to several times per day.

In some embodiments, the methods according to this aspect of the invention further include administration of one or more other agents for treating viral infections, e.g., antiviral agents or immunomodulatory agents. In certain embodiments, the other agent is an inhibitor of HCV RdRp, HCV helicase, HCV protease, or another HCV target protein. In certain other embodiments, the other agent is a broad-spectrum antiviral or immunomodulatory agent, e.g., ribavirin, interferon, or a derivative thereof.

The other agent or agents can be administered at the same time as the HCV RdRp inhibitor, or can be administered at a different time. Sequential or alternating therapy regimens are also contemplated within the scope of the invention.

EXAMPLES

Chemical Synthesis

NMR spectra were acquired on a Mercuryplus 400 MHz NMR Spectrometer (Varian), using CDCl3 or DMSO-d6 as solvents. LC-MS data was obtained using an Agilent 1100 Series LC/MSD (quadrupole, API-ES (Atmospheric Pressure Interface Electrospray)) with a capillary voltage set to 3500 V and running in positive mode.

Purification via reverse phase chromatography was accomplished using a C18 reverse phase column with a gradient of 0.1% trifluoroacetic acid in water to 95:5 acetonitrile:water at a flow rate of 20 mL/min. Samples were collected using a UV (Gilson, 254 nm) or mass spectra (Agilent 1100 Series LC/MSD model SL) signal.

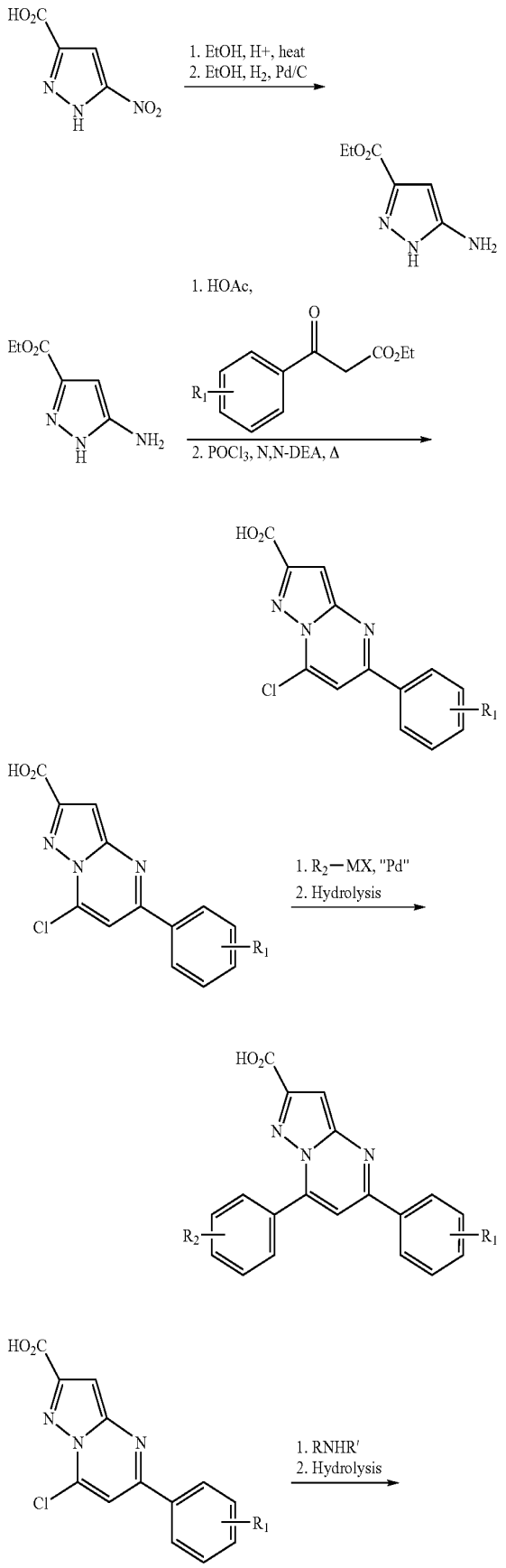
Normal phase silica gel chromatography on a Biotage instrument was accomplished using a Quad UV System (P/N 07052) utilizing KP-SIL 32–63 um columns, 60A with flash cartridges 12+M or 25+M.

Abbreviations used in the Examples

AcOH	Acetic acid
DCM	Dichloromethane
DIAD	Diisopropylazodicarboxylate
DIEA	Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DME	Dimethoxyethane
DMF	Dimethylformamide
DMFDMA	N,N-Dimethylformamide dimethylacetal
DMSO	Dimethyl sulfoxide
EtOAc	Ethyl acetate
EtOH	Ethanol
HATU	N,N,N',N'-Tetramethyl-O-(7-Azabenzotriazol-1-yl)Uronium hexafluorophosphate
Hex	hexanes
HPLC	High pressure liquid chromatography
mCPBA	meta-Chloroperoxybenzoic acid
MeOH	Methanol
Pyr	Pyridine
RT	Room temperature
THF	Tetrahydrofuran
TLC	Thin layer chromatography

Representative compounds of formula (I), wherein G^1 is —C(O)—OH, were prepared according the synthetic route outlined in Scheme 1.

Scheme 1



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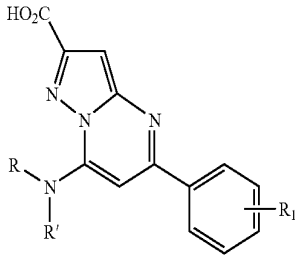
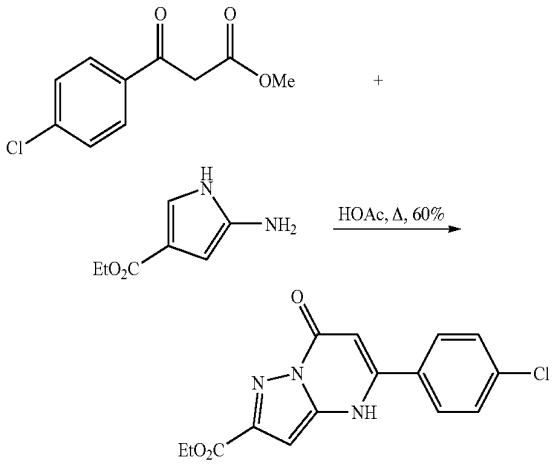


Example 1

7-Biphenyl-4-yl-5-(4-chlorophenyl)pyrazole[1,5a] pyrimidine-2-carbocylic acid ethyl ester

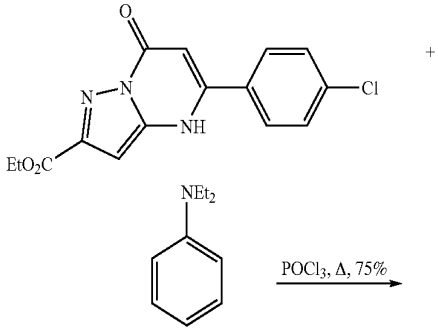
Step 1: 5-(4-chlorophenyl)-7-oxo-4,7-dihydropyrazolo[1,5α]pyrimidine-2-carboxylic acid ethyl ester



A mixture of methyl 4-chlorobenzoylacetate (2.13 g, 10 mmol) and ethyl 5-amino-3-pyrazole carboxylate (1.55 g, 10 mmol) in glacial acetic acid were heated to reflux for 20 hours. A shiny precipitate formed during the reaction. The reaction mixture was cooled, diluted with ethyl acetate and filtered. The precipitate was washed with ethyl acetate to afford an off-white shiny solid (1.92 g, 60%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.8 (bs, 1H), 7.87 (d, 2H, J=6.4 Hz), 7.67 (d, 2H, J=6.4 Hz), 6.55 (s, 1H), 6.21 (s, 1H), 4.34 (q, 2H, J=6.8 Hz), 1.35 (t, 3H, J=6.8 Hz). MS calcd for $C_{15}H_{13}ClN_3O_3$ $[M+H]^+$ 318.057, found 318.0.

Step 2: 7-Chloro-5-(4-chlorophenyl)pyrazolo[1,5α]pyrimidine-2-carboxylic acid ethyl ester



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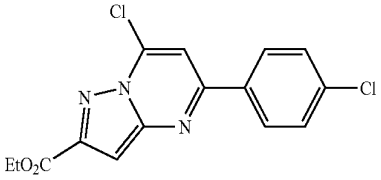
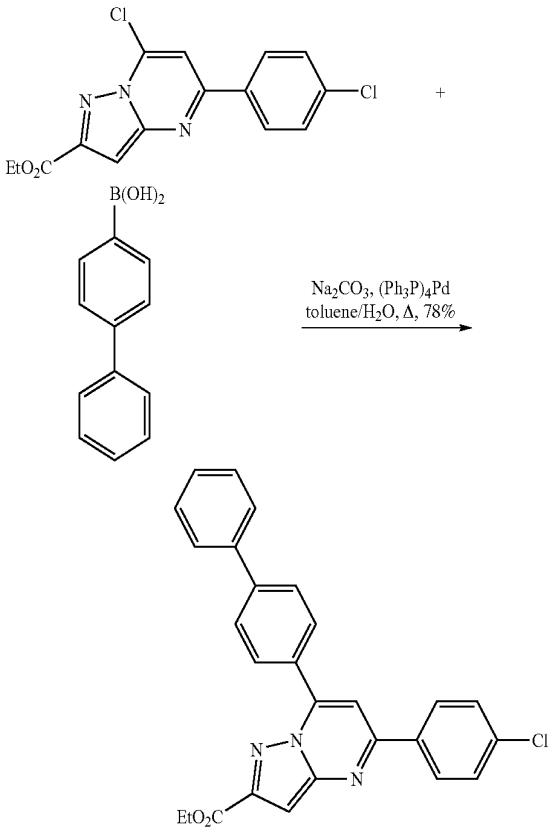


To suspension of 5-(4-chloro-phenyl)-7-oxo-4,7-dihydro-pyrazolo[1,5a]pyrimidine-2-carboxylic acid ethyl ester (1.92 g, 6.04 mmol) and N,N-diethylaniline (2.4 mL, 15.1 mmol) was added phosphorous oxychloride (6 mL). The reaction mixture was heated to reflux for 3 hours. The reaction mixture solidified upon cooling. The reaction mixture was dissolved in dichloromethane and concentrated. The solid was dissolved in dichloromethane and washed with successively with cold water (3×100 mL), saturated sodium bicarbonate solution (1×100 mL) and brine. The organic layer was dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, 1% ethyl acetate/dichloromethane) afforded a yellow solid (1.53 g, 75%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, 2H, J=8.8 Hz), 7.52 (s, 1H), 7.51 (d, 2H, J=8.8 Hz), 7.33 (s, 1H), 4.53 (q, 2H, J=7.2 Hz), 1.49 (t, 3H, J=6.8 Hz). MS calcd for $C_{15}H_{12}Cl_2N_3O_2$ $[M+H]^+$ 336.023, found 336.0.

Step 3: 7-Biphenyl-4-yl-5-(4-chlorophenyl_prazolo[1,5α]pyrimidine-2-carboxylic acid ethyl ester

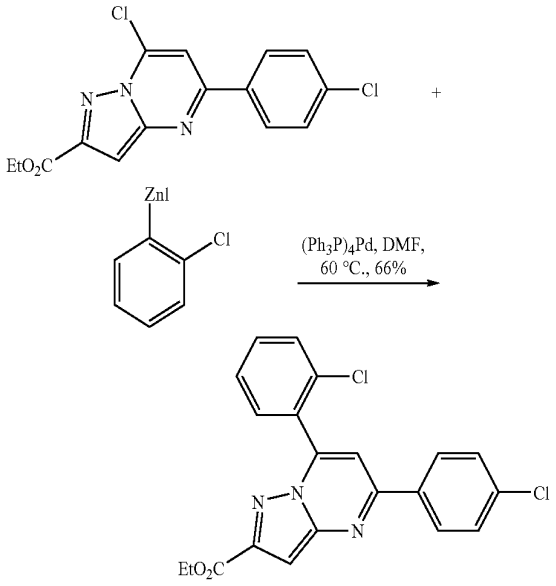


To a reaction tube containing 7-chloro-5-(4-chloro-phenyl)-pyrazolo[1,5a]pyrimidine-2-carboxylic acid ethyl ester (50 mg, 0.15 mmol), 4-(phenyl)phenyl boronic acid (36 mg, 0.18 mmol), sodium carbonate (35 mg, 0.33 mmol) and tetrakis(triphenylphosphine) palladium(0) (17 mg, 0.015 mmol) was added toluene (5 mL) and water (1 mL). The reaction tube was evacuated and flushed with argon. The reaction mixture was heated to reflux overnight. After cooling the reaction mixture was diluted with ethyl acetate (10 mL) and water (15 mL). The organic layer was separated, washed with saturated sodium chloride solution, dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, dichloromethane) afforded a pale yellow solid (53 mg, 78%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, 2H, J=6.4 Hz), 8.12 (d, 2H, J=6.8 Hz), 7.81 (d, 2H, J=6.4 Hz), 7.68 (d, 2H, J=7.2 Hz), 7.55–7.40 (m, 8H), 7.31 (s, 1H), 6.90 (d, 1H, J=8.8 Hz), 4.49 (q, 2H, J=7.2 Hz), 1.47 (t, 3H, J=6.8 Hz). MS calcd for $C_{27}H_{21}ClN_3O_2$ $[M+H]^+$ 454.12, found 454.0.

Example 2

5-(4-Chlorophenyl-7-(2-chlorophenyl)pyrazole[1,5a] pyrimidine-2-carboxylic acid ethyl ester

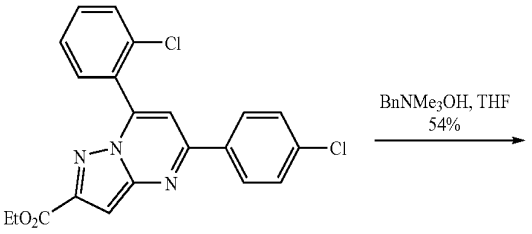


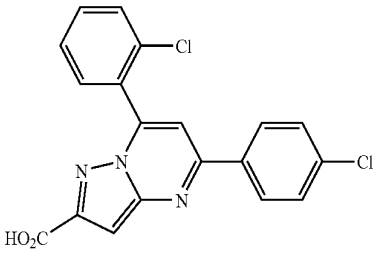
To a reaction tube containing 7-chloro-5-(4-chloro-phenyl)-pyrazolo[1,5a]pyrimidine-2-carboxylic acid ethyl ester 50 mg, 0.15 mmol), and tetrakis(triphenylphosphine) palladium(0) (17 mg, 0.015 mmol) in dimethylformamide (2 mL) was added 0.5 M 2-chlorophenyl zinc iodide in THF (0.38 mL, 0.19 mmol). The reaction tube was evacuated and flushed with argon. The reaction mixture was heated to 60° C. overnight. After cooling the reaction mixture was diluted with ethyl acetate (10 mL) and saturated ammonium chloride solution (10 mL). The organic layer was separated, washed with water and saturated sodium chloride solution, dried over sodium sulfate and concentrated. Purification by column chromatography (SiO_2, dichloromethane) afforded a pale yellow solid (51 mg, 66%) with a purity of 80%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, 2H, J=8.8 Hz), 7.70–7.45 (m, 6H), 7.40 (s, 1H), 7.30 (s, 1H), 4.45 (q, 2H, J=6.8 Hz), 1.43 (t, 3H, J=6.8 Hz). MS calcd for $C_{21}H_{16}Cl_2N_3O_2$ $[M+H]^+$ 412.05, found 412.0.

Example 3

5-(4-Chlorophenyl-7-(2-chlorophenyl)pyrazole[1,5a] pyrimidine-2-carboxylic acid





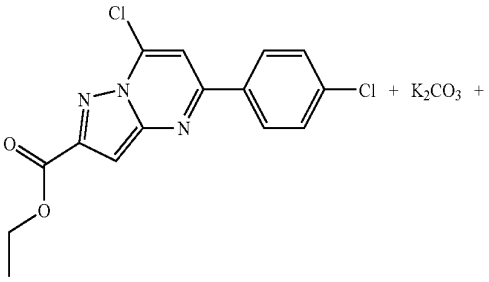
To 5-(4-chloro-phenyl-7-(2-chloro-phenyl)-pyrazolo[1,5a]pyrimidine-2-carboxylic acid ethyl ester (50 mg, 0.12 mmol) in tetrahydrofuran (3 mL) was added benzyltrimethylammonium hydroxide (2.2 M in methanol, 222 μL, 0.49 mmol) at room temperature. The reaction was stirred for 1.5 hours before p-toluenesulphonic acid resin (275 mg, ~4.5 equivalents) was added. The reaction mixture stirred for 1 hour. The mixture was filtered and concentrated. Purification by HPLC preparative chromatography afforded an off-white solid (25 mg, 54%). This compound corresponds to entry 106 in the Table 1.

^{1}H NMR (400 MHz, DMSO-d_6) δ 13.45 (bs, 1H), 8.33 (d, 2H, J=6.4 Hz), 7.99 (s, 1H), 7.80–7.6 (m, 6H), 7.25 (s, 1H). MS calcd for $C_{19}H_{12}Cl_2N_3O_2$ $[M+H]^+$ 384.02, found 384.0.

Example 4

Synthesis of pyrazolo[1,5a]pyrimidinyl amino derivatives

Step 1:



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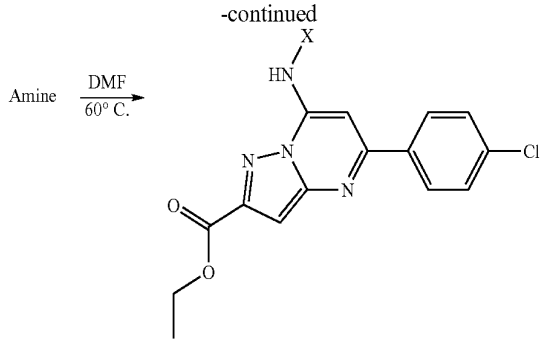


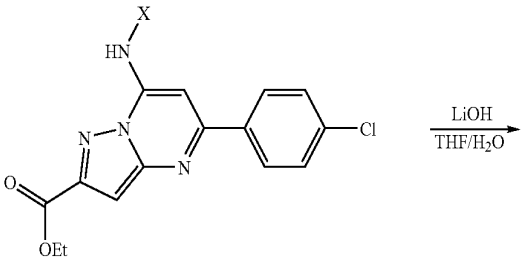
X = benzyl, cyclohexyl, morpholine, etc

A mixture of the 7-chloropyrazolo[1,5a]pyrimidine (0.05 mmol), amine (0.05 mmol) and potassium carbonate (0.1 mmol) in DMF (1.5 mL) was stirred for 16 h at 60° C.

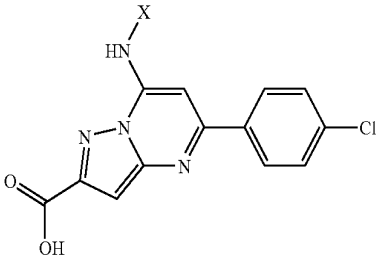
The reaction was allowed to cool to room temperature and then diluted with ethyl acetate (10 mL). The resultant mixture was extracted with water (×2) and saturated brine. The ethyl acetate layer was dried over anhydrous sodium sulfate and concentrated.

MS(+, 30V) calcd for $C_{23}H_{21}ClN_4O_2$ $[M+H]^+$ 421.14, found 421.2.

Step 2:



X = benzyl, cyclohexyly, morpholine, etc



X = benzyl, cyclohexyly, morpholine, etc

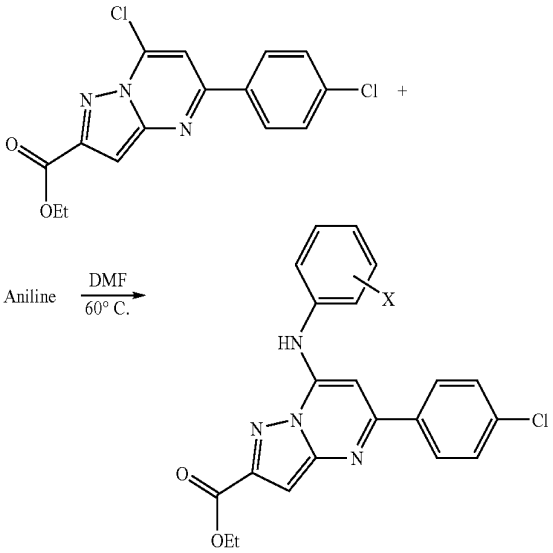
To the pyrazolo[1,5a]pyrimidine amino compound (0.05 mmol) in THF(1.5 mL) and water (0.5 mL) was added 1M LiOH (200 μl, 0.2 mmol) and stirred at RT for 16 h. The reaction was diluted with ethyl acetate (10 mL) and acidified to pH 2, transferred to a separatory funnel and the layers separated. The organic layer was washed with saturated brine, dried over anhydrous sodium sulfate and concentrated.

For the above case where the amino group was DL-alpha-methylbenzylamine (Entry 78): MS(+, 30V) calcd for $C_{21}H_{17}ClN_4O_2$ $[M+H]^+$ 393.10, found 393.0.

Example 5

Synthesis of Amino and Anilino Pyrazolo[1,5a]pyrimidine Derivatives

Step 1:



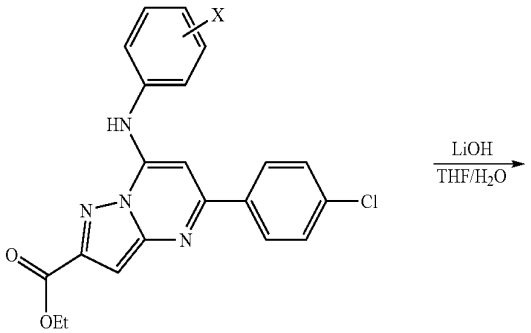
X = 3-chloro, 2-phenoxy, etc

A mixture of the 7-chloropyrazolo[1,5a]pyrimidine (0.05 mmol), aniline (0.05 mmol) and potassium carbonate (0.1 mmol) in DMF (1.5 mL) was stirred for 16 h at 60° C.

The reaction was allowed to cool to room temperature and then diluted with ethyl acetate (10 mL). The resultant mixture was extracted with water (×2) and saturated brine. The ethyl acetate layer was dried over anhydrous sodium sulfate and concentrated.

MS (+, 30V) calcd for $C_{21}H_{17}ClN_4O_2$ $[M+H]^+$ 393.10, found 393.0.

Step 2:



X = 3-chloro, 2-phenoxy, etc

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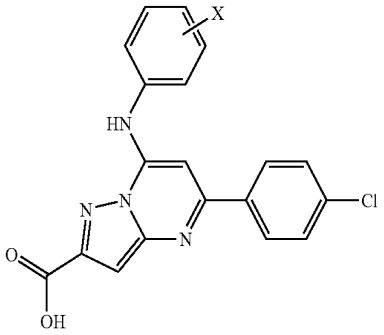


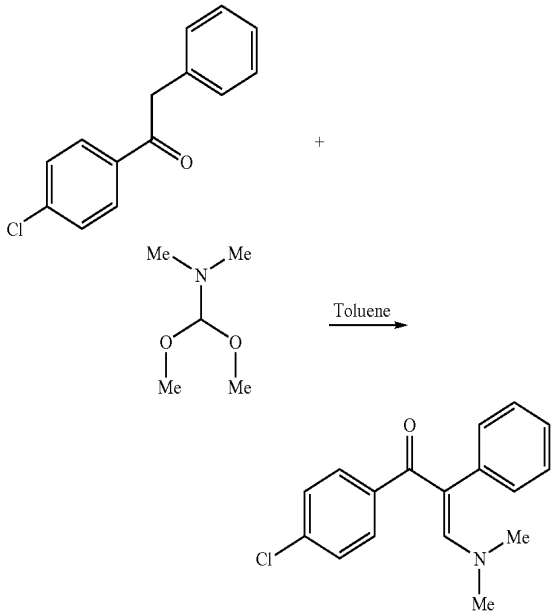
X = 3-chloro, 2-phenoxy, etc

For X=H (entry 76): MS (+, 30V) calcd for $C_{19}H_{13}ClN_4O_2$ $[M+H]^+$ 365.07, found 365.0.

Example 6

Synthesis of 6,7-Diarylpyrazolo[1,5a]pyrimidine carboxylates

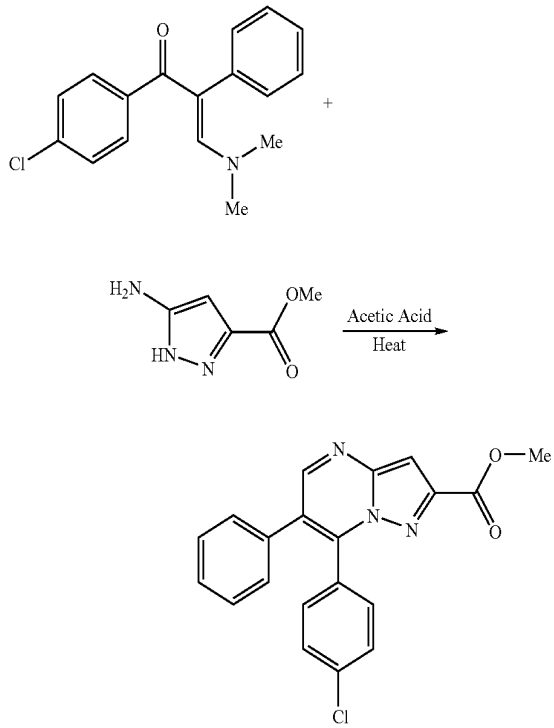
Step 1:



To a solution of benzyl 4-chlorophenyl ketone (230 mg, 1 mmol) in dry toluene (10 mL) under argon was added N,N-Dimethylformamide dimethylacetal (DMFDMA) (159 μl, 1.2 mmol) dropwise at RT. After 12 h DMFDMA (4 μl, 0.03 mmol) was added and the mixture heated to 50° C. for another 24 h. Then, during 5 days, DMFDMA (4 μl, 0.03 mmol) was added each day and the temperature increased about 15° C. everyday. The fifth day, as the reaction finished (TLC monitoring), the solvent was removed to yield the enaminoketone (285 mg, 100%) as a red/brown oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.35(s, 1H), 7.38 (m, 2H), 7.25 (m, 6H), 7.16 (m, 2H), 2.8 (s, 6H). MS (+, 30V) calcd for $C_{17}H_{16}ClNO$ $[M+H]^+$ 286.09, found 286.05.

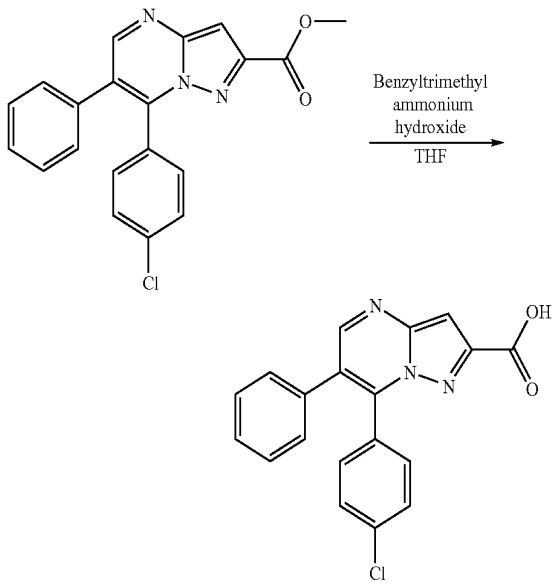
Step 2:



To the enaminoketone compound (285 mg, 1 mmol) in acetic acid (10 mL) was added 3-amino-5-carbemethoxy-pyrazole (141 mg, 1 mmol). The reaction was heated to 118° C. and stirred at 118° C. for 16 h. The reaction mixture was concentrated. The pyrazolopyrimidine product was purified by column chromatography (SiO2, 5% ethyl acetate/DCM) yielding a white solid (335 mg, 89%)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.66 (s broad, 1H), 7.44 (m, 2H), 7.35 (m, 6H), 7.17 (m, 2H), 3.98 (s, 3H). MS (+, 30V) calcd for $C_{20}H_{14}ClN_3O_2$ $[M+H]^+$ 364.08, found 364.05.

Step 3:



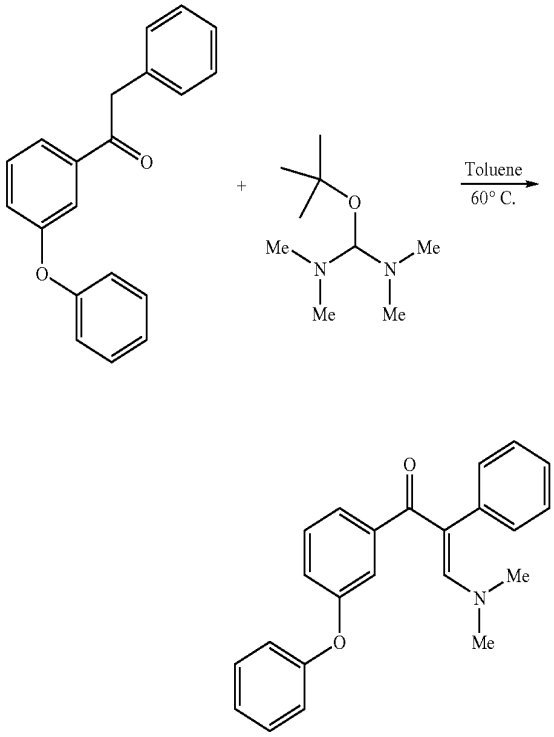
To the 7-(4-chloro-phenyl)-6-phenyl-pyrazolo[1,5]pyrimidine-2-carboxylic acid methyl ester (98 mg, 0.27 mmol) in THF (5 mL) was added benzyltrimethyl ammonium hydroxide (40 wt. % solution in methanol)(491 μl, 1.1 mmol) and the mixture stirred at room temperature for 16 h. TLC (DCM/MeOH/AcOH 90:10:1) indicated that the reaction was complete. The reaction mixture was diluted with ethyl acetate (10 mL) and acidified to pH 2 with 1N HCl. Transferred to a separatory funnel and separated the layers, the organic layer was washed with brine (×1), dried over sodium sulfate and concentrated. The pyrazolopyrimidine product was purified by PREP-LC yielding a pale yellow solid (46 mg, 49%). This corresponds to entry 236 in the Table 1.

^{1}H NMR (DMSO, 400 MHz): δ 8.74(s, 1H), 7.49 (s, 4H), 7.28 (m, 6H). MS (+, 30V) calcd for $C_{19}H_{11},ClN_3O_2$ $[M+H]^+$ 350.08, found 350.05.

Example 7

Synthesis of 6,7-Diarylpyrazolo[1,5a]pyrimidine tetrazoles

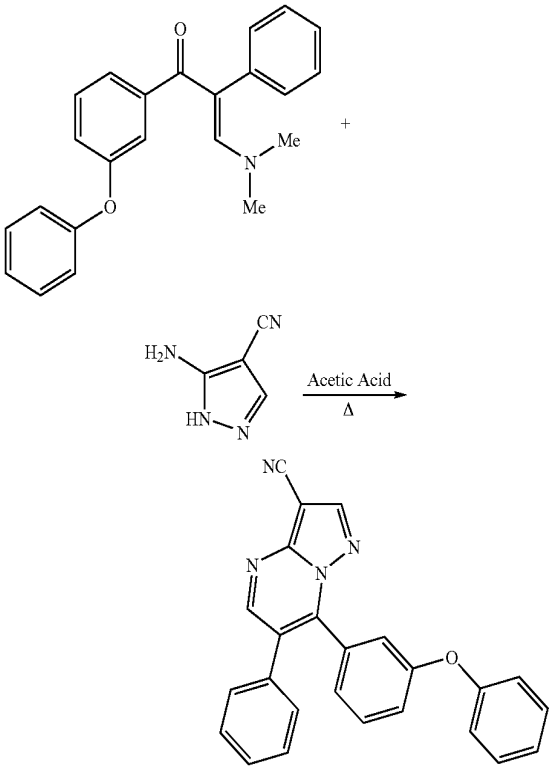
Step 1:



To a solution of benzyl 3-phenoxyphenyl ketone (523 mg, 1.8 mmol) in dry toluene (5 mL) under argon was added tert-butoxy bis(dimethylamino)methane (524 μl, 2.54 mmol) dropwise at RT. The reaction mixture was heated to 60° C. for 16 h. TLC indicated the reaction was complete. The solvent was removed to yield the enaminoketone (617 mg, 100%) as a red/brown oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.39(s, 1H), 7.25 (m, 12H), 6.99 (dd, 2H), 2.75 (s broad, 6H). MS (+, 30V) calcd for $C_{23}H_{21}NO_2$ $[M+H]^+$ 344.16, found 344.05.

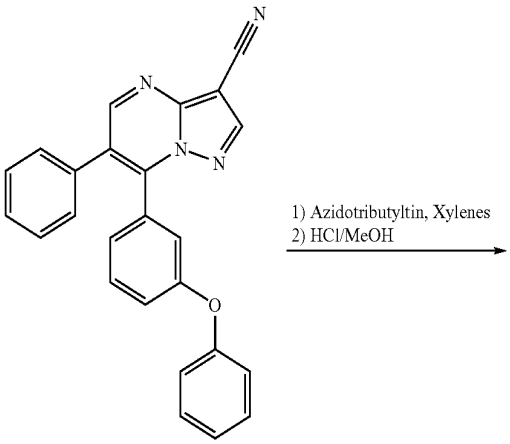
Step 2:



To the enaminoketone compound (150 mg, 0.44 mmol) in acetic acid (5 mL) was added 3-aminopyrazole-4-carbonitrile (48 mgs, 0.44 mmol). The reaction was heated to 118° C. and stirred at 118° C. for 16 h. The reaction mixture was concentrated. The pyrazolopyrimidine product was purified by column chromatography (SiO2, 5% ethyl acetate/DCM) yielding a white solid (117 mg, 68%)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.82 (s, 1H), 8.38 (s, 1H), 7.45 (m, 4H), 7.31 (m, 3H) 7.15 (m, 4H), 6.85 (t, 1H), 6.78 (dd, 2H). MS (+, 30V) calcd for $C_{25}H_{16}N_4O$ $[M+H]^+$ 389.13, found 389.05.

Step 3:



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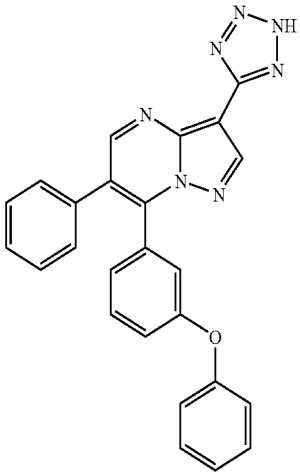


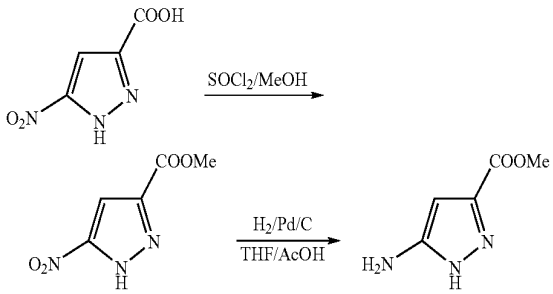
To the pyrazolopyrimidine nitrile (102 mg, 0.26 mmol) in xylenes (5 mL) was added azidotributyltin (144 μl, 0.52 mmol). The resulting mixture was heated to 110° C. under argon for 60 h. After 60 h the solvent was evaporated off, acetonitrile (10 mL) was added and the solution was washed with hexanes (8×10 mL). The acetonitrile phase was dried over anhydrous sodium sulfate and concentrated to yield the desired pyrazole pyrimidine tin protected tetrazole as a yellow gum (187 mg, 98%).

This yellow gum was taken up in methanol (5 mL). To the resulting solution was added hydrogen chloride (1.0M solution in diethyl ether) (1 mL, 1 mmol) and stirred at RT for 3 h. The reaction mixture was diluted with ethyl acetate (10 mL) and washed with aq. saturated sodium bicarbonate (×2) and brine (×1). The organic layer was dried over sodium sulfate and concentrated. The residue was triturated with hexane to give the free tetrazole product as a yellow solid (10.7 mg, 10%). This corresponds to entry 250 in the Table 1.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.85(s, 1H), 8.75 (s, 1H), 7.4 (m, 6H), 7.28 (m, 1H), 7.15 (m, 5H), 6.95 (t, 1H), 6.82 (dd, 2H). MS (+, 30V) calcd for $C_{23}H_{17}N_7O$ $[M+H]^+$ 432.15, found 432.05.

Example 8

Synthesis of 5-amino-1H-pyrazole-3-carboxylic acid methyl ester



To a solution of 25.8 g (164 mmol) of 5-nitro-1H-pyrazole-3-carboxylic acid in 250 mL of anhydrous methanol (MeOH) was added dropwise 10.3 mL (141 mmol) of thionyl chloride, and the resulting mixture was heated at reflux overnight, then cooled to rt and concentrated to give 27.6 g (98% yield) of 5-nitro-1H-pyrazole-3-carboxylic acid methyl ester as a solid. ^{1}H NMR ($CDCl_3$) δ 6.08 (s, 1H), 3.91 (s, 3H).

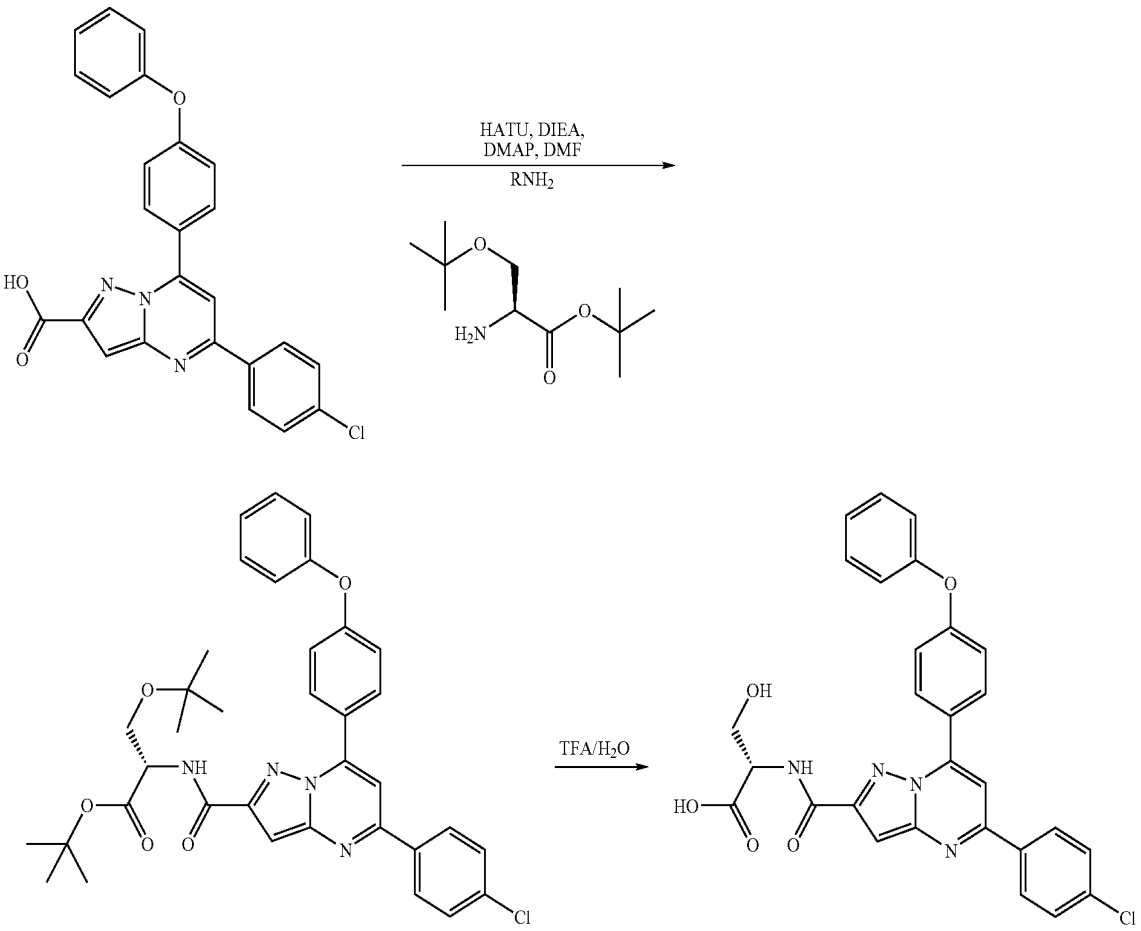
10.25 g (60 mmol) of 5-nitro-1H-pyrazole-3-carboxylic acid methyl ester was dissolved in 75 mL of acetic acid (AcOH) and 75 mL of tetrahydrofuran (THF). After a vacuum and argon cycle, 2.05 g (20% weight) of palladium on carbon (Pd/C 10 wt %) was added, the mixture was degassed again and filled with hydrogen from a balloon. The reaction mixture was stirred at rt under hydrogen atmosphere for 2 days. Analysis by thin layer chromatography (TLC) showed complete conversion of starting material to product. The mixture was then concentrated, the resulting purple colored oil was taken in 300 mL of ether, the finely dispersed purple impurity was filtered off, and the ether filtrate was evaporated to give 7.23 g (85% yield) of 5-amino-1H-pyrazole-3-carboxylic acid methyl ester as an off-white solid as indicated by ^{1}H NMR; whose structure was confirmed using ^{1}H NMR

Example 9

Synthesis of 2-{[5-(4-chloro-phenyl)-7-(4-phenoxy-phenyl)-pyrazolo[1,5-a]pyrimidine-2-carbonyl]-amino}-3-hydroxy-propionic acid

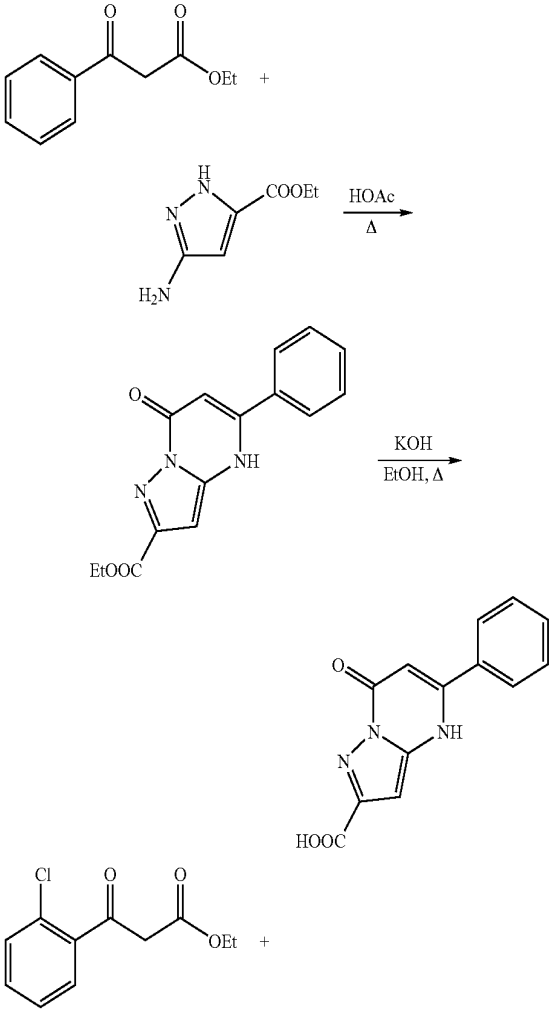
To a solution of 10 mg (0.023 mmol) of 5-(4-chloro-phenyl)-7-(4-phenoxy-phenyl)-pyrazolo[1,5-α]pyrimidine-2-carboxylic acid in 1 mL of dimethylformamide (DMF) was added 0.016 mL (0.068 mmol) of diisopropylethylamine (DIEA), 6.3 mg (0.025 mmol) of L-serine-(tBu)OtBu hydrochloride, a few crystals of dimethylaminopyridine (DMAP cat), followed by 10.3 mg (0.027 mmol) of HATU, and the resulting mixture was stirred at rt for 3 h. The reaction mixture was then diluted with ethyl acetate, washed with 0.1 N sodium hydroxide solution, water and brine. The organic layer was dried over sodium sulfate and concentrated to afford 3-tert-butoxy-2-{[5-(4-chloro-phenyl)-7-(4-phenoxy-phenyl)-pyrazolo[1,5-α]pyrimidine-2-carbonyl]-amino}-propionic acid tert-butyl ester which was used without any further purification in the next step.

A sample of 3-tert-butoxy-2-{[5-(4-chloro-phenyl)-7-(4-phenoxy-phenyl)-pyrazolo[1,5-α]pyrimidine-2-carbonyl]-amino}-propionic acid tert-butyl ester was treated with 1 mL of 95:5 trifluoroacetic acid (TFA):H_2O, and the resulting solution was stirred at rt for 1.5 h, after which time it was quenched by the addition of 2 mL of 1:1 acetonitrile:water. The mixture was then concentrated and lyophilized to afford 11.2 mg (93% yield over 2 steps) of desired 2-{[5-(4-chloro-phenyl)-7-(4-phenoxy-phenyl)-pyrazolo[1,5-α]pyrimidine-2-carbonyl]-amino}-3-hydroxy-propionic acid, as a solid whose ^{1}H NMR spectrum was consistent with its structure. For entry 260: LC-MS calcd. for $C_{28}H_{21}ClN_4O_5$ $[M+H]^+$: 529.12; found: 529.1.



Example 10

Synthesis of 7-oxo-5-phenyl-4,7-dihydro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid and 5-(2-Chloro-phenyl)-7-oxo-4,7-dihydro-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid



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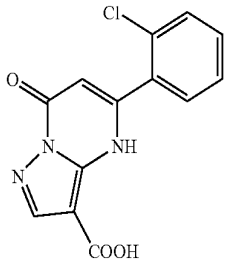


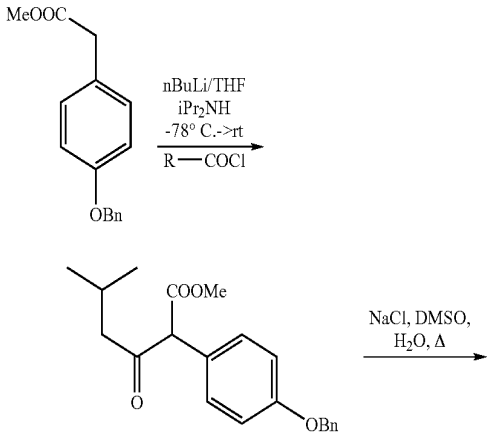
A solution of 0.56 mL (3.22 mmol) of 3-oxo-3-phenyl-propionic acid ethyl ester and 0.50 g (3.22 mmol) 5-amino-2H-pyrazole-3-carboxylic acid ethyl ester in 4 mL of acetic acid (HOAc) was heated at reflux for 4 h, during which time a precipitate formed. The precipitate was filtered off, washed with ethyl acetate and dried to give 0.51 g (56% yield) of 7-oxo-5-phenyl-4,7-dihydro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid ethyl ester as a solid as indicated by ^{1}H NMR; LC-MS—calcd for $C_{15}H_{13}N_3O_3$ $[M^+ + H]^+$: 284.1, found: 284.1.

To a solution of 50 mg (0.18 mmol) of 7-oxo-5-phenyl-4,7-dihydro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid ethyl ester in 4 mL of ethanol (EtOH) was added 26 mg (0.40 mmol) of potassium hydroxide (KOH) and the resulting mixture was heated at reflux for 60 h. The reaction mixture was then acidified with 4 M HCl in dioxane solution, and diluted with ethyl acetate. The organic extract was washed with water and brine, dried over sodium sulfate, and concentrated to give desired 7-oxo-5-phenyl-4,7-dihydro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid as indicated by ^{1}H NMR; LC-MS—calcd for $C_{13}H_9N_3O_3$ $[M^+ + H]^+$: 256.06, found: 256.1. This corresponds to entry 619.

5-(2-Chloro-phenyl)-7-oxo-4,7-dihydro-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (entry 620) was synthesized following the same synthetic sequence, starting from 3-(2-chloro-phenyl)-3-oxo-propionic acid ethyl ester, and performing the cyclization with 5-amino-1H-pyrazole-4-carboxylic acid ethyl ester.

Example 11

Synthesis of 6-(4-benzyloxy-phenyl)-7-isobutyl-3-(1H-tetrazol-5-yl)-pyrazolo[1,5-a]pyrimidine



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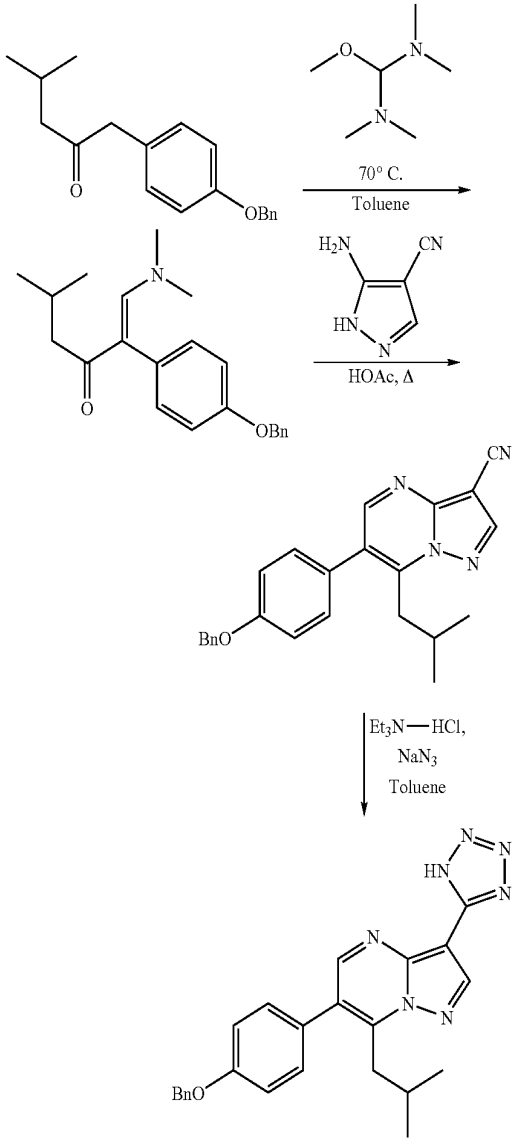
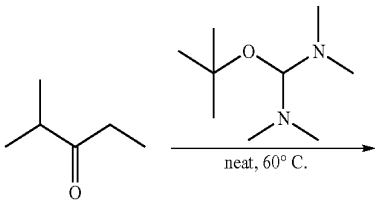


Synthesis of 6-(4-benzyloxy-phenyl)-7-isobutyl-3-(1H-tetrazol-5-yl)-pyrazolo[1,5-a]pyrimidine (410) was accomplished as depicted above, via transformations that are described elsewhere in this document for structurally similar compounds. Other compounds with modifications at the 7 position were synthesized in a similar manner.

Example 12

Synthesis of 7-isopropyl-6-methyl-3-(1H-tetrazol-5-yl)-pyrazolo[1,5-a]pyrimidine



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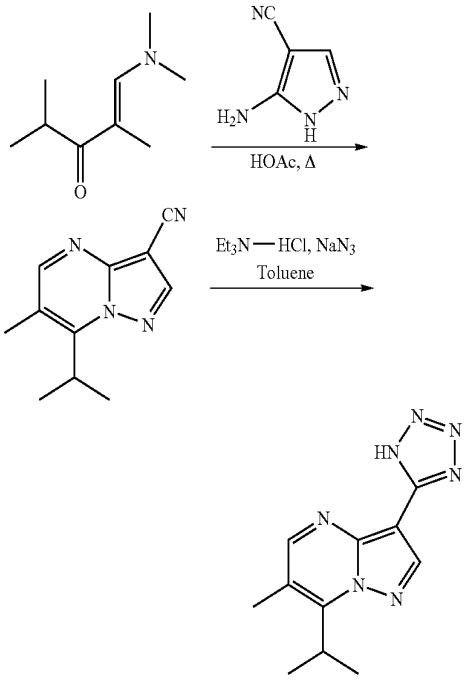
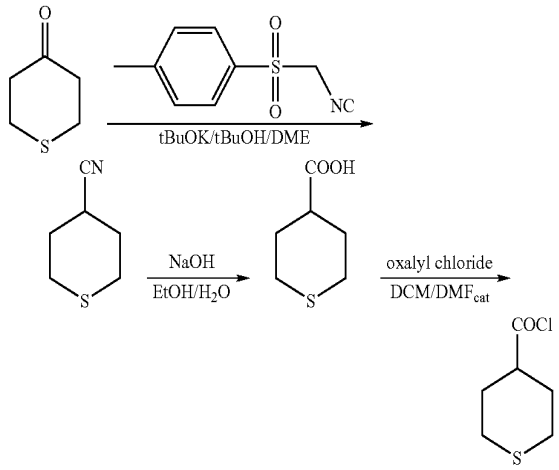


Synthesis of 7-isopropyl-6-methyl-3-(1H-tetrazol-5-yl)-pyrazolo[1,5-a]pyrimidine (390) was accomplished as depicted above, starting from the commercially available 2-methyl-pentan-3-one, via known transformations that were previously described for structurally similar compounds. 7-Ethyl-3-(1H-tetrazol-5-yl)-pyrazolo[1,5-a]pyrimidine (392), 7-cyclohexyl-6-methyl-3-(1H-tetrazol-5-yl)-pyrazolo[1,5-a]pyrimidine (391), and 7-cyclohexyl-6-methyl-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (394) were prepared following the same synthetic sequence.

Example 13

Synthesis of 6-(4-Benzyloxy-phenyl)-7-(tetrahydro-thiopyran-4-yl)-3-(1H-tetrazol-5-yl)-pyrazolo[1,5-a] pyrimidine

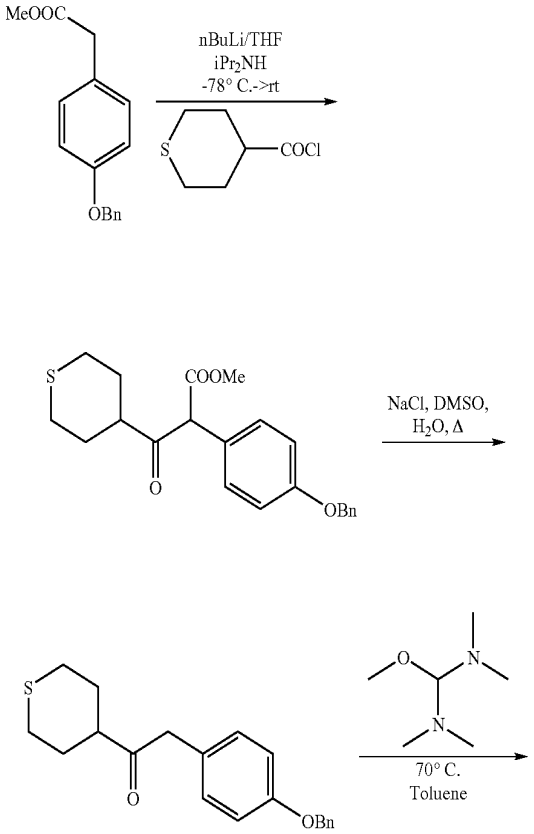


According to a modification of a literature procedure (Helv. Chim. Acta 1997, 80, 1528) to an ice cold solution of

2.0 g (17.2 mmol) of tetrahydro-thiopyran-4-one, and 3.69 g (18.9 mmol) of 1-isocyanomethanesulfonyl-4-methyl-benzene in 100 mL of 1,2-dimethoxyethane (DME) was added 34.4 mL (34.4 mmol) of potassium t-butoxide (1 M solution in t-butanol), and the resulting mixture was stirred at rt for 3 h. The reaction mixture was diluted with diethyl ether, washed with saturated sodium bicarbonate solution, dried over sodium sulfate and concentrated to give 2.05 g (93% yield) of desired tetrahydro-thiopyran-4-carbonitrile as indicated by ^{1}H NMR.

A solution of 1.97 g (15.5 mmol) of tetrahydro-thiopyran-4-carbonitrile in 5 mL of ethanol (EtOH) was added to a solution of 6.2 g (155 mmol) of sodium hydroxide (NaOH) in 30 mL of EtOH and 15 mL of water, and the resulting mixture was heated at reflux for 4 h. The reaction mixture was cooled in an ice bath, acidified with concentrated hydrochloric acid to pH=2, and then concentrated to give a precipitate which was filtered to afford 1.36 g (60%) of desired tetrahydro-thiopyran-4-carboxylic acid as a brown crystalline solid as indicated by ^{1}H NMR.

To an ice cold solution of 1.36 g (9.32 mmol) tetrahydro-thiopyran-4-carboxylic acid in 25 mL of dichloromethane (DCAM) was added dropwise 1.1 mL (12.6 mmol) of oxalyl chloride, and the resulting mixture was stirred at 0° C. for 2 h. Then 2 μL of dimethylformamide (DMF cat) was added, and the reaction mixture was stirred at rt for 2 h, and concentrated to give 1.43 g (93%) of desired tetrahydro-thiopyran-4-carbonyl chloride as a brown oil as indicated by ^{1}H NMR. The product was used with out any further purification in the next step toward the preparation of 6-(4-Benzyloxy-phenyl)-7-(tetrahydro-thiopyran-4-yl)-3-(1H-tetrazol-5-yl)-pyrazolo[1,5-a]pyrimidine (below, entry 375).



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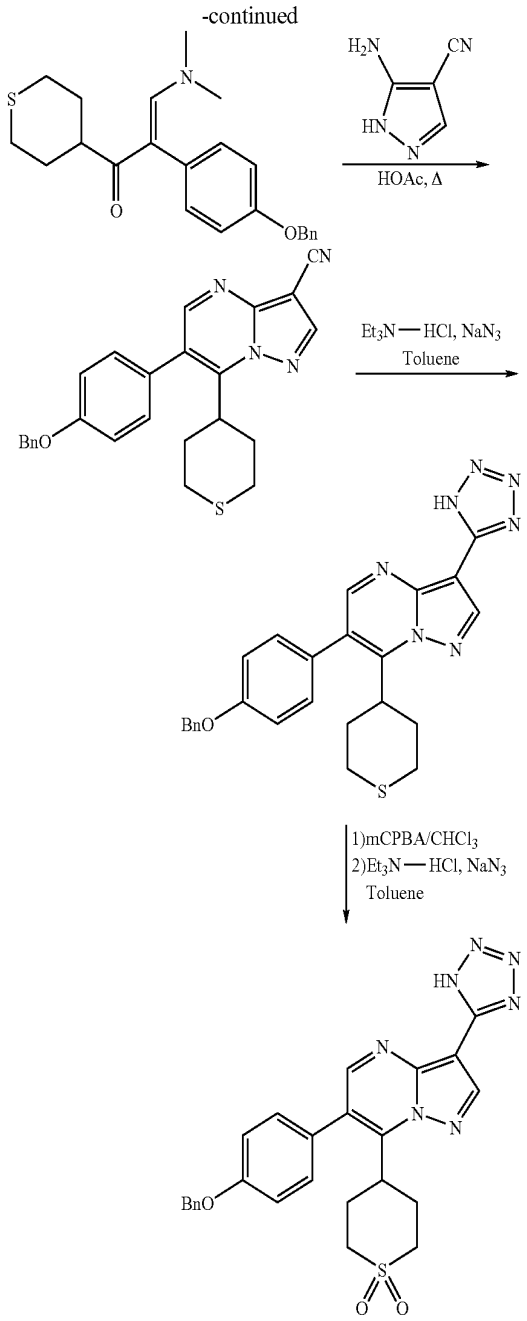
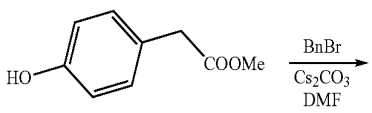


Example 14

Synthesis of 6-(4-Benzyloxy-phenyl)-7-(tetrahydro-pyran-4-yl)-3-(1H-tetrazol-5-yl)-pyrazolo[1,5-a] pyrimidine

6-(4-Benzyloxy-phenyl)-7-(tetrahydro-pyran-4-yl)-3-(1H-tetrazol-5-yl)-pyrazolo[1,5-a]pyrimidine was synthesized using the same experimental scheme.



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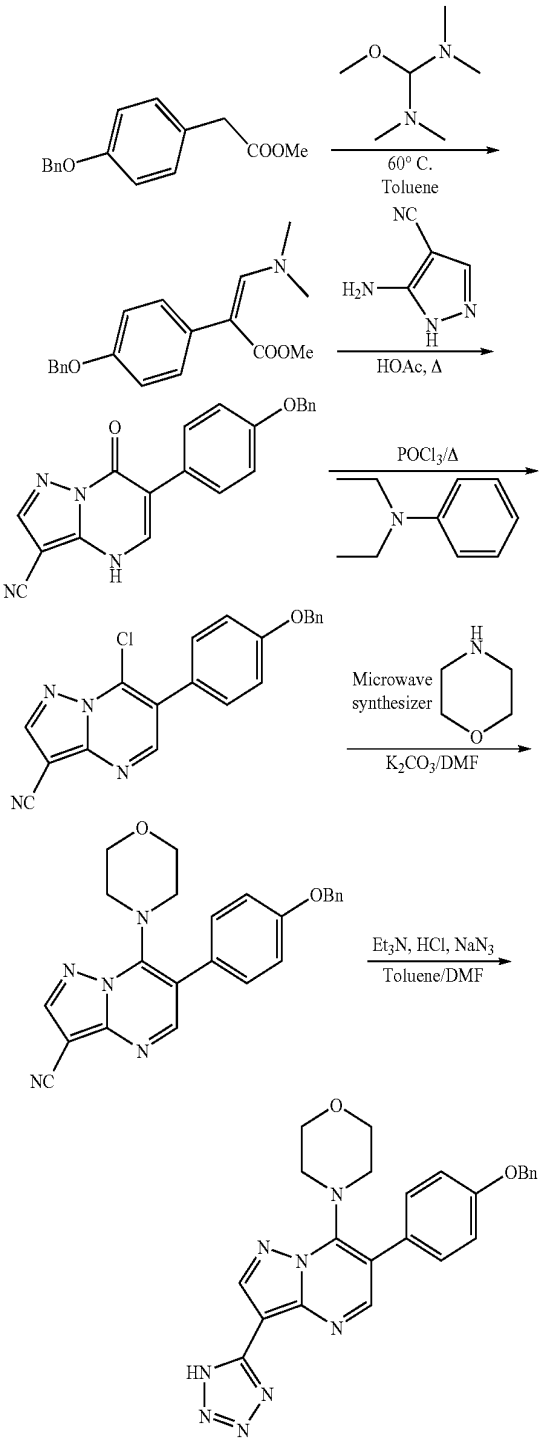


Example 15

Synthesis of 6-(4-benzyloxy-phenyl)-7-morpholin-4-yl-3-(1H-tetrazol-5-yl)-pyrazolo[1,5-a]pyrimidine

A solution of 15 g (90.3 mmol) of methyl 4-hydroxyphenylacetate in 25 mL of dimethylformamide (DMF) was added 32.4 g (99.3 mmol) of cesium carbonate, followed by 13.4 mL (112.9 mmol) of benzyl bromide (BnBr), and the resulting heterogeneous mixture was stirred at rt for 72 h. The reaction mixture was filtered, the solids were washed with ethyl acetate, and the combined organic extracts were concentrated to give a residue which was chromatographed on silica gel (25% hexane in dichloromethane) to afford 19.1 g (83% yield) of desired (4-benzyloxy-phenyl)-acetic acid methyl ester as indicated by ^{1}H NMR; LC-MS—calcd for $C_{16}H_{16}O_3$ $[M^+ + H]^+$: 257.11, found: 257.2.

According to a modified literature procedure (Wasserman, H. H.; Ives, J. L. *J. Org. Chem.* 1985, 50, 3573–3580) a solution of 1.0 g (3.9 mmol) of (4-benzyloxy-phenyl)-acetic acid methyl ester in 4 mL of toluene was flushed with argon. To this solution was added 0.842 mL g (5.5 mmol) of methoxy bis(dimethylamino)methane, and the resulting mixture was stirred at 65° C. under argon overnight. The reaction mixture was concentrated to give 1.21 g of desired 2-(4-benzyloxy-phenyl)-3-dimethylamino-acrylic acid methyl ester as indicated by ^{1}H NMR (containing traces of starting material). The product was used without any further purification in the next step.

A solution of 1.21 g (3.9 mmol) of 2-(4-benzyloxy-phenyl)-3-dimethylamino-acrylic acid methyl ester and 0.422 g (3.9 mmol) of 5-amino-1H-pyrazole-4-carbonitrile in 5 mL of acetic acid (HOAc) was heated at reflux overnight, during which time a precipitate formed. The reaction mixture was cooled to rt, diluted with 20% ethyl acetate in hexane solution, and filtered to give 0.86 g (65% over 2 steps) of 6-(4-benzyloxy-phenyl)-7-oxo-4,7-dihydro-pyrazolo[1,5-a]pyrimidine-3-carbonitrile as a tan colored solid as indicated by ^{1}H NMR; LC-MS—calcd for $C_{20}H_{14}N_4O_2$ $[M^+ + H]^+$: 343.11, found: 343.1.

A slurry of 0.86 g (2.5 mmol) of 6-(4-benzyloxy-phenyl)-7-oxo-4,7-dihydro-pyrazolo[1,5-a]pyrimidine-3-carbonitrile, 1.0 mL (6.3 mmol) of N,N-diethylaniline, and 2 mL (21.5 mmol) of phosphorus oxychloride ($POCl_3$) was heated at reflux for 7 h, during which time the reaction mixture became olive in color. The mixture was cooled to rt, poured over ice, and extracted with dichloromethane/chloroform. The combined extracts were washed with water (3 times), saturated sodium bicarbonate solution (2 times), brine, dried over sodium sulfate and evaporated to give a residue which was chromatographed on silica gel (dichloromethane) to afford 0.637 (70% yield) of 6-(4-benzyloxy-phenyl)-7-chloro-pyrazolo[1,5-a]pyrimidine-3-carbonitrile as indicated by ^{1}H NMR; LC-MS—calcd for $C_{20}H_{13}ClN_4O$ $[M^+ + H]^+$: 361.07, found: 361.1.

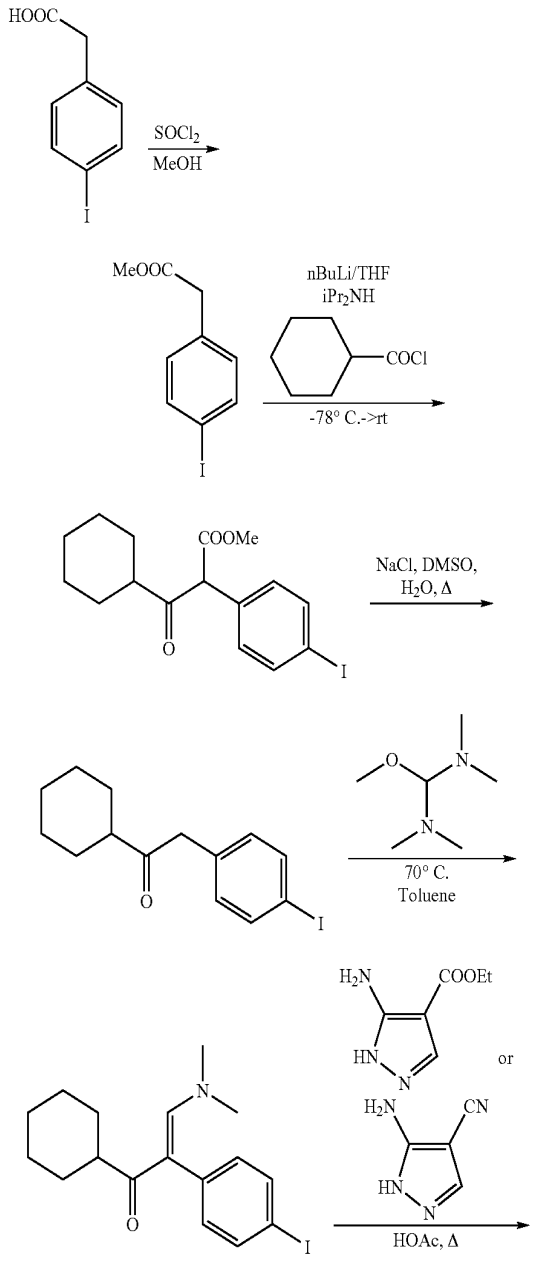
A solution of 50 mg (0.138 mmol) of 6-(4-benzyloxy-phenyl)-7-chloro-pyrazolo[1,5-a]pyrimidine-3-carbonitrile in 2 mL of dimethylformamide in a 5 mL microwave vessel, was added 25 mg (0.18 mmol) of potassium carbonate, followed by 15 mg (0.166 mmol) of morpholine, and the mixture was heated in a microwave synthesizer (Emrys system from Personal Chemistry, 300 W) at 160° C. for 5 min. Since analysis by LC-MS indicated product formation, the reaction mixture was diluted with ethyl acetate, washed with brine (2 times), dried over sodium sulfate and concentrated to give a residue which was purified via reverse-phase chromatography using Gilson to afford (after lyophilization) desired 6-(4-benzyloxy-phenyl)-7-morpholin-4-yl-pyrazolo[1,5-a]pyrimidine-3-carbonitrile (90% purity) as indicated by ^{1}H NMR; LC-MS—calcd for $C_{24}H_{21}N_5O_2$ $[M^+ + H]^+$: 412.17, found: 412.1.

According to a modification of a literature procedure (Herr, R. J. *Bioorg. Med. Chem.* 2002, 10, 3379–3393) a solution of 35 mg (0.085 mmol) of 6-(4-benzyloxy-phenyl)-7-morpholin-4-yl-pyrazolo[1,5-a]pyrimidine-3-carbonitrile in 1.5 mL of toluene and 0.5 mL of dimethylformamide was added 71 mg (0.513 mmol) of triethylamine hydrochloride (Et_3N—HCl), and 33 mg (0.513 mmol) of sodium azide and

the resulting heterogeneous mixture was heated at reflux for 72 h, during which time 71 mg (0.513 mmol) of triethylamine hydrochloride (Et_3N—HCl), and 33 mg (0.513 mmol) of sodium azide was added to the reaction mixture after every 24 h. The mixture was then cooled to rt, filtered and concentrated to a residue which was purified via reverse-phase chromatography to afford (after lyophilization) 15 mg (38% yield) of 6-(4-benzyloxy-phenyl)-7-morpholin-4-yl-3-(1H-tetrazol-5-yl)-pyrazolo[1,5-a]pyrimidine (370) as a solid as indicated by ^{1}H-NMR. (LC-MS calcd for $C_{24}H_{22}N_8O_2$ $[M^+ + H]^+$ 455.18; found 455.2.

Example 16

Synthesis of 7-cyclohexyl-6-(4-iodo-phenyl)-pyrazolo[1,5-a]pyrimidine-3-carbonitrile



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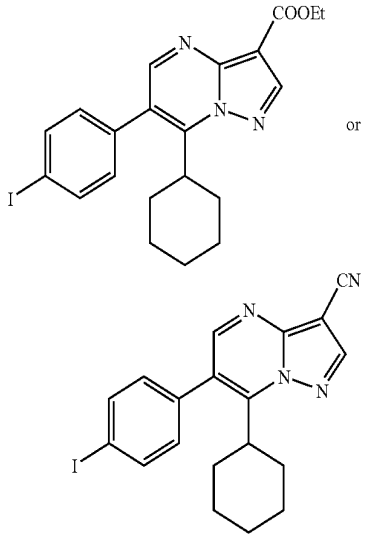


A solution of 5 g (19 mmol) of (4-iodo-phenyl)-acetic acid in 50 mL of methanol (MeOH) was added dropwise 3.5 mL (48 mmol) of thionyl chloride ($SOCl_2$), and the resulting mixture was stirred at rt for 36 h, after which time analysis by thin layer chromatography (TLC) indicated product formation. The mixture was concentrated to give 4.5 g (86% yield) of (4-iodo-phenyl)-acetic acid methyl ester as a pale beige oil as indicated by ^{1}H NMR.

A solution of 2.88 mL (20.5 mmol) of diisopropylamine (iPr_2NH) in 50 mL of tetrahydrofuran (THF) was flushed with argon and cooled to −78° C. To this solution was added dropwise 8.2 mL (20.5 mmol) of n-butyllithium (nBuLi) 2.5 M solution in hexane, and the resulting mixture was stirred at −78° C. for 20 min, after which time a solution of 4.5 g (16.3 mmol) of (4-iodo-phenyl)-acetic acid methyl ester in 25 mL of THF was added dropwise. The mixture was allowed to warm up to rt for 40 min, then it was cooled again to −78° C., and 2.62 mL (19.6 mmol) of cyclohexanecarbonyl chloride was added dropwise, and the resulting mixture was allowed to warm up to rt, and stirred at rt overnight under argon. The reaction mixture was quenched on ice by the addition of saturated ammonium chloride solution, and extracted with ethyl acetate. The combined organic extracts were washed with water, brine, dried over sodium sulfate and concentrated to give 7 g of a burgundy oil which was chromatographed on silica gel (Biotage; 10% ethyl acetate in hexane) to afford 5.06 g (80% yield) of desired 3-cyclohexyl-2-(4-iodo-phenyl)-3-oxo-propionic acid methyl ester as a pale yellow solid as indicated by ^{1}H NMR (1:2.6 keto:enol ratio). LC-MS—calcd for $C_{16}H_{19}IO_3$ $[M^+ + H]^+$: 387.04, found: 387.0.

According to a modified literature procedure (Collins, I. et al *J. Med. Chem.* 2002, 45, 1887–1900) a solution of 5.06 g (13.1 mmol) of 3-cyclohexyl-2-(4-iodo-phenyl)-3-oxo-propionic acid methyl ester in 80 mL of dimethylsulfoxide (DMSO) was added a solution of 1.53 g (26.2 mmol) of sodium chloride (NaCl) in 5.8 mL of water (H_2O), and the resulting mixture was heated at 150° C. for 3 h during which time a white solid formed. The reaction mixture was cooled to rt, poured into 500 mL of water, and extracted thoroughly with ethyl acetate. The combined organic extracts were

washed with water (3 times), brine, dried over sodium sulfate and concentrated to give 4.13 g (96% yield) of desired 1-cyclohexyl-2-(4-iodo-phenyl)-ethanone as a yellow solid as indicated by ^{1}H NMR (containing small traces of impurities). The product was used without any further purification in the next step.

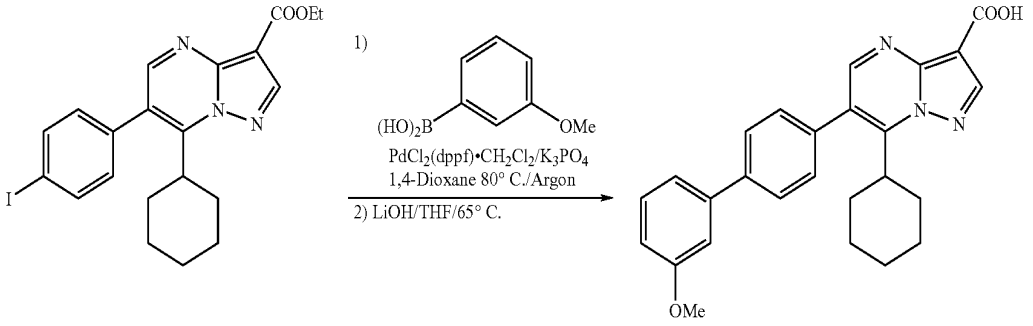
According to a modified literature procedure (Wasserman, H. H.; Ives, J. L. *J. Org. Chem.* 1985, 50, 3573–3580) a solution of 4.13 g (12.6 mmol) of 1-cyclohexyl-2-(4-iodo-phenyl)-ethanone in 20 mL of toluene was flushed with argon. To this solution was added 2.7 mL (17.6 mmol) of methoxy bis(dimethylamino)methane, and the resulting mixture was stirred at 70° C. under argon overnight. The reaction mixture was concentrated to give 5.07 g of crude 1-cyclohexyl-3-dimethylamino-2-(4-iodo-phenyl)-propenone as indicated by ^{1}H NMR (containing traces of starting material). The product was used without any further purification in the next step.

A solution of 2.55 g (6.32 mmol max) of crude 1-cyclohexyl-3-dimethylamino-2-(4-iodo-phenyl)-propenone, and 0.98 g (6.32 mmol) of 5-amino-1H-pyrazole-4-carboxylic acid ethyl ester in 30 mL of acetic acid (HOAc) was heated at reflux for 66 h, during which time a precipitate formed. The precipitate was filtered off and discarded, and the acetic acid filtrate was concentrated to a solid residue, which was washed with 1:1 ethyl acetate:hexane and dried to give 1.67 g (55% yield) of 7-cyclohexyl-6-(4-iodo-phenyl)-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid ethyl ester as a pale yellow solid. ^{1}H NMR ($CDCl_3$) δ 8.57 (s, 1H), 8.53 (s, 1H), 7.86–7.83 (d, J=8.4 Hz, 2H), 7.1–7.06 (d, J=8.4 Hz, 2H), 4.46 (q, 2H, J=7.2 Hz), 3.31–3.21 (m, 1H), 2.62–2.41 (m, 2H), 1.87–1.82 (m, 2H), 1.74–1.66 (m, 3H), 1.44 (t, 3H, J=7.2 Hz), 1.41–1.21 (m, 3H).

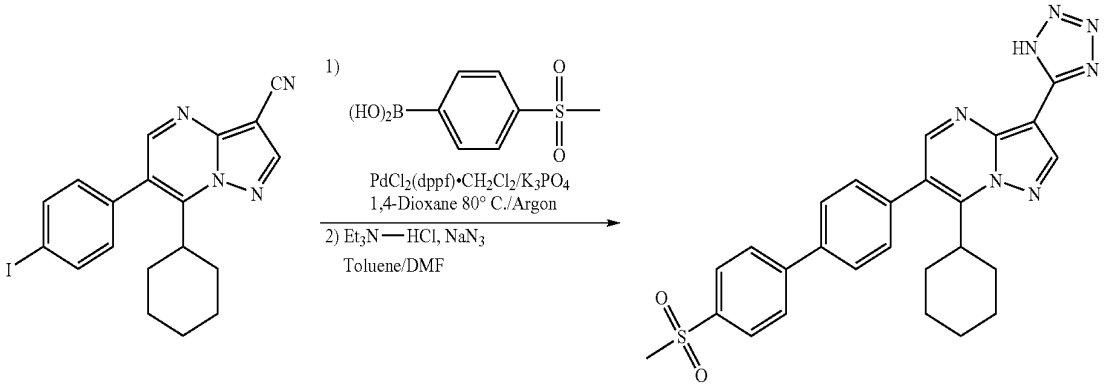
A solution of 1.66 g (4.1 mmol max) of crude 1-cyclohexyl-3-dimethylamino-2-(4-iodo-phenyl)-propenone, and 0.44 g (4.1 mmol) of 5-amino-1H-pyrazole-4-carbonitrile in 20 mL of acetic acid (HOAc) was heated at reflux for 66 h, during which time a finely dispersed precipitate formed. Since all attempts to filter off the precipitate were unsuccessful, the reaction mixture was concentrated to give a brown residue which was chromatographed on silica gel (Biotage; 2% ethyl acetate in dichloromethane) to afford 1.09 g (62% yield) of 7-cyclohexyl-6-(4-iodo-phenyl)-pyrazolo[1,5-a]pyrimidine-3-carbonitrile as a yellow solid. ^{1}H NMR ($CDCl_3$) δ 8.49 (s, 1H), 8.39 (s, 1H), 7.88–7.86 (d, J=8.4 Hz, 2H), 7.07–7.05 (d, J=8.4 Hz, 2H), 4.13 (q, 2H, J=7.2 Hz), 3.28–3.21 (m, 1H), 2.59–2.47 (m, 2H), 1.87–1.84 (m, 2H), 1.75–1.65 (m, 3H), 1.28 (t, 3H, J=7.2 Hz), 1.39–1.20 (m, 3H).

Example 17

Synthesis of 7-cyclohexyl-6-(3'-methoxy-biphenyl-4-yl)-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid, 7-cyclohexyl-6-(4'-methanesulfonyl-biphenyl-4-yl)-3-(1H-tetrazol-5-yl)-pyrazolo[1,5-a]pyrimidine, and 6-(4-benzyl-phenyl)-7-cyclohexyl-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid



(446)



(443)

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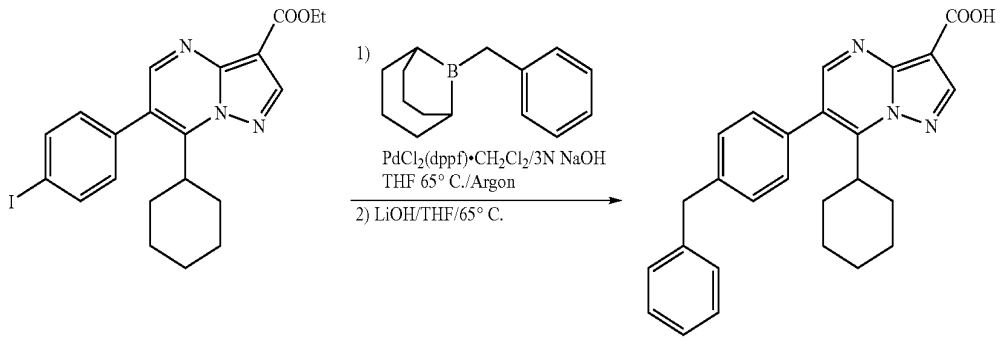


(444)

A mixture of 60 mg (0.126 mmol) of 7-cyclohexyl-6-(4-iodo-phenyl)-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid ethyl ester, 29 mg (0.19 mmol, 1.5 equiv) of 3-methoxyphenylboronic acid, 5 mg (0.0063 mmol, 5 mol %) of Pd catalyst, and 80 mg (0.378 mmol, 3 equiv) of potassium phosphate was placed into a carousel tube. After a vacuum and argon cycle, 1,4-dioxane (3 mL) was added, and the resulting mixture was heated at 80° C. under argon for 14 h. Since analysis by LC-MS revealed unreacted starting material still present, 29 mg (0.19 mmol, 1.5 equiv) of 3-methoxyphenylboronic acid, 10 mg (0.012 mmol, 10 mol %) of Pd catalyst, and 80 mg (0.378 mmol, 3 equiv) of potassium phosphate was added and heating was continued for 24 h. The reaction mixture was then diluted with ethyl acetate, filtered through a small pad of Celite, dried over sodium sulfate and evaporated to give a brown residue (crude coupling product), which was chromatographed on silica gel (Biotage; gradient elution 2% to 5% ethyl acetate in dichloromethane) to afford 47 mg (82% yield) of desired 7-cyclohexyl-6-(3'-methoxy-biphenyl-4-yl)-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid ethyl ester as indicated by ^{1}H NMR; LC-MS—calcd for $C_{28}H_{29}N_3O_3$ $[M^+ + H]^+$: 456.22, found: 456.2.

To a solution of 47 mg (0.103 mmol) of 7-cyclohexyl-6-(3'-methoxy-biphenyl-4-yl)-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid ethyl ester in 3 mL of tetrahydrofuran was added 0.62 mL (0.62 mmol) of 1 M LiOH solution, and the resulting mixture was heated at reflux overnight. The reaction mixture was then acidified with 1 M HCl solution to pH=2, and extracted with ethyl acetate. The combined organic extracts were dried over sodium sulfate, and concentrated to give a residue which was purified via reverse-phase chromatography to afford (after lyophilization) 15 mg (34% yield) of 7-cyclohexyl-6-(3'-methoxy-biphenyl-4-yl)-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (446) as a solid (90% purity) as indicated by ^{1}H NMR; LC-MS—calcd for $C_{26}H_{25}N_3O_3$ $[M^+ + H]^+$: 428.19, found: 428.2.

A mixture of 65 mg (0.15 mmol) of 7-cyclohexyl-6-(4-iodo-phenyl)-pyrazolo[1,5-a]pyrimidine-3-carbonitrile, 45 mg (0.225 mmol, 1.5 equiv) of 4-(methanesulfonyl)phenylboronic acid, 6 mg (0.0075 mmol, 5 mol %) of Pd catalyst, and 95 mg (0.45 mmol, 3 equiv) of potassium phosphate was placed into a carousel tube. After a vacuum and argon cycle, 1,4-dioxane (3 mL) was added, and the resulting mixture was heated at 80° C. under argon for 14 h. Since analysis by LC-MS revealed unreacted starting material still present, 45 mg (0.225 mmol, 1.5 equiv) of 4-(methanesulfonyl)phenylboronic acid, 12 mg (0.015 mmol, 10 mol %) of Pd catalyst, and 95 mg (0.45 mmol, 3 equiv) of potassium phosphate was added and heating was continued for 24 h. The reaction mixture was then diluted with ethyl acetate, filtered through a small pad of Celite, dried over sodium sulfate and evaporated to give a brown residue (crude coupling product), which was chromatographed on silica gel (Biotage; gradient elution 2% to 10% ethyl acetate in dichloromethane) to afford 42 mg (62% yield) of desired 7-cyclohexyl-6-(4'-methanesulfonyl-biphenyl-4-yl)-pyrazolo[1,5-a]pyrimidine-3-carbonitrile as indicated by ^{1}H NMR; LC-MS—calcd for $C_{26}H_{24}N_4O_2S$ $[M^+ + H]^+$: 457.16, found: 457.1.

To a solution of 42 mg (0.092 mmol) of 7-cyclohexyl-6-(4'-methanesulfonyl-biphenyl-4-yl)-pyrazolo[1,5-a]pyrimidine-3-carbonitrile in 1 mL of toluene and 1.2 mL of dimethylformamide (DMF) was added 76 mg (0.55 mmol) of triethylamine hydrochloride (Et_3N—HCl), and 36 mg (0.55 mmol) of sodium azide and the resulting heterogeneous mixture was heated at 120° C. for 72 h, during which time 76 mg (0.55 mmol) of triethylamine hydrochloride (Et_3N—HCl), and 36 mg (0.55 mmol) of sodium azide was added to the reaction mixture after every 24 h. The mixture was then cooled to rt, filtered and concentrated to a residue which was purified via reverse-phase chromatography to afford (after lyophilization) 7 mg (15% yield) of 7-cyclohexyl-6-(4'-methanesulfonyl-biphenyl-4-yl)-3-(1H-tetrazol-5-yl)-pyrazolo[1,5-a]pyrimidine as a white solid (90% purity, entry 443) as indicated by ^{1}H-NMR; LC-MS calcd for $C_{26}H_{25}N_7O_2S$ $[M^+ + H]^+$ 500.18; found 500.2.

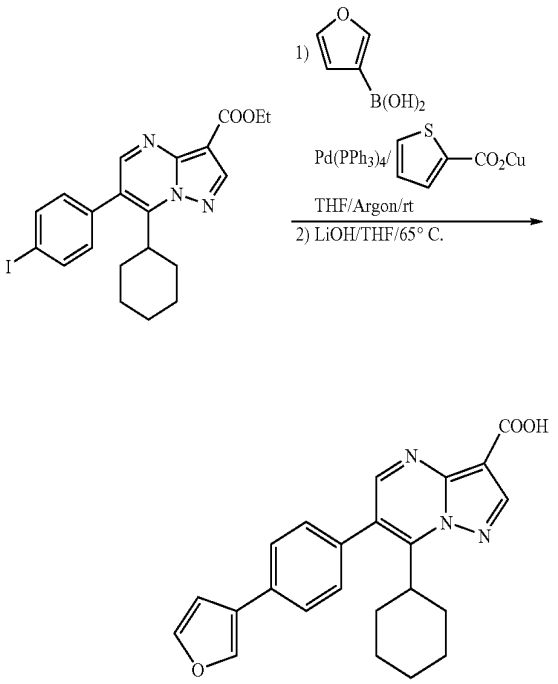
According to a modification of a literature procedure (Suzuki, A. et al *Tetrahedron Lett.* 1986, 27, 6369–6372) a mixture of 57 mg (0.12 mmol) of 7-cyclohexyl-6-(4-iodo-phenyl)-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid ethyl ester and 5 mg (0.006 mmol, 5 mol %) of Pd catalyst was placed into a carousel tube. After a vacuum and argon cycle, tetrahydrofuran (THF) (2 mL) was added, followed by 0.29 mL (0.144 mmol, 1.2 equiv) of B-Benzyl-9-BBN 0.5 M solution in THF, and 0.12 mL (0.36 mmol, 3 equiv) of 3 N NaOH solution, and the resulting mixture was heated reflux under argon overnight. Since analysis by LC-MS revealed unreacted starting material still present, 0.12 mL (0.06 mmol) of B-Benzyl-9-BBN, 5 mg (0.006 mmol, 5 mol %) of Pd catalyst, and 0.12 mL (0.36 mmol) of 3 N NaOH solution was added and heating was continued for 24 h. The reaction mixture was then diluted with ethyl acetate, washed with

water, dried over sodium sulfate, passed through a small pad of Celite, and evaporated to give a brown residue (crude coupling product), which was chromatographed on silica gel (Biotage; 2% ethyl acetate in dichloromethane) to afford 36 mg (68% yield) of desired 6-(4-benzyl-phenyl)-7-cyclohexyl-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid ethyl ester as indicated by ^{1}H NMR (containing traces of impurities); LC-MS—calcd for $C_{28}H_{29}N_3O_2$ $[M^+ + H]^+$: 440.23, found: 440.2.

To a solution of 36 mg (0.082 mmol) of 6-(4-benzyl-phenyl)-7-cyclohexyl-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid ethyl ester in 3 mL of tetrahydrofuran was added 0.5 mL (0.5 mmol) of 1 M LiOH solution, and the resulting mixture was heated at reflux overnight. The reaction mixture was then acidified with 1 M HCl solution to pH=2, and extracted with ethyl acetate. The combined organic extracts were dried over sodium sulfate, and concentrated to give a residue which was purified via reverse-phase chromatography to afford (after lyophilization) 7 mg (21% yield) of 6-(4-benzyl-phenyl)-7-cyclohexyl-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid as a solid (90% purity, entry 444) as indicated by ^{1}H NMR; LC-MS—calcd for $C_{26}H_{25}N_3O_2$ $[M^+ + H]^+$: 412.19, found: 412.3.

Example 18

Synthesis of 7-cyclohexyl-6-(4-furan-3-yl-phenyl)-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid

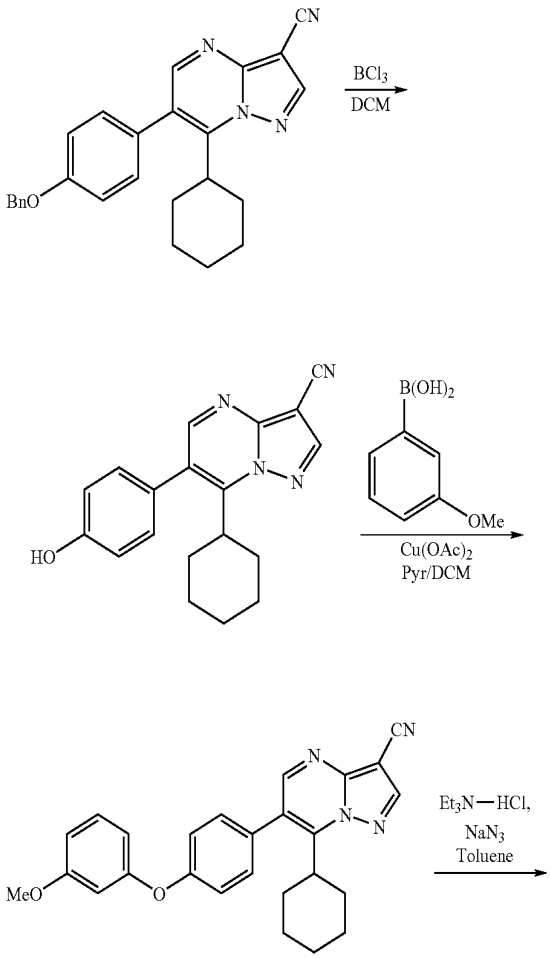


According to a modification of a literature procedure (Savarin C.; Liebeskind, L. S. *Org. Lett.* 2001, 3, 2149–2152) a mixture of 24 mg (0.05 mmol) of 7-cyclohexyl-6-(4-iodo-phenyl)-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid ethyl ester, 7 mg (0.06 mmol, 1.2 equiv) of 3-furylboronic acid, 3 mg (0.0025 mmol, 5 mol %) of $Pd(PPh_3)_4$, and 12 mg (0.06 mmol, 1.2 equiv) of copper(I) thiophene-2-carboxylate (CuTC) was placed into a Schlenk flask. After a vacuum and argon cycle, tetrahydrofuran (1.2 mL) was added, and the resulting mixture was stirred at rt under argon overnight. The reaction mixture was diluted with water and extracted with ethyl acetate. The combined ethyl acetate extracts were washed with brine, filtered through a small pad of Celite, dried over sodium sulfate and evaporated to give 28 mg of a yellow oil (crude coupling product) which was used in the next reaction without any further purification; LC-MS—calcd for $C_{25}H_{25}N_3O_3$ $[M^+ + H]^+$: 416.19, found: 416.2.

The above residue was taken in tetrahydrofuran (2 mL) and 0.3 mL (0.3 mmol, 5 equiv) of 1 M LiOH solution was added, and the resulting mixture was heated at reflux overnight. The reaction mixture was then diluted with ethyl acetate, and acidified with 1N HCl solution to pH 2. The organic extract was washed with brine, dried over sodium sulfate and evaporated to give a residue which was purified via reverse-phase chromatography to afford (after lyophilization) 4 mg (20% yield) of 7-cyclohexyl-6-(4-furan-3-yl-phenyl)-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (445) as a white solid (90% purity), as indicated by ^{1}H-NMR; LC-MS calcd for $C_{23}H_{21}N_3O_3$ $[M^+ + H]^+$: 388.16, found: 388.1.

Example 19

Synthesis of 7-cyclohexyl-6-[4-(3-methoxy-phenoxy)-phenyl]-3-(1H-tetrazol-5-yl)-pyrazolo[1,5-a]pyrimidine



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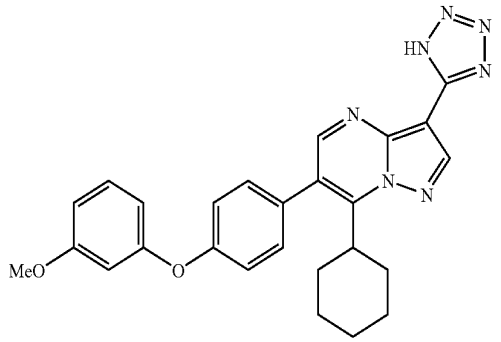


The starting material in this sequence was synthesized following the same experimental procedure that was used to prepare a related intermediate where the benzyloxy group (OBn) was replaced by iodine (I).

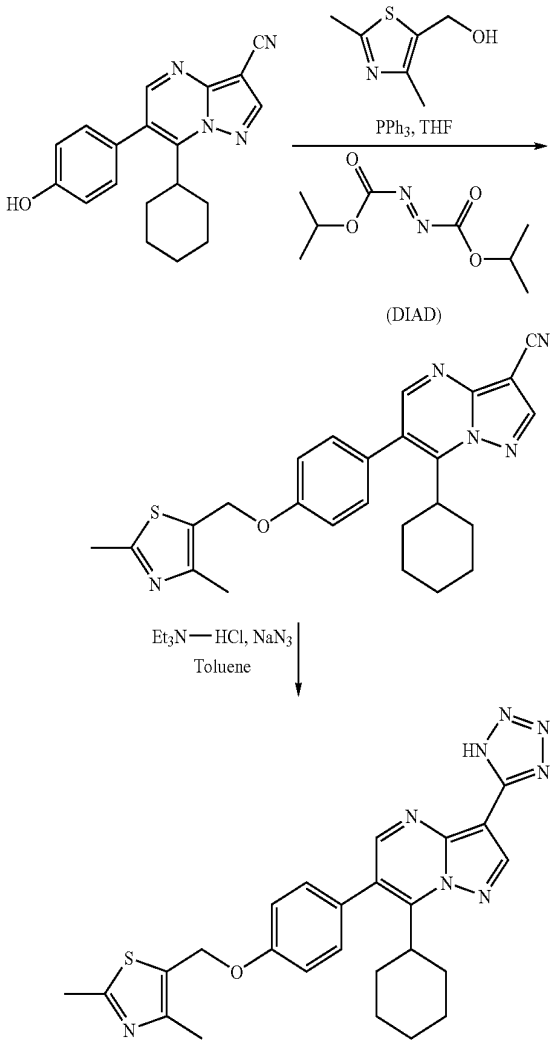
A solution of 800 mg (1.95 mmol) of 6-(4-benzyloxy-phenyl)-7-cyclohexyl-pyrazolo[1,5-a]pyrimidine-3-carbonitrile in 5 mL of dichloromethane (DCM) was cooled to −78° C. To the above cold solution was added 2.93 mL (2.93 mmol) of boron trichloride (BCl_3) 1 M solution in DCM and the resulting mixture was stirred at −78° C. for 90 min. Since analysis by thin layer chromatography (TLC) revealed that starting material was still present, excess boron trichloride (BCl_3) (3 equiv) was added, and the reaction was quenched at −78° C. with 5 mL of methanol. The mixture was allowed to warm up to rt, saturated sodium bicarbonate solution was added, and the mixture was extracted with DCM. The combined organic extracts were washed with water, brine, dried over sodium sulfate and evaporated to give 754 mg of an off-white solid which was chromatographed on silica gel (5% ethyl acetate in DCM) to give 560 mg (90% yield) of desired 7-cyclohexyl-6-(4-hydroxy-phenyl)-pyrazolo[1,5-a] pyrimidine-3-carbonitrile as a white solid. LC-MS—calcd for $C_{19}H_{18}N_4O$ $[M^+ + H]^+$: 319.15, found: 319.1. ^{1}H NMR ($CDCl_3$) δ 8.53 (s, 1H), 8.38 (s, 1H), 7.20–7.18 (d, J=8.4 Hz, 2H), 7.00–6.98 (d, J=8.4 Hz, 2H), 5.43 (s, 1H, OH), 3.34–3.28 (m, 1H), 2.58–2.44 (m, 2H), 1.86–1.82 (m, 2H), 1.74–1.68 (m, 3H), 1.41–1.18 (m, 3H).

An aqua-green mixture of 50 mg (0.157 mmol) of 7-cyclohexyl-6-(4-hydroxy-phenyl)-pyrazolo[1,5-a]pyrimidine-3-carbonitrile, 43 mg (0.235 mmol) of copper (II) acetate ($Cu(OAc)_2$), 48 mg (0.314 mmol) of 3-methoxyphenylboronic acid, 0.025 mL (0.31 mmol) of pyridine (pyr), and 5 mL of DCM was stirred at rt for 68 h while opened to air. The reaction mixture was filtered through Celite, while rinsing the Celite pad with ethyl acetate and chloroform. The combined organic filtrates were concentrated to a green solid residue which was partitioned between ethyl acetate and water and extracted with ethyl acetate. The combined organic extracts were washed with water (3 times), brine, dried over sodium sulfate and evaporated to give 74 mg of a brown residue which was chromatographed on silica gel (Biotage; DCM) to give 38 mg (58% yield) of desired 7-cyclohexyl-6-[4-(3-methoxy-phenoxy)-phenyl]-pyrazolo [1,5-a]pyrimidine-3-carbonitrile as a colorless oil as indicated by ^{1}H-NMR; LC-MS—calcd for $C_{26}H_{24}N_4O_2$ $[M^+ + H]^+$: 425.19, found: 425.1.

Conversion of 7-cyclohexyl-6-[4-(3-methoxy-phenoxy)-phenyl]-pyrazolo[1,5-a]pyrimidine-3-carbonitrile to the corresponding tetrazole 7-cyclohexyl-6-[4-(3-methoxy-phenoxy)-phenyl]-3-(1H-tetrazol-5-yl)-pyrazolo[1,5-a] pyrimidine (301) was accomplished via a described experimental described elsewhere in this document.

Example 20

Synthesis of 7-cyclohexyl-6-[4-(2,4-dimethyl-thiazol-5-ylmethoxy)-phenyl]-3-(1H-tetrazol-5-yl)-pyrazolo[1,5-a]pyrimidine

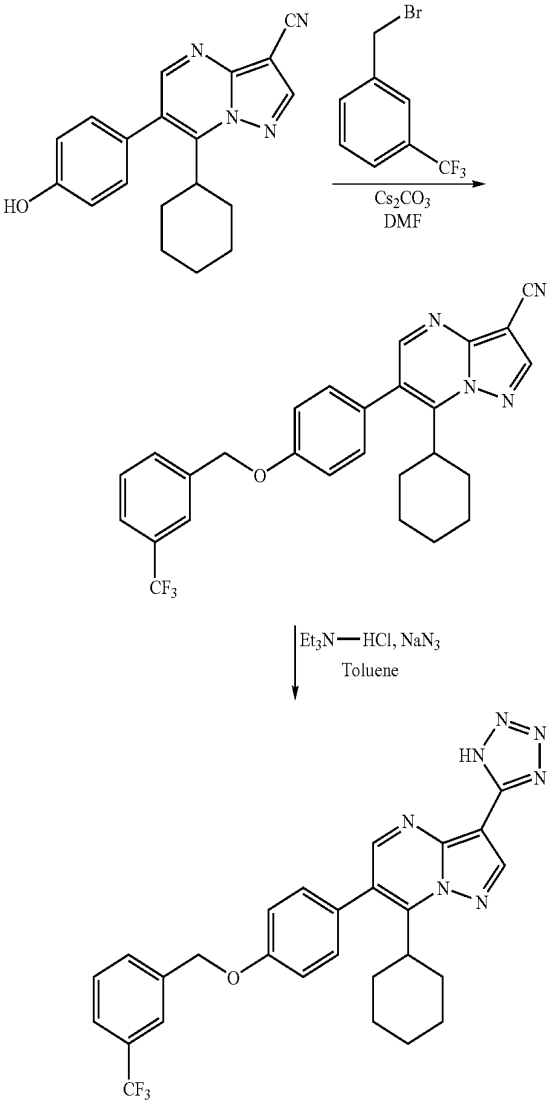


To an ice cold mixture of 40 mg (0.13 mmol) of 7-cyclohexyl-6-(4-hydroxy-phenyl)-pyrazolo[1,5-a]pyrimidine-3-carbonitrile in 3 mL of tetrahydrofuran (THF) was added 74 mg (0.52 mmol) of (2,4-dimethyl-thiazol-5-yl)-methanol, 136 mg (0.52 mmol) of triphenylphosphine (PPh_3), followed by 0.102 mL (0.52 mmol) of diisopropyl azodicarboxylate (DIAD) and the mixture was allowed to warm up to rt and stirred at rt overnight. The reaction mixture was then concentrated and the residue was chromatographed on silica gel (Biotage; 10% ethyl acetate in DCM) to give desired 7-cyclohexyl-6-[4-(2,4-dimethyl-thiazol-5-ylmethoxy)-phenyl]-pyrazolo[1,5-a]pyrimidine-3-carbonitrile as indicated by ^{1}H-NMR; LC-MS—calcd for $C_{25}H_{25}N_5OS$ $[M^+ + H]^+$: 444.18, found: 444.2.

Conversion of 7-cyclohexyl-6-[4-(2,4-dimethyl-thiazol-5-ylmethoxy)-phenyl]-pyrazolo[1,5-a]pyrimidine-3-carbonitrile to the corresponding tetrazole 7-cyclohexyl-6-[4-(2,4-dimethyl-thiazol-5-ylmethoxy)-phenyl]-3-(1H-tetrazol-5-yl)-pyrazolo[1,5-a]pyrimidine (358) was accomplished via a procedure described elsewhere.

Example 21

Synthesis of 7-cyclohexyl-3-(1H-tetrazol-5-yl)-6-[4-(3-trifluoromethyl-benzyloxy)-phenyl]-pyrazolo[1,5-a]pyrimidine

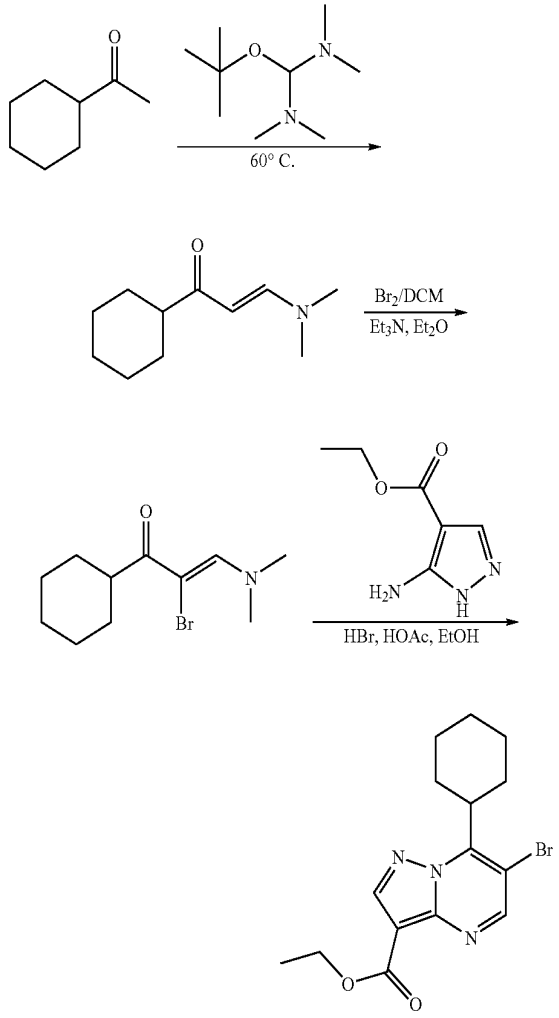


To a solution of 53 mg (0.17 mmol) of 7-cyclohexyl-6-(4-hydroxy-phenyl)-pyrazolo[1,5-a]pyrimidine-3-carbonitrile in 3 mL of dimethylformamide (DMF) was added 72 mg (0.22 mmol) of cesium carbonate (Cs_2CO_3), followed by 0.034 mL (0.22 mmol) of 3-(trifluoromethyl)-benzyl bromide, and the resulting heterogeneous mixture was stirred at rt overnight. The reaction mixture was diluted with water and extracted with ethyl acetate, and the combined organic extracts were concentrated to give a residue which was chromatographed on silica gel (Biotage; DCM) to afford 65 mg (80% yield) of desired 7-cyclohexyl-6-[4-(3-trifluoromethyl-benzyloxy)-phenyl]-pyrazolo[1,5-a]pyrimidine-3-carbonitrile as indicated by ^{1}H NMR; LC-MS—calcd for $C_{27}H_{23}F_3N_4O$ $[M^+ + H]^+$: 477.18, found: 477.1.

Conversion of 7-cyclohexyl-6-[4-(3-trifluoromethyl-benzyloxy)-phenyl]-pyrazolo[1,5-a]pyrimidine-3-carbonitrile to the corresponding tetrazole 7-cyclohexyl-3-(1H-tetrazol-5-yl)-6-[4-(3-trifluoromethyl-benzyloxy)-phenyl]-pyrazolo[1,5-a]pyrimidine (331) was accomplished via a procedure described elsewhere in this document.

Example 22

Synthesis of 6-bromo-7-cyclohexyl-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid ethyl ester



A mixture of 3.0 g (23.8 mmol) of cyclohexyl methyl ketone and 4.56 g (26.2 mmol) of t-butoxybis(dimethylamino)methane (Bredereck's reagent) was stirred at 60° C. overnight. The reaction mixture was then concentrated to give 4.0 g (93% yield) of 1-cyclohexyl-3-dimethylamino-propenone as an orange oil as indicated by ^{1}H NMR. This product was used in the next reaction without any further purification.

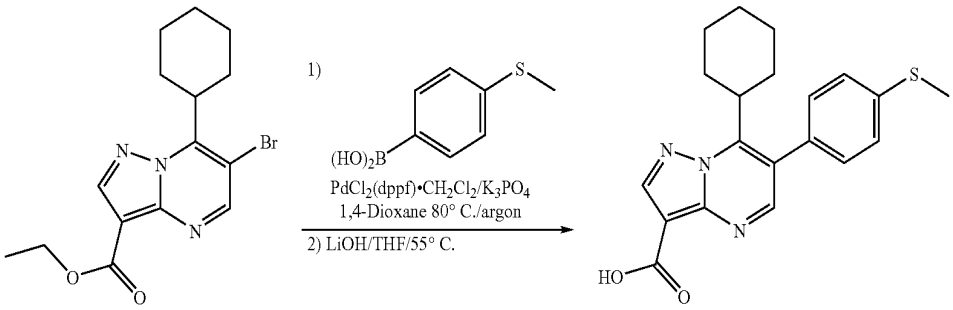
To an ice cold solution of 1.18 g (6.51 mmol) of 1-cyclohexyl-3-dimethylamino-propenone in 8 mL of dichloromethane was added dropwise 1.04 g (6.51 mmol) of bromine via an addition funnel. The reaction mixture was stirred at 0° C. for 0.5 h and then 0.9 mL (6.51 mmol) of triethylamine in 10 mL of ether was added dropwise. The mixture was stirred at 0° C. for 1 h and allowed to warm up to rt. A light yellow solid precipitated from the solution, and it was separated by filtration. The filtrate was then concen-

trated to give 1.69 g of 2-bromo-1-cyclohexyl-3-dimethylamino-propenone as a brown solid as indicated by ^{1}H NMR. The product was used in the next reaction without any further purification.

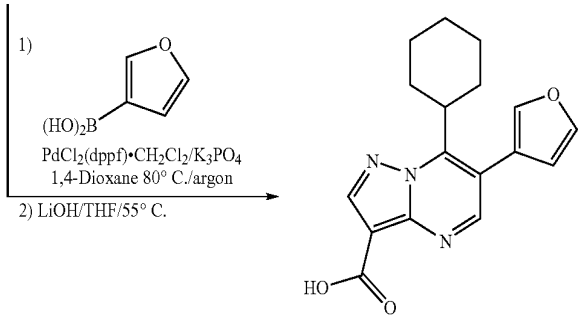
To a mixture of 1.69 g (6.50 mmol) of 2-bromo-1-cyclohexyl-3-dimethylamino-propenone and 1.01 g (6.50 mmol) of 3-amino-1H-pyrazole-4-carboxylic acid ethyl ester in 6 mL of ethanol was added 1.0 mL of 30% hydrogen bromide in acetic acid solution, and the resulting mixture was heated at reflux for 1 h. Then the reaction mixture was cooled to rt and concentrated to give a residue which was chromatographed on silica gel (gradient elution with dichloromethane to 25% ethyl acetate in dichloromethane) to give 620 mg (27% over 2 steps) of 6-bromo-7-cyclohexyl-pyrazolo[1,5-α]pyrimidine-3-carboxylic acid ethyl ester as indicated by ^{1}H NMR (δ 8.70 (s, 1H), 8.49 (s, 1H), 4.44 (q, J=6.8 Hz, 2H), 2.70–2.57 (b, 1H), 1.98–1.90 (m, 2H), 1.87–1.78 (m, 2H), 1.78–1.69 (m, 2H), 1.59–1.42 (m, 4H), 1.43 (t, J=6.8 Hz, 3H)); LC-MS—calcd for $C_{15}H_{18}BrN_3O_2$ $[M^+ + H]^+$: 352.06, found: 352.0.

Example 23

Synthesis of 7-cyclohexyl-6-(4-methanesulfanyl-phenyl)-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid and 7-cyclohexyl-6-furan-3-yl-pyrazolo[1,5-a] pyrimidine-3-carboxylic acid



(472)



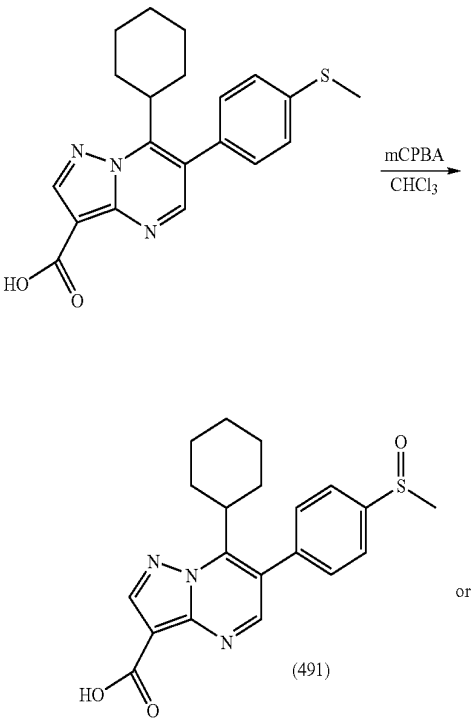
(465)

A mixture of 14 mg (0.085 mmol) of 4-methylsulfanyl-phenylboronic acid, 2 mg (0.0028 mmol) of Pd catalyst, and 45 mg (0.213 mmol) of potassium phosphate was placed into a 4 mL vial. To this mixture 25 mg (0.077 mmol) of 6-bromo-7-cyclohexyl-pyrazolo[1,5-α]pyrimidine-3-carboxylic acid ethyl ester in 1.5 mL of 1,4-dioxane was added, the resulting mixture was flushed with argon and stirred at 80° C. (oil bath) overnight. The reaction mixture was then diluted with ethyl acetate, filtered through a small pad of Celite, and evaporated (savant) to give a residue (crude coupling product). This residue was dissolved in 1 mL of tetrahydrofuran (THF) and treated with 0.5 mL (0.5 mmol) of 1 M LiOH solution, and the resulting mixture was stirred at rt overnight. Since analysis by thin layer chromatography (TLC) revealed that the reaction was not complete, the mixture was then shaken at 55° C. (sand bath) for 15 h. The reaction mixture was diluted with ethyl acetate, and acidified with 1 M HCl solution to pH=2. The organic layer was separated and concentrated (savant) to give a residue which was purified via reverse-phase chromatography (using Gilson) to afford (after lyophilization) 14 mg (56% overall yield) of 7-cyclohexyl-6-(4-methylsulfanyl-phenyl)-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (472) as a solid as indicated by ^{1}H NMR; LC-MS—calcd for $C_{20}H_{21}N_3O_2S$ $[M^+ + H]^+$: 368.14, found: 368.2.

The same experimental procedure was used for the synthesis of 7-cyclohexyl-6-furan-3-yl-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (465) which was obtained as a solid as indicated by ^{1}H NMR; LC-MS—calcd for $C_{17}H_{17}N_3O_3$ $[M^+ + H]^+$: 312.13, found: 312.1.

Example 24

Synthesis of 7-Cyclohexyl-6-(4-methanesulfonyl-phenyl)-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid and 7-Cyclohexyl-6-(4-methanesulfinyl-phenyl)-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid



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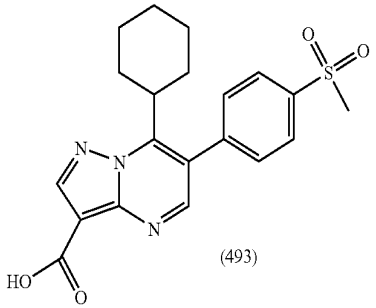
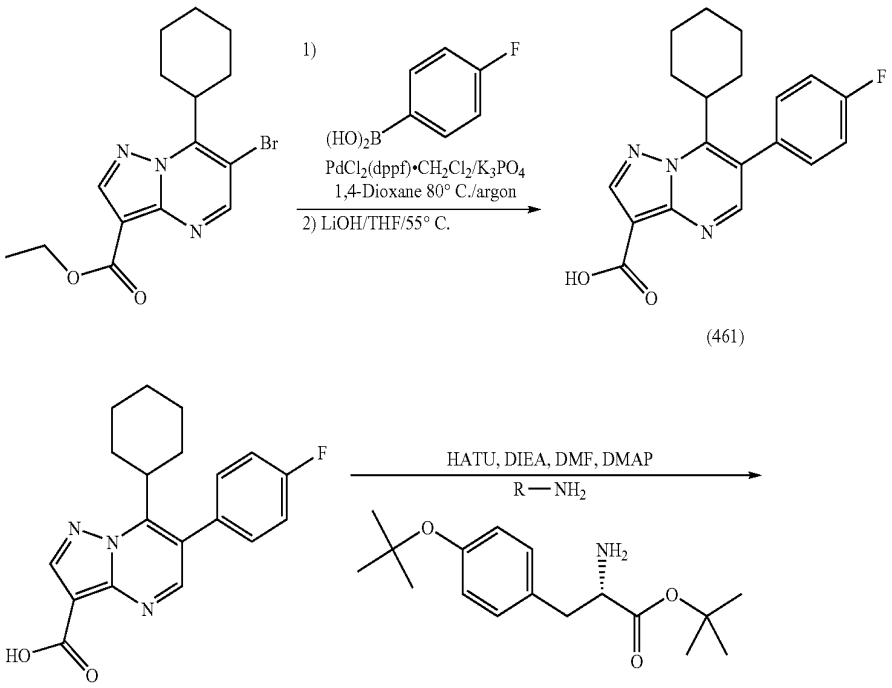


To a cloudy solution of 14 mg (0.038 mmol) of 7-cyclohexyl-6-(4-methylsulfanyl-phenyl)-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid in 2 mL of chloroform was added 9 mg (1.5 equiv) of m-chloroperoxybenzoic acid (mCPBA) and the cloudy solution became clear. Since after 5 min of stirring at rt TLC indicated disappearance of starting material, the mixture was concentrated to a residue which was purified via reverse-phase chromatography (using Gilson) to afford (after lyophilization) 10 mg (69% yield) of 7-cyclohexyl-6-(4-methanesulfinyl-phenyl)-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (491) as a solid as indicated by LC-MS—calcd for $C_{20}H_{21}N_3O_3S$ $[M^+ + H]^+$: 384.13, found: 384.2.

Note that when the same experimental procedure was carried out with 2.2 equiv of mCPBA, 7-Cyclohexyl-6-(4-methanesulfonyl-phenyl)-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (493) was obtained.

Example 25

2-{[7-cyclohexyl-6-(4-fluoro-phenyl)-pyrazolo[1,5-a]pyrimidine-3-carbonyl]-amino}-3-(4-hydroxy-phenyl)-propionic acid



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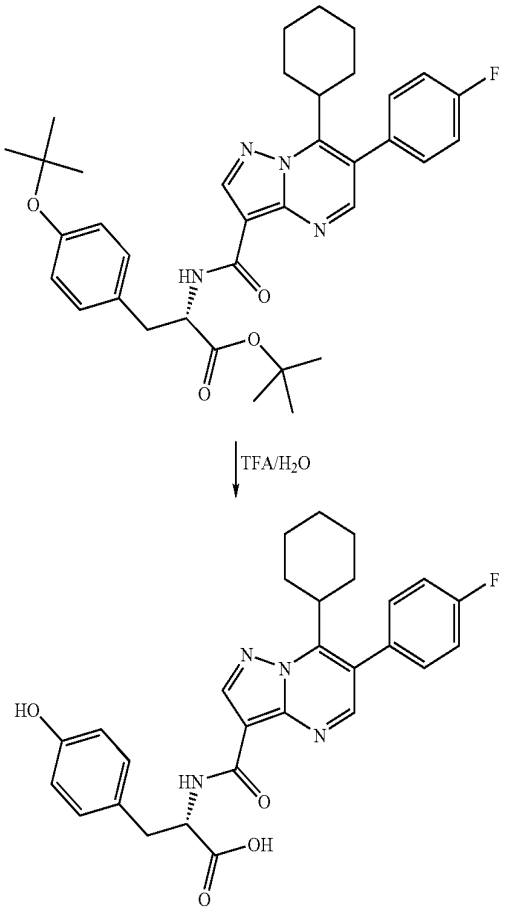


(505)

7-cyclohexyl-6-(4-fluoro-phenyl)-pyrazolo[1,5-α]pyrimidine-3-carboxylic acid (461) was obtained via a Suzuki reaction that was previously described in another section. The analytical data for this compound is given below. δ $CDCl_3$ 8.66 (s, 1H), 8.51 (s, 1H), 7.30–7.27 (m, 2), 7.26–7.21 (m, 2H), 3.26 (m, 1H), 2.59–2.53 (m, 2H), 1.87–1.84 (m, 2H), 1.75–1.68 (m, 3H), 1.40–1.22 (m, 3H). LC-MS calcd. for $C_{19}H_{18}FN_3O_2$ $[M^+ + H]^+$: 340.15; found: 340.1.

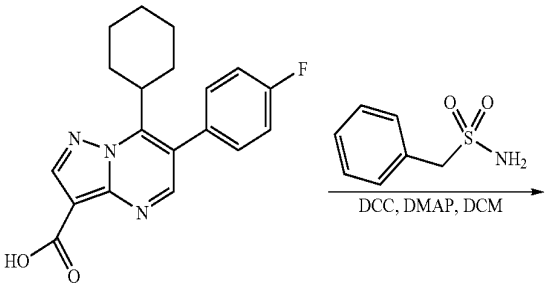
To a solution of 15.0 mg (0.044 mmol) of 7-cyclohexyl-6-(4-fluoro-phenyl)-pyrazolo[1,5-α]pyrimidine-3-carboxylic acid in 2 mL of dimethylformamide (DMF) was added 0.019 mL (0.132 mmol) of diisopropylethylamine (DIEA), a few crystals of dimethylaminopyridine (DMAP cat), 17.4 mg (0.053 mmol) of H-Tyr(tBu)-OtBu.HCl, followed by 20 mg (0.053 mmol) of HATU, and the resulting mixture was stirred at rt overnight. The reaction mixture was diluted with ethyl acetate, washed with 0.1 N sodium hydroxide solution (2 times) and brine. The separated organic layer was dried over sodium sulfate and concentrated to give 3-(4-tert-butoxy-phenyl)-2-{[7-cyclohexyl-6-(4-fluoro-phenyl)-pyrazolo[1,5-α]pyrimidine-3-carbonyl]-amino}-propionic acid tert-butyl ester, which was used without any further purification in the next step.

A sample of crude 3-(4-tert-butoxy-phenyl)-2-{[7-cyclohexyl-6-(4-fluoro-phenyl)-pyrazolo[1,5-α]pyrimidine-3-carbonyl]-amino}-propionic acid tert-butyl ester was treated with 1 mL of 95:5 trifluoroacetic acid (TFA): H_2O and the resulting solution was stirred at rt for 1 h. Then the reaction mixture was quenched with 2 mL of 1:1 acetonitrile:water, concentrated, and the residue was purified via reverse-phase chromatography to afford (after lyophilization)10 mg (45% yield over two steps) of desired 2-{[7-cyclohexyl-6-(4-fluoro-phenyl)-pyrazolo[1,5-a]pyrimidine-3-carbonyl]-amino}-3-(4-hydroxy-phenyl)-propionic acid (505) as a solid as indicated by ^1H NMR; LC-MS calcd. for $C_{28}H_{27}FN_4O_4$ $[M^+ + H]^+$: 503.2; found: 503.2.

Note that in the cases where methyl or ethyl esters were utilized a second deprotection step, a typical aqueous LiOH mediated saponification, was employed to generate the requisite carboxylic acid.

Example 26

Synthesis of N-[7-cyclohexyl-6-(4-fluoro-phenyl)-pyrazolo[1,5-a]pyrimidine-3-carbonyl]-C-phenyl-methanesulfonamide



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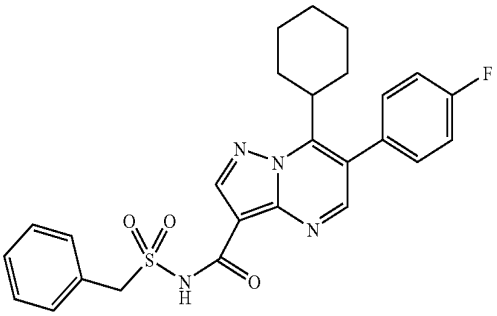
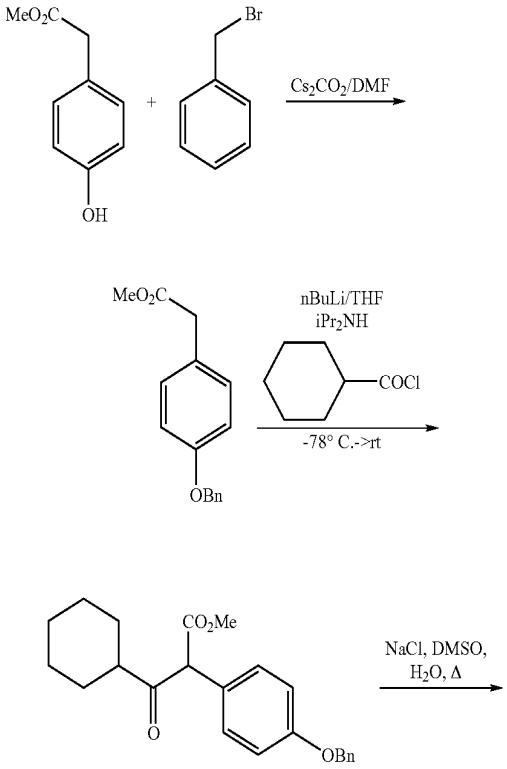


To a solution of 20 mg (0.059 mmol) of 7-cyclohexyl-6-(4-fluoro-phenyl)-pyrazolo[1,5-α]pyrimidine-3-carboxylic acid in 2 mL of dichloromethane (DCM) was a few crystals of DMAP (cat), 12 mg (0.071 mmol) of toluenesulfonamide, followed by 0.071 mL (0.071 mmol) of 1 M dicyclohexylcarbodiimide(DCC) solution in DCM. The reaction mixture was stirred at rt overnight, concentrated, and the resulting residue was purified by reverse-phase chromatography (Gilson) to afford (after lyophilization) 15 mg (51% yield) of desired N-[7-cyclohexyl-6-(4-fluoro-phenyl)-pyrazolo[1,5-α]pyrimidine-3-carbonyl]-C-phenyl-methanesulfonamide (533) as a solid as indicated by ^{1}H NMR; LC-MS calcd. for $C_{26}H_{25}FN_4O_3S$ $[M^+ + H]^+$: 493.16; found: 493.1.

Example 27

Synthesis of 6-(4-benzyloxy-phenyl)-3-bromo-7-cyclohexyl-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid



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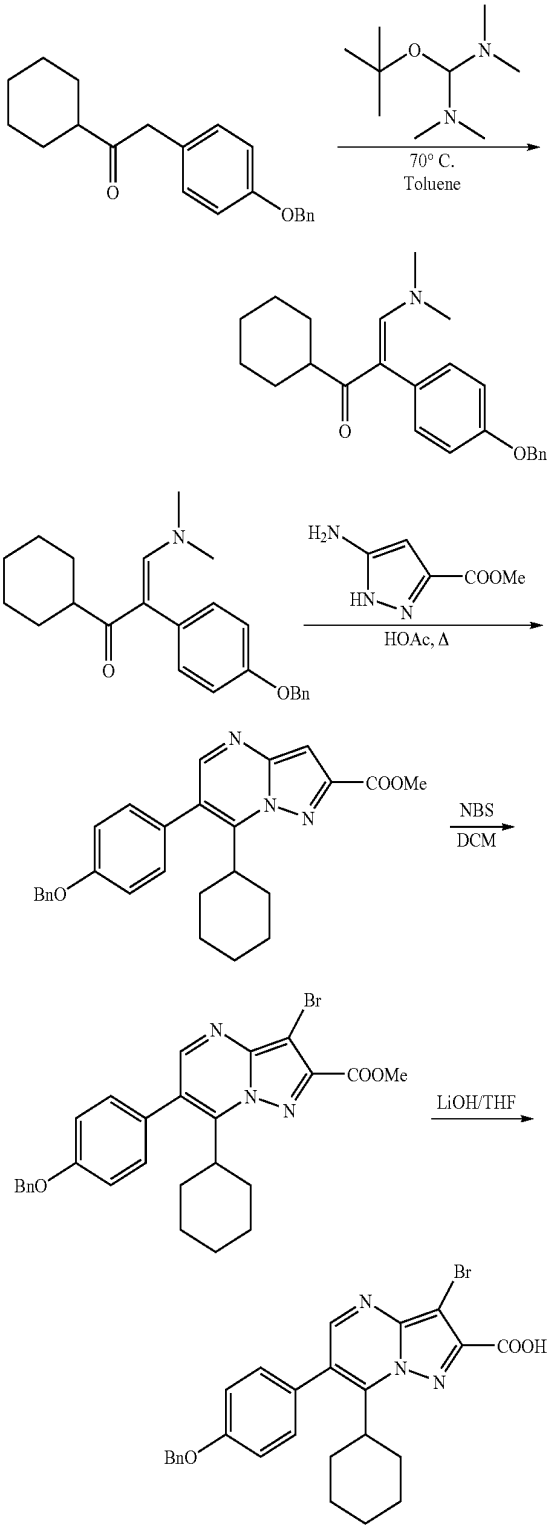


A solution of 0.718 g (1.97 mmol) of 2-(4-benzyloxy-phenyl)-1-cyclohexyl-3-dimethylamino-propenone and 0.28 g (1.97 mmol) of 5-amino-1H-pyrazole-3-carboxylic acid methyl ester in 20 mL of acetic acid (HOAc) was heated at reflux overnight. The reaction mixture was cooled to rt and concentrated to give a residue which was chromatographed on silica gel (5% ethyl acetate in dichloromethane) to afford 0.643 g (74% yield) of 6-(4-benzyloxy-phenyl)-7-cyclo-

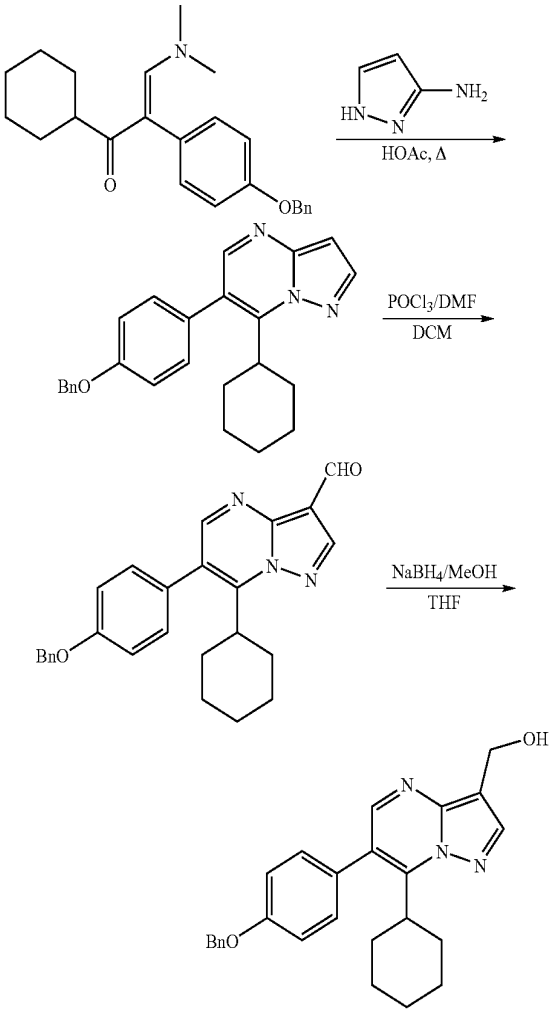
hexyl-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid methyl ester as a beige solid as indicated by ^{1}H NMR.

To an ice cold solution of 50 mg (0.113 mmol) of 6-(4-benzyloxy-phenyl)-7-cyclohexyl-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid methyl ester in 2 mL of dichloromethane (DCM) was added a solution of 21 mg (0.118 mmol) of N-bromosuccinimide (NBS) in 1 mL of DCM and the resulting mixture was allowed to warm up to rt and stirred at rt overnight. The reaction mixture was concentrated to give a residue which was chromatographed on silica gel (5% ethyl acetate in dichloromethane) to afford 7 mg (11% yield) of 6-(4-benzyloxy-phenyl)-3-bromo-7-cyclohexyl-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid methyl ester as a colorless oil as indicated by ^{1}H NMR (90% purity); LC-MS—calcd for $C_{27}H_{26}BrN_3O_3$ $[M^+ + H]^+$: 520.12, found: 520.0.

Saponification of 6-(4-benzyloxy-phenyl)-3-bromo-7-cyclohexyl-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid methyl ester to the carboxylic acid (477) was carried out utilizing a previously described procedure.

Example 28

Synthesis of [6-(4-benzyloxy-phenyl)-7-cyclohexyl-pyrazolo[1,5-a]pyrimidin-3-yl]-methanol



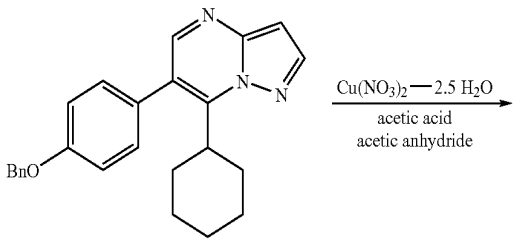
A solution of 4.37 g (12 mmol) of 2-(4-benzyloxy-phenyl)-1-cyclohexyl-3-dimethylamino-propenone and 1.0 g (12 mmol) of 1H-pyrazol-3-ylamine in 40 mL of acetic acid (HOAc) was heated at reflux overnight. The reaction mixture was cooled to rt and concentrated to give a beige solid residue which was chromatographed on silica gel (2% ethyl acetate in dichloromethane) to afford 3.38 g (74% yield) of 6-(4-benzyloxy-phenyl)-7-cyclohexyl-pyrazolo[1,5-a]pyrimidine as a white solid as indicated by ^{1}H NMR.

To an ice cold solution of 300 mg (0.78 mmol) of 6-(4-benzyloxy-phenyl)-7-cyclohexyl-pyrazolo[1,5-a]pyrimidine in 2 mL of dimethylformamide (DMF) and 1 mL of dichloromethane (DCM) was added 0.085 mL (0.9 mmol) of phosphorus oxychloride ($POCl_3$) and the resulting mixture was allowed to warm up to rt and stirred at rt for 4 h when analysis by thin layer chromatography (TLC) indicated complete conversion of starting material to product. The reaction mixture poured into ice-water, and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over sodium sulfate and evaporated to give 335 mg of 6-(4-benzyloxy-phenyl)-7-cyclohexyl-pyrazolo[1,5-a]pyrimidine-3-carbaldehyde (436) as a beige solid as indicated by ^{1}H NMR; LC-MS—calcd for $C_{26}H_{25}N_3O_2$ $[M^+ + H]^+$: 412.19, found: 412.1.

To a stirred solution of 4.4 mg (0.115 mmol) of sodium borohydride ($NaBH_4$) in 2 mL of methanol (MeOH) was added a solution of 35 mg (0.104 mmol) of 6-(4-benzyloxy-phenyl)-7-cyclohexyl-pyrazolo[1,5-a]pyrimidine-3-carbaldehyde in 3 mL of tetrahydrofuran (THF) and the resulting mixture was stirred at rt for 30 min when analysis by TLC indicated complete conversion of starting material to product. The reaction mixture was quenched by the addition of saturated ammonium chloride solution, and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over sodium sulfate and evaporated to give (after lyophilization) 20 mg (47% yield) of [6-(4-benzyloxy-phenyl)-7-cyclohexyl-pyrazolo[1,5-a]pyrimidin-3-yl]-methanol (479) as a white solid (85% purity) as indicated by ^{1}H NMR (containing small traces of starting material); LC-MS—calcd for $C_{26}H_{27}N_3O_2$ $[M^+ + H]^+$: 414.21, found: 414.2.

Example 29

Synthesis of cyclopropanecarboxylic acid [6-(4-benzyloxy-phenyl)-7-cyclohexyl-pyrazolo[1,5-a]pyrimidin-3-yl]-amide and ethanesulfonic acid [6-(4-benzyloxy-phenyl)-7-cyclohexyl-pyrazolo[1,5-a]pyrimidin-3-yl]-amide



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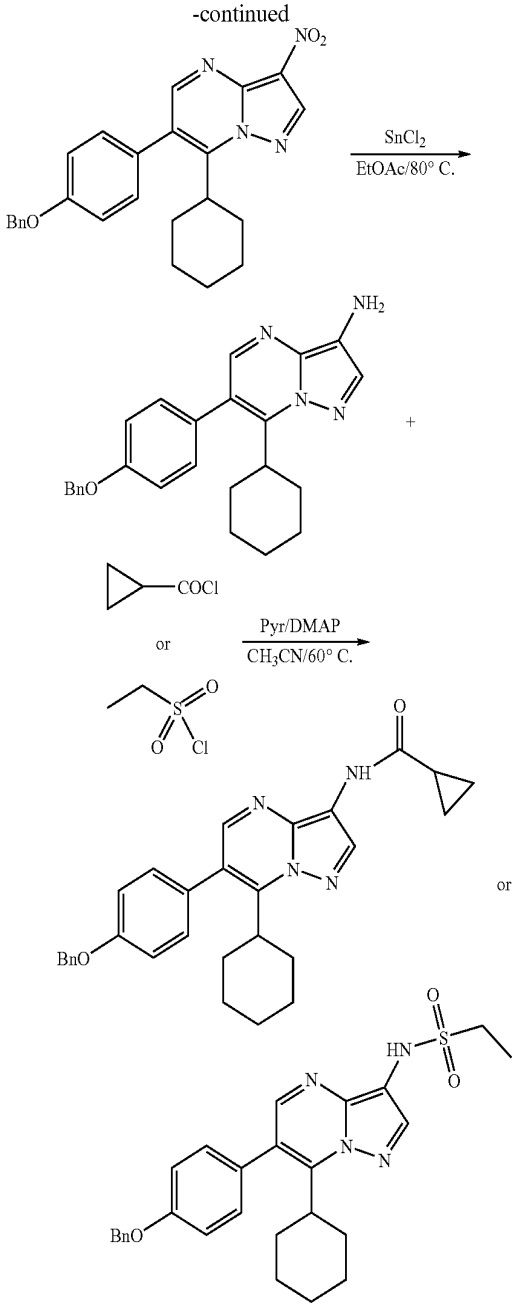


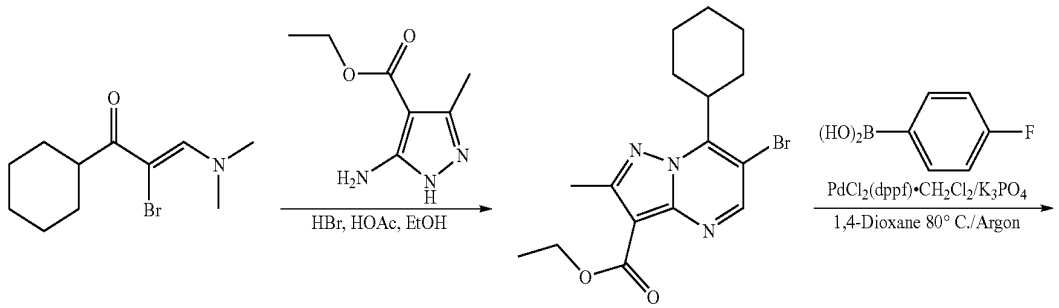
To a mixture of 25 mg (0.109 mmol) of copper (II) nitrate dihydrate ($Cu(NO_3)_2$-2.5 H_2O) in 1.5 mL of acetic acid and 3 mL of acetic anhydride at 35° C. was added portionwise (over 15 min) 40 mg (0.104 mmol) of 6-(4-benzyloxy-phenyl)-7-cyclohexyl-pyrazolo[1,5-a]pyrimidine and the resulting mixture was stirred at 35° C. overnight. The reaction mixture was diluted with dichloromethane, and washed with 0.1 N sodium hydroxide solution, water and brine. The organic extract was dried over sodium sulfate and evaporated to give 43 mg of purple residue which was chromatographed on silica gel (Biotage; dichloromethane) to afford 18 mg (41%) of 6-(4-benzyloxy-phenyl)-7-cyclohexyl-3-nitro-pyrazolo[1,5-a]pyrimidine as an off-white residue (90% purity) as indicated by ^{1}H NMR; LC-MS—calcd for $C_{25}H_{24}N_4O_3$ $[M^+ + H]^+$: 429.18, found: 429.2.

To a solution of 18 mg (0.042 mmol) of 6-(4-benzyloxy-phenyl)-7-cyclohexyl-3-nitro-pyrazolo[1,5-a]pyrimidine in 3 mL of ethyl acetate (EtOAc) was added 40 mg (0.21 mmol) of tin (II) chloride ($SnCl_2$) and the resulting mixture was stirred at 80° C. under argon for 8 h when analysis by TLC indicated only 75% conversion of starting material to product. Therefore, 40 mg (0.21 mmol) of tin (II) chloride ($SnCl_2$) was added, the reaction mixture was heated at 80° C. for 8 h when analysis by TLC indicated complete conversion of starting material to product. The mixture was diluted with ethyl acetate, washed with saturated sodium bicarbonate solution, water, brine, dried over sodium sulfate and evaporated to give (after lyophilization) 6 mg (36% yield) of 6-(4-benzyloxy-phenyl)-7-cyclohexyl-pyrazolo[1,5-a]pyrimidin-3-ylamine as a yellow solid as indicated by ^{1}H NMR; LC-MS—calcd for $C_{25}H_{26}N_4O$ $[M^+ + H]^+$: 399.21, found: 399.2.

To a solution of 30 mg (0.075 mmol) 6-(4-benzyloxy-phenyl)-7-cyclohexyl-pyrazolo[1,5-a]pyrimidin-3-ylamine in 2 mL of acetonitrile (CH_3CN) was added 0.018 mL (0.225 mmol) of pyridine (pyr), followed by 16 mg (0.2 mmol) of cyclopropylcarbonyl chloride or 19 mg (0.15 mmol) of ethanesulfonyl chloride, and 1 mg of dimethylaminopyridine (DMAP) and the resulting mixture was stirred at 60° C. overnight. Since analysis by LC-MS revealed product formation, the reaction mixture was concentrated to give a residue which was purified via reverse-phase chromatography to afford (after lyophilization) 17 mg (49% yield) of cyclopropanecarboxylic acid [6-(4-benzyloxy-phenyl)-7-cyclohexyl-pyrazolo[1,5-a]pyrimidin-3-yl]-amide (415) as a yellow solid or 17 mg (46% yield) of ethanesulfonic acid [6-(4-benzyloxy-phenyl)-7-cyclohexyl-pyrazolo[1,5-a]pyrimidin-3-yl]-amide (421) as a yellow solid as indicated by LC-MS—calcd for $C_{29}H_{30}N_4O_2$ $[M^+ + H]^+$: 467.24, found: 467.2; calcd for $C_{27}H_{30}N_4O_3S$ $[M^+ + H]^+$: 491.2, found: 491.2.

Example 30

Synthesis of 2-{[7-Cyclohexyl-6-(4-fluoro-phenyl)-2-methyl-pyrazolo[1,5-a]pyrimidine-3-carbonyl]-amino}-3-(4-hydroxy-phenyl)-propionic acid



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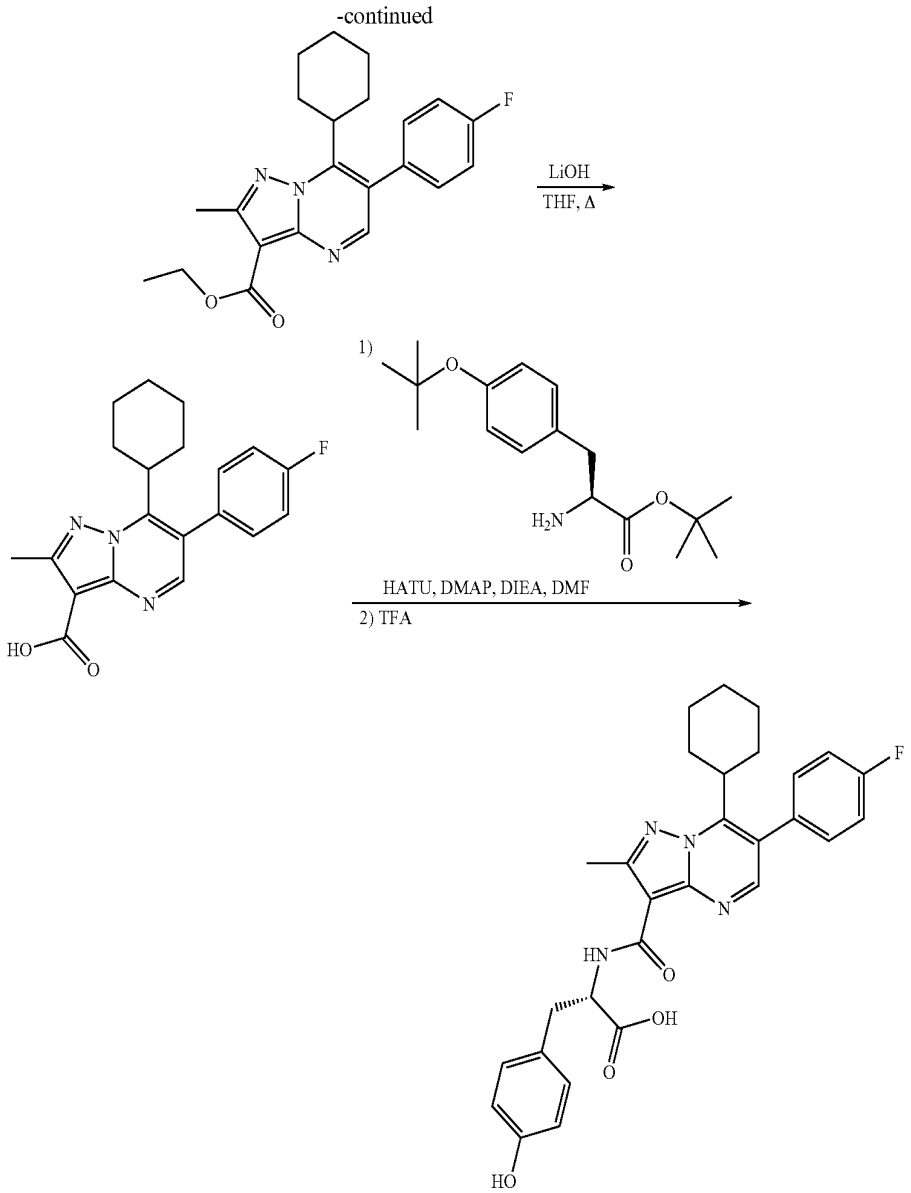


A solution of 1.04 (4 mmol) of 2-bromo-1-cyclohexyl-3-dimethylamino-propenone and 0.676 g (4 mmol) of 5-amino-3-methyl-1H-pyrazole-4-carboxylic acid ethyl ester in 10 mL of ethanol was added 0.65 mL of 30% hydrogen bromide in acetic acid solution, and the resulting mixture was heated at reflux for 1 h. The reaction mixture was cooled to rt and concentrated to give a brown residue which sonicated with 30% ethyl acetate in hexane to give a precipitate which was filtered, and then washed twice with ethyl acetate. The combined organic extracts were evaporated to give 1.32 g of a orange solid which was chromatographed on silica gel (gradient elution with dichloromethane, followed by 2% to 10% ethyl acetate in dichloromethane) to afford 0.756 g (52%) of 6-bromo-7-cyclohexyl-2-methyl-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid ethyl ester as a yellow solid as indicated by ^{1}H NMR; LC-MS—calcd for $C_{16}H_{20}BrN_3O_2$ $[M^+ + H]^+$: 366.07, found: 366.1.

A mixture of 187 mg (0.5 mmol) of 6-bromo-7-cyclohexyl-2-methyl-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid ethyl ester, 105 mg (0.75 mmol, 1.5 equiv) of 4-fluorophenylboronic acid, 20 mg (0.025 mmol, 5 mol %) of Pd catalyst, and 318 mg (1.5 mmol, 3 equiv) of potassium phosphate was placed into a carousel tube. After a vacuum and argon cycle, 1,4-dioxane (7 mL) was added, and the resulting mixture was heated at 80° C. under argon for 14 h. The reaction mixture was diluted with ethyl acetate, filtered through a small pad of Celite, dried over sodium sulfate and evaporated to give a brown residue which was chromatographed on silica gel (gradient elution with 2%, 5% to 10% ethyl acetate in dichloromethane) to afford 0.178 g (94%) of 7-cyclohexyl-6-(4-fluoro-phenyl)-2-methyl-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid ethyl ester as an off-white solid as indicated by ^{1}H NMR; LC-MS—calcd for $C_{22}H_{24}FN_3O_2$ $[M^+ + H]^+$: 382.19, found: 382.1.

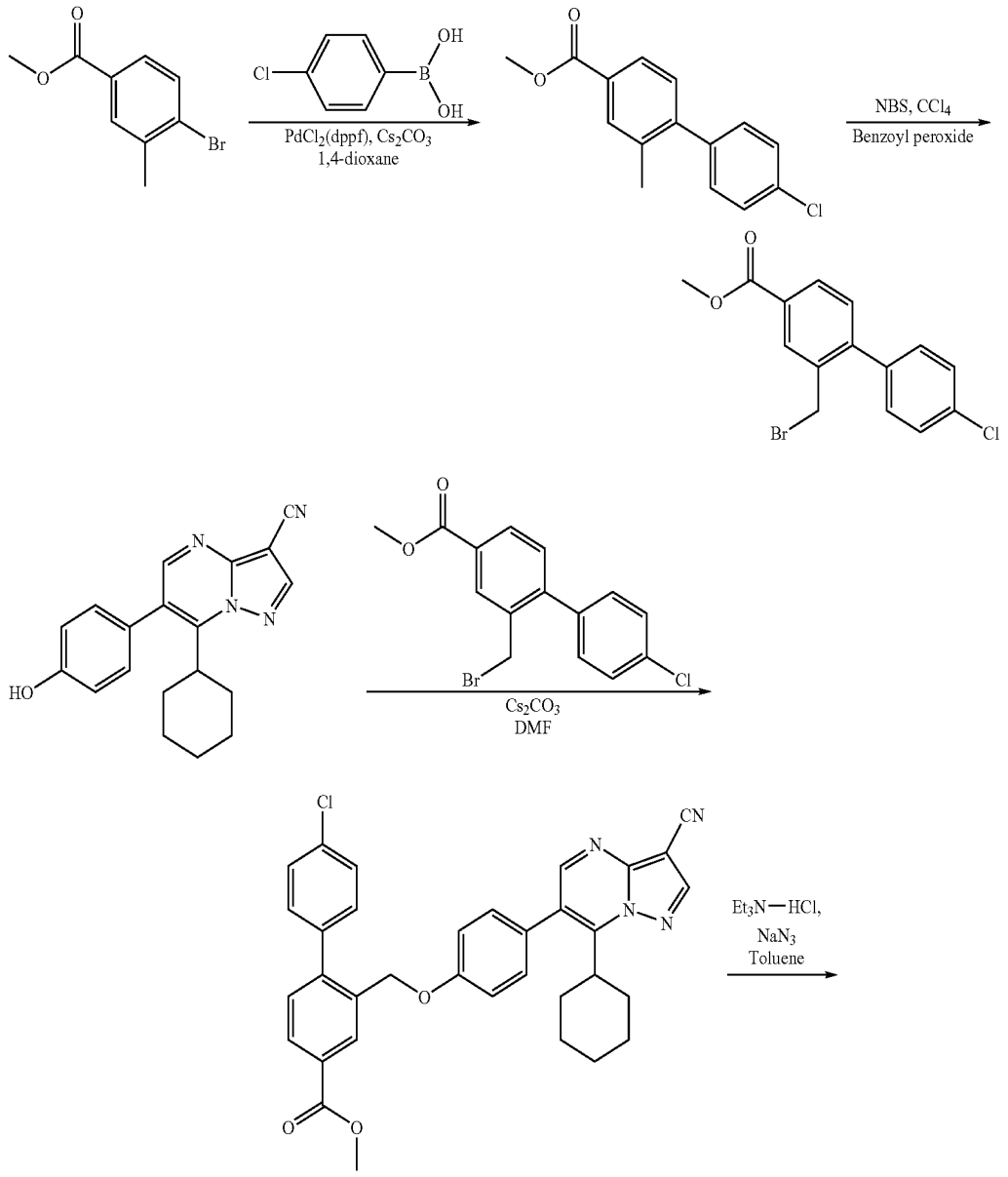
To a solution of 178 mg (0.46 mmol) of 7-cyclohexyl-6-(4-fluoro-phenyl)-2-methyl-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid ethyl ester in 9 mL of tetrahydrofuran was added 2.8 mL (2.8 mmol) of 1 M LiOH solution, and the mixture was heated at reflux for 15 h. Since analysis by TLC

revealed that starting material was still present, 2.8 mL (2.8 mmol) of 1 M LiOH solution was added, and reflux was continued for 60 h. The reaction mixture was then cooled to rt, concentrated, diluted with water, acidified with 10% HCl solution to pH=2, and extracted with ethyl acetate. The combined organic extracts were dried over sodium sulfate, and evaporated to give 156 mg (96% yield, 90% purity) of 7-cyclohexyl-6-(4-fluoro-phenyl)-2-methyl-pyrazolo[1,5-a] pyrimidine-3-carboxylic acid (515) as a beige solid as indicated by ^{1}H NMR; LC-MS—calcd for $C_{20}H_{20}FN_3O_2$ $[M^+ + H]^+$: 354.15, found: 354.2.

A solution of 36 mg (0.1 mmol) 7-cyclohexyl-6-(4-fluoro-phenyl)-2-methyl-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid in 2 mL of dimethylformamide was cooled at 0° C. To the above cold solution was added 0.053 mL (0.3 mmol) of N,N-diisopropylethylamine (DIEA), followed by 38 mg (0.1 mmol) of HATU, and 37 mg (0.11 mmol) of 2-amino-3-(4-tert-butoxy-phenyl)-propionic acid tert-butyl ester, and a few crystals of 4-dimethylaminopyridine (DMAP), and the resulting mixture was allowed to warm up to rt, and stirred at rt overnight. The reaction mixture was then diluted with ethyl acetate, washed with 0.1 N NaOH solution, water, and brine, dried over sodium sulfate and evaporated to give a residue which was treated with 2 mL of 95:5 trifluoroacetic acid (TFA):water, and stirred at rt for 2.5 h. The mixture was quenched by the addition of 10 mL of 1:1 acetonitrile:water solution, and concentrated to give a residue which was purified via reverse-phase chromatography using Gilson to afford (after lyophilization) 8 mg (16% over 2 steps) of 2-{[7-Cyclohexyl-6-(4-fluoro-phenyl)-2-methyl-pyrazolo [1,5-a]pyrimidine-3-carbonyl]-amino}-3-(4-hydroxy-phenyl)-propionic acid as a white solid (92% purity, entry 517), as indicated by ^{1}H-NMR. (LC-MS calcd for $C_{29}H_{29}FN_4O_4$ $[M+H]^+$ 517.22; found 517.2).

Example 31

Synthesis of 4'-chloro-2-{4-[7-cyclohexyl-3-(1H-tetrazol-5-yl)-pyrazolo[1,5-a]pyrimidin-6-yl]-phenoxymethyl}-biphenyl-4-carboxylic acid



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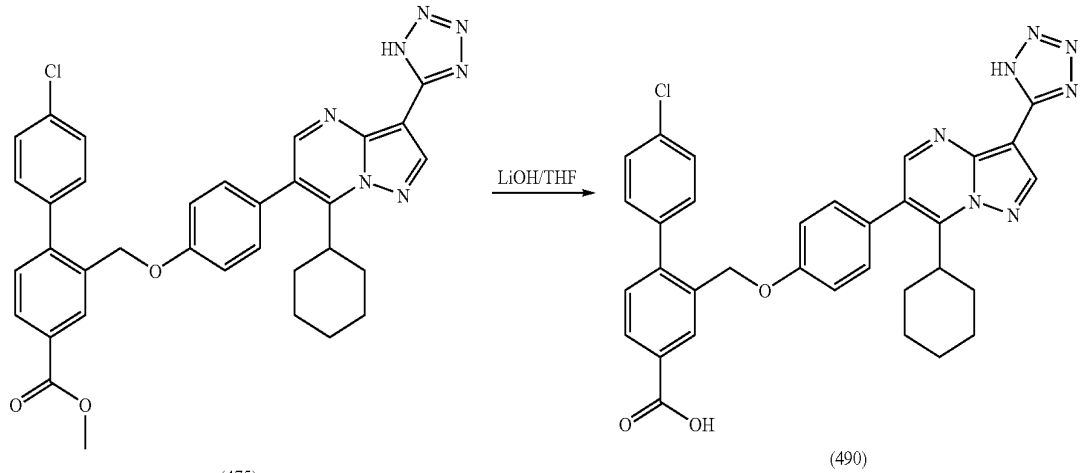


(475) (490)

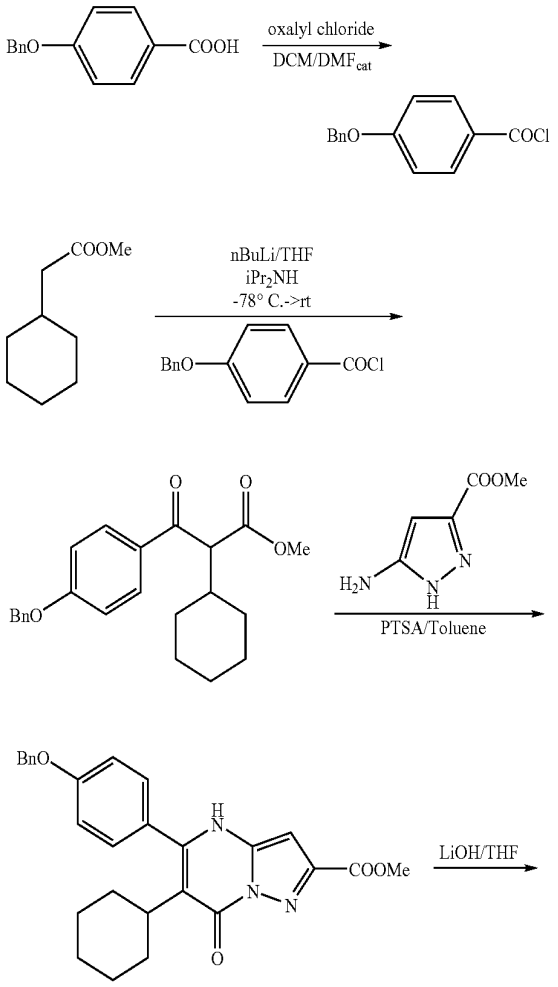
A mixture of 250 mg (1.09 mmol) of 4-bromo-3-methylbenzoic acid methyl ester, 204 mg (1.31 mmol) of 4-chlorophenylboronic acid, 1.06 g (3.27 mmol) of cesium carbonate (Cs_2CO_3) and $PdCl_2$(dppf) catalyst (5 mol %) was flushed with argon. To this mixture was added 3 mL of 1,4-dioxane and the reaction mixture was heated to 80° C. overnight. The mixture was then cooled to rt, and filtered through a pad of Celite while rinsing the pad with ethyl acetate. The filtrate was washed with brine, dried over sodium sulfate and concentrated to give a residue which was chromatographed on silica gel (5% ethyl acetate in hexane) to afford 191 mg (67%) of desired 4'-chloro-2-methylbiphenyl-4-carboxylic acid methyl ester, as an oil as indicated by ^{1}H NMR; LC-MS calcd for $C_{15}H_{13}ClO_2$ $[M^+ + H]^+$: 261.07, found: 261.1.

To a solution of 191 mg (0.73 mmol) of 4'-chloro-2-methyl-biphenyl-4-carboxylic acid methyl ester in 4 mL of carbon tetrachloride (CCl_4) was added 9.7 mg (0.04 mmol) of benzoyl peroxide, followed by 124 mg (0.696 mmol) of N-bromosuccinimide (NBS), and the reaction mixture was heated at reflux for 6 h. The mixture was cooled to rt, diluted with dichloromethane and washed with water and brine. The organic layer was dried over sodium sulfate and concentrated to give 132 mg (53%) of 2-bromomethyl-4'-chloro-biphenyl-4-carboxylic acid methyl ester, as an oil, which was used without any further purification in the next step. ^{1}H NMR δ $CDCl_3$ 8.10 (s, 1H), 7.91–7.89 (d, J=8.0 Hz, 1H), 7.37–7.35 (d, J=8.3 Hz, 2H), 7.30–7.18 (d, J=8.7 Hz, 2H), 7.22–7.20 (d, J=8.0 Hz, 1H), 4.30 (s, 2H), 3.87 (s, 3H).

Alkylation of 7-cyclohexyl-6-(4-hydroxy-phenyl)-pyrazolo[1,5-a]pyrimidine-3-carbonitrile with 2-bromomethyl-4'-chloro-biphenyl-4-carboxylic acid methyl ester was carried out in dimethylformamide (DMF) using cesium carbonate and following a previously described experimental procedure to give 4'-chloro-2-[4-(3-cyano-7-cyclohexyl-pyrazolo[1,5-a]pyrimidin-6-yl)-phenoxymethyl]-biphenyl-4-carboxylic acid methyl ester. This compound was converted to its corresponding tetrazole 4'-chloro-2-{4-[7-cyclohexyl-3-(1H-tetrazol-5-yl)-pyrazolo[1,5-a]pyrimidin-6-yl]-phenoxymethyl}-biphenyl-4-carboxylic acid methyl ester (475) via a previously described procedure. Finally, 4'-chloro-2-{4-[7-cyclohexyl-3-(1H-tetrazol-5-yl)-pyrazolo[1,5-a]pyrimidin-6-yl]-phenoxymethyl}-biphenyl-4-carboxylic acid (490) was obtained following a standard LiOH saponification protocol.

Example 32

Synthesis of 5-(4-benzyloxy-phenyl)-6-cyclohexyl-7-oxo-4,7-dihydro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid



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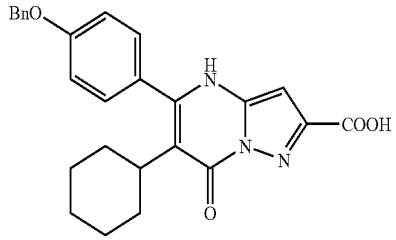


(538)

To a mixture of 5.0 g (21.9 mmol) of 4-benzyloxy-benzoic acid in 25 mL of dichloromethane (DCM) was added dropwise 10 mL (114 mmol) of oxalyl chloride, followed by 5 μL of dimethylformamide (DMF cat) and the reaction mixture was heated at reflux for 3 h, and concentrated to give 5.32 g (98%) of desired 4-benzyloxy-benzoyl chloride as a yellow solid as indicated by ^{1}H NMR. The product was used without any further purification in the next step.

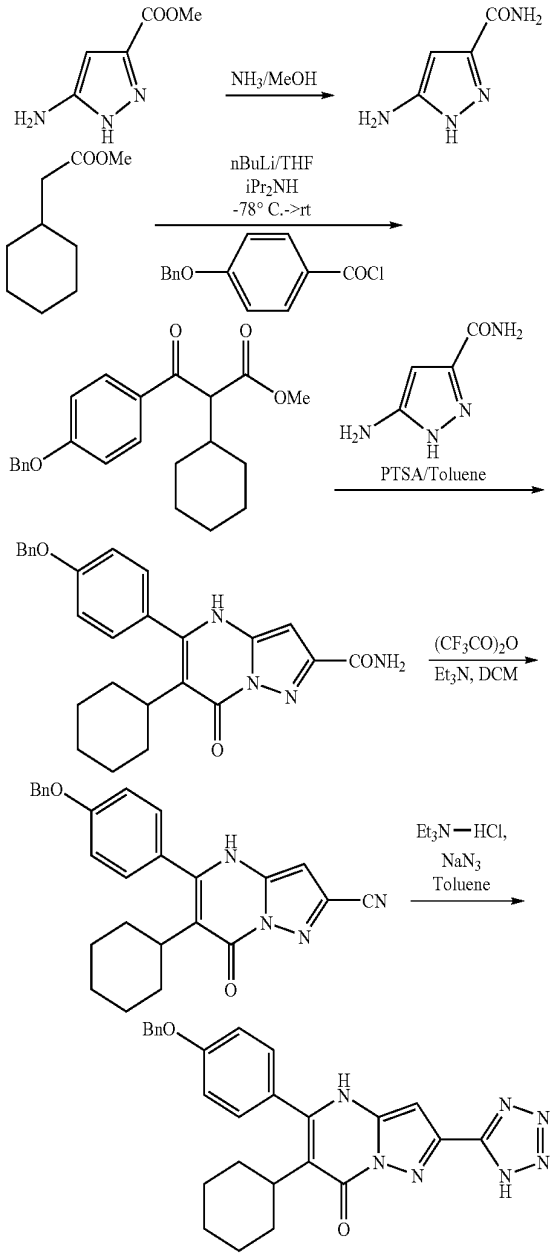
A solution of 0.35 mL (2.5 mmol) of diisopropylamine (iPr_2NH) in 7 mL of tetrahydrofuran (THF) was flushed with argon and cooled to −78° C. To this solution was added dropwise 1 mL (2.5 mmol) of n-butyllithium (nBuLi) 2.5 M solution in hexane, and the resulting mixture was stirred at −78° C. for 20 min, after which time 0.33 mL (2 mmol) of methyl cyclohexylacetate was added dropwise. The mixture was allowed to warm up to rt for 40 min, then it was cooled again to −78° C., and a solution of 0.592 g (2.4 mmol) of 4-benzyloxy-benzoyl chloride in 8 mL of THF was added dropwise, and the resulting mixture was allowed to warm up to rt, and stirred at rt overnight under argon. The reaction mixture was quenched on ice by the addition of saturated ammonium chloride solution, and extracted with ethyl acetate. The combined organic extracts were washed with water, brine, dried over sodium sulfate and concentrated to give 0.83 g of a yellow solid residue which was chromatographed on silica gel (Biotage; 25% hexane in dichloromethane) to afford 0.306 g (42% yield) of desired 3-(4-benzyloxy-phenyl)-2-cyclohexyl-3-oxo-propionic acid methyl ester as a white solid as indicated by ^{1}H NMR; LC-MS—calcd for $C_{23}H_{26}O_4$ $[M^+ + H]^+$: 367.18, found: 367.2.

A mixture of 274 mg (0.747 mmol) of 3-(4-benzyloxy-phenyl)-2-cyclohexyl-3-oxo-propionic acid methyl ester, 106 mg (0.747 mmol) of 5-amino-1H-pyrazole-3-carboxylic acid methyl ester, 15 mg (10 mol %) of p-toluenesulfonic acid monohydrate (PTSA), and 10 mL of toluene was heated at reflux for 88 h. The reaction mixture was then concentrated to a residue which was chromatographed on silica gel (Biotage; gradient elution 2% to 20% ethyl acetate in dichloromethane) to afford 55 mg (16% yield) of desired 5-(4-benzyloxy-phenyl)-6-cyclohexyl-7-oxo-4,7-dihydro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid methyl ester as a solid as indicated by ^{1}H NMR; LC-MS—calcd for $C_{27}H_{27}N_3O_4$ $[M^+ + H]^+$: 458.2, found: 458.2.

This material was then converted to 5-(4-benzyloxy-phenyl)-6-cyclohexyl-7-oxo-4,7-dihydro-pyrazolo[1,5-a] pyrimidine-2-carboxylic acid via the well known LiOH saponification protocol (55% yield, entry 538); LC-MS—calcd for $C_{26}H_{25}N_3O_4$ $[M^+ + H]^+$: 444.18, found: 444.2.

Example 33

Synthesis of 5-(4-benzyloxy-phenyl)-6-cyclohexyl-2-(1H-tetrazol-5-yl)-4H-pyrazolo[1,5-a]pyrimidin-7-one



(551)

A solution of 1.0 g (7 mmol) of 5-amino-1H-pyrazole-3-carboxylic acid methyl ester in 10 mL of methanol (MeOH) in a sealed tube was saturated with ammonia (NH_3), and the sealed tube mixture was stirred at rt overnight. Since analysis by thin layer chromatography (TLC) revealed that the reaction was not complete, the mixture was then heated at 80° for 1 day. The reaction mixture was then cooled, the sealed tube was opened, and the solvent was evaporated to give 0.9 g of desired 5-amino-1H-pyrazole-3-carboxylic acid amide as indicated by ^{1}H NMR; LC-MS—calcd for $C_4H_6N_4O$ $[M^+ + H]^+$: 127.05, found: 127.2.

The preparation of 3-(4-benzyloxy-phenyl)-2-cyclohexyl-3-oxo-propionic acid methyl ester is described elsewhere in this document.

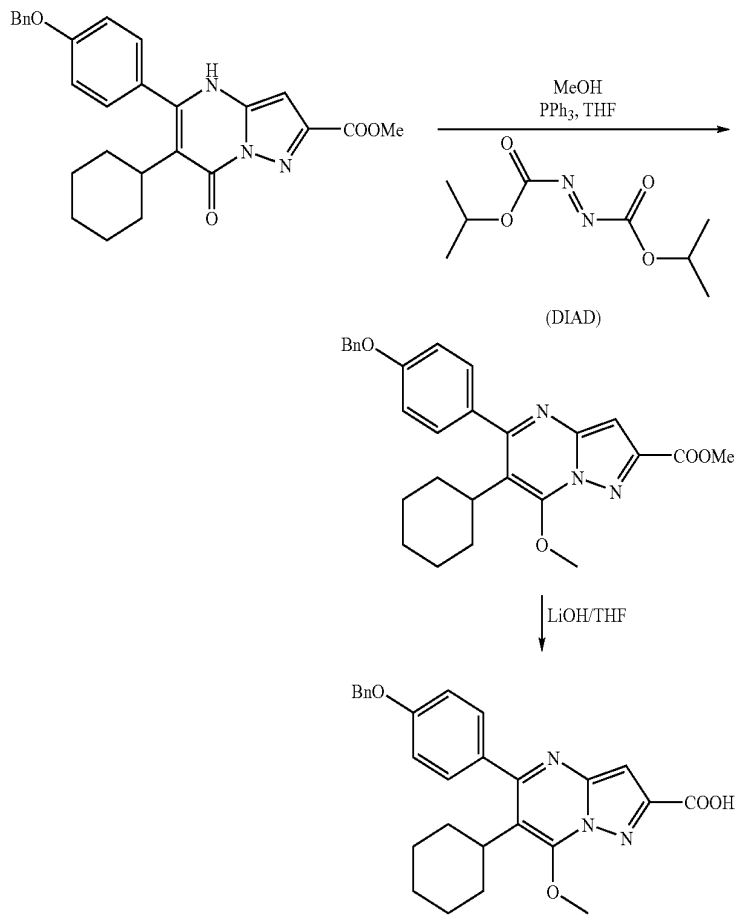
A mixture of 1.0 g (2.7 mmol) of 3-(4-benzyloxy-phenyl)-2-cyclohexyl-3-oxo-propionic acid methyl ester, 340 mg (2.7 mmol) of 5-amino-1H-pyrazole-3-carboxylic acid amide, 51 mg (10 mol %) of p-toluenesulfonic acid monohydrate (PTSA), and 15 mL of toluene was heated at reflux for 72 h. The reaction mixture was then concentrated to a residue which chromatographed on silica gel (Biotage; gradient elution 15% ethyl acetate in dichloromethane to 6% methanol in dichloromethane) to give a residue which was further purified via reverse-phase chromatography (Gilson) to afford (after lyophilization) 22 mg (2% yield) of desired 5-(4-benzyloxy-phenyl)-6-cyclohexyl-7-oxo-4,7-dihydro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid amide as indicated by ^{1}H-NMR; LC-MS calcd for $C_{26}H_{26}N_4O_3$ $[M^+ + H]^+$: 443.2, found: 443.2.

and concentrated to a residue which was purified via reverse-phase chromatography to afford (after lyophilization) 3 mg (14% yield) of desired 5-(4-benzyloxy-phenyl)-6-cyclohexyl-7-oxo-4,7-dihydro-pyrazolo[1,5-a]pyrimidine-2-carbonitrile as indicated by LC-MS calcd for $C_{26}H_{24}N_4O_2$ $[M^+ + H]^+$: 425.19, found: 425.2.

This material was then converted to the corresponding tetrazole 5-(4-benzyloxy-phenyl)-6-cyclohexyl-2-(1H-tetrazol-5-yl)-4H-pyrazolo[1,5-a]pyrimidin-7-one (551) via a previously described (sodium azide, triethylamine hydrochloride) experimental procedure (54% yield); LC-MS—calcd for $C_{26}H_{25}N_7O_2$ $[M^+ + H]^+$: 468.21, found: 468.2.

Example 34

Synthesis of 5-(4-benzyloxy-phenyl)-6-cyclohexyl-7-methoxy-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid



(329)

To a mixture of 22 mg (0.05 mmol) of 5-(4-benzyloxy-phenyl)-6-cyclohexyl-7-oxo-4,7-dihydro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid amide in 1 mL of dichloromethane (DCM) was added 0.04 mL (0.3 mmol) of triethylamine (Et_3N), and the resulting mixture was cooled in an ice bath. Then 0.021 mL (0.15 mmol) of trifluoroacetic anhydride ($(CF_3CO)_2O$) was added during which time the mixture became homogeneous, and was stirred for 2.5 h. The reaction mixture was quenched by the addition of water,

To an ice cold mixture of 22 mg (0.048 mmol) of 5-(4-benzyloxy-phenyl)-6-cyclohexyl-7-oxo-4,7-dihydro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid methyl ester in 3 mL of tetrahydrofuran (THF) was added 0.008 mL (0.192 mmol) of methanol (MeOH), 50 mg (0.192 mmol) of triphenylphosphine (PPh_3), followed by 0.038 mL (0.192 mmol) of diisopropyl azodicarboxylate (DIAD) and the mixture was allowed to warm up to rt and stirred at rt for 2 h when analysis by thin layer chromatography (TLC)

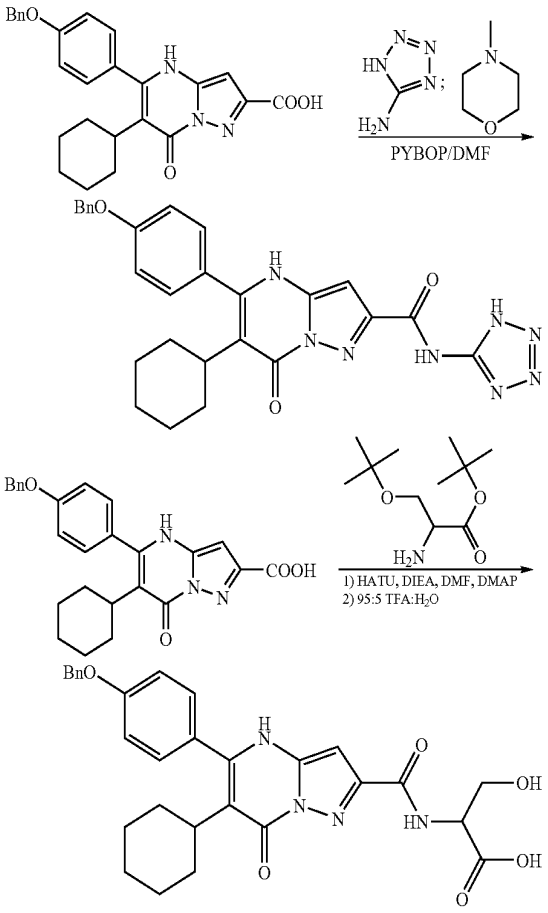
revealed complete consumption of starting material. The reaction mixture was then concentrated and the residue was chromatographed on silica gel (Biotage; gradient elution dichloromethane (DCM) to 10% ethyl acetate in DCM) to give 24 mg of desired 5-(4-benzyloxy-phenyl)-6-cyclohexyl-7-methoxy-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid methyl ester as indicated by ^{1}H-NMR (containing traces of impurities).

Note that 5-(4-benzyloxy-phenyl)-6-cyclohexyl-7-methoxy-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid methyl ester was also obtained using an alkylation procedure (dimethylsulfate, with acetonitrile as solvent).

Conversion of 5-(4-benzyloxy-phenyl)-6-cyclohexyl-7-methoxy-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid methyl ester to the corresponding acid 5-(4-benzyloxy-phenyl)-6-cyclohexyl-7-methoxy-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid (329) was accomplished via the well known LiOH saponification protocol; LC-MS—calcd for $C_{27}H_{27}N_3O_4$ $[M^+ + H]^+$: 458.2, found: 458.2.

Example 35

Synthesis of 2-{[5-(4-benzyloxy-phenyl)-6-cyclohexyl-7-oxo-4,7-dihydro-pyrazolo[1,5-a]pyrimidine-2-carbonyl]-amino}-3-hydroxy-propionic acid

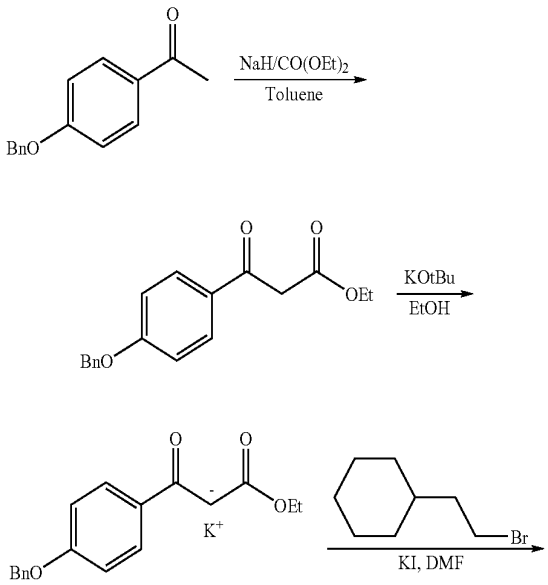


To a solution of 71 mg (0.16 mmol) of 5-(4-benzyloxy-phenyl)-6-cyclohexyl-7-oxo-4,7-dihydro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid in 4 mL of dimethylformamide (DMF) was added 0.053 mL (0.48 mmol) of 4-methylmorpholine, 14 mg (0.164 mmol) of 5-aminotetrazole, followed by 100 mg (0.192 mmol) of PYBOP when the solution turned yellow, and the resulting mixture was stirred at rt for 41 h. The reaction mixture was concentrated to give a residue which was purified via reverse-phase chromatography to afford 29 mg (35% yield) of desired 5-(4-benzyloxy-phenyl)-6-cyclohexyl-7-oxo-4,7-dihydro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid (1H-tetrazol-5-yl)-amide (540) as a solid as indicated by ^{1}H-NMR; LC-MS calcd. for $C_{27}H_{26}N_8O_3$ $[M^+ + H]^+$: 511.21; found: 511.1.

To a solution of 67 mg (0.15 mmol) of 5-(4-benzyloxy-phenyl)-6-cyclohexyl-7-oxo-4,7-dihydro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid in 3 mL of DMF was added 0.13 mL (0.75 mmol) of diisopropylethylamine (DIEA), a few crystals of dimethylaminopyridine (DMAP cat), 50 mg (0.195 mmol) of 2-amino-3-tert-butoxy-propionic acid tert-butyl ester hydrochloride, followed by 74 mg (0.195 mmol) of HATU, and the resulting mixture was stirred at rt overnight. The reaction mixture was diluted with ethyl acetate, washed with 0.1 N sodium hydroxide solution (2 times) and brine. The separated organic layer was dried over sodium sulfate and concentrated to give a residue which was treated with 3 mL of 95:5 trifluoroacetic acid (TFA):water, stirred at rt for 2 h, and quenched by the addition of 1:1 acetonitrile: water. The resulting mixture was concentrated to give a residue which was purified via reverse-phase chromatography to afford (after lyophilization) 14 mg (17%) of desired 2-{[5-(4-benzyloxy-phenyl)-6-cyclohexyl-7-oxo-4,7-dihydro-pyrazolo[1,5-a]pyrimidine-2-carbonyl]-amino}-3-hydroxy-propionic acid (544) as a white solid as indicated by ^{1}H-NMR; LC-MS calcd. for $C_{29}H_{30}N_4O_6$ $[M^+ + H]^+$: 531.22; found: 531.2.

Example 36

Synthesis of 5-(4-benzyloxy-phenyl)-6-(2-cyclohexyl-ethyl)-7-oxo-4,7-dihydro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid and 6-(2-cyclohexyl-ethyl)-5-furan-3-yl-7-oxo-4,7-dihydro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid



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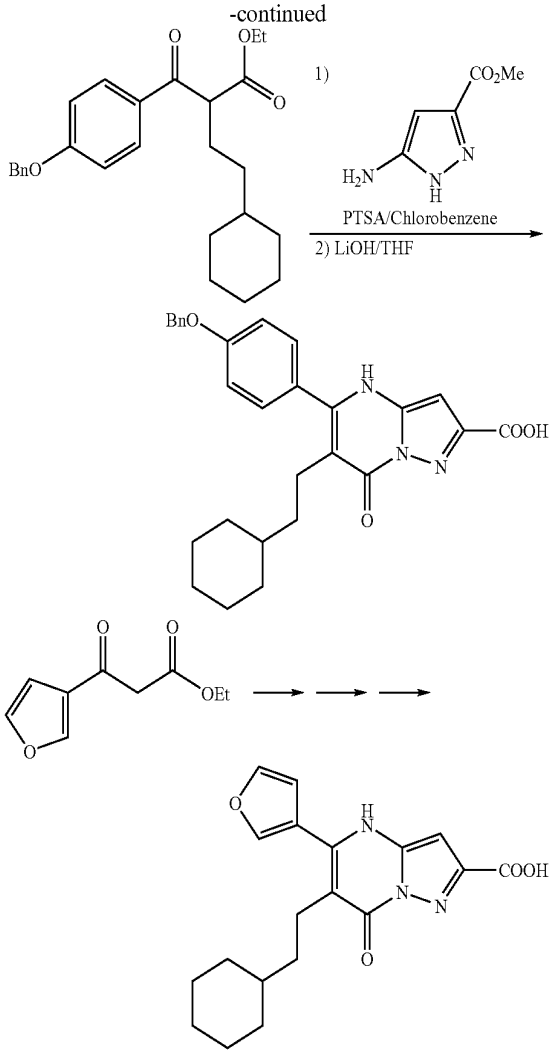


To a refluxing mixture of 7.0 g (175 mmol) of sodium hydride (NaH 60% dispersion in mineral oil) and 10.45 g (88.5 mmol) of diethyl carbonate ($CO(OEt)_2$) in 100 mL of toluene was added dropwise via an addition funnel a mixture of 10 g (44.3 mmol) of 1-(4-benzyloxy-phenyl)-ethanone in 20 mL of toluene, and the resulting mixture was heated at reflux under argon for 1 h. The reaction mixture was then cooled to 0° C., quenched by the addition of 40 mL of acetic acid, during which time a yellow precipitate formed, and it dissolved upon subsequent addition of water. The separated organic layer was washed with saturated sodium bicarbonate solution, water and brine, dried over sodium sulfate and concentrated to give a residue which was chromatographed on silica gel (10% hexane in dichloromethane) to afford 9.2 g (70% yield) of desired 3-(4-benzyloxy-phenyl)-3-oxo-propionic acid ethyl ester as indicated by ^{1}H NMR.

To a solution of 2 g (6.7 mmol) of 3-(4-benzyloxy-phenyl)-3-oxo-propionic acid ethyl ester in 12 mL of ethanol (heated slightly for complete dissolution) was added dropwise 7 mL (7 mmol) of potassium t-butoxide (KOtBu 1 M solution in t-butanol), during which time a precipitate formed. The reaction mixture was stirred at rt for 20 min, then diethyl ether was added and the precipitate was collected by filtration, washed with ether and dried to afford 2.2 g (98% yield) of desired 3-(4-benzyloxy-phenyl)-3-oxo-propionic acid ethyl ester potassium salt as indicated by ^{1}H NMR.

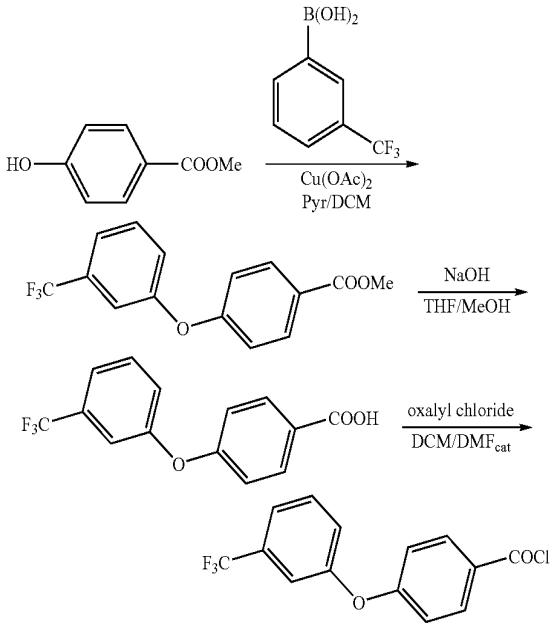
A mixture 100 mg (0.3 mmol) of 3-(4-benzyloxy-phenyl)-3-oxo-propionic acid ethyl ester potassium salt, 86 mg (0.45 mmol) of 2-cyclohexylethyl bromide, and 17 mg (0.1 mmol) of potassium iodide (KI) in 1 mL of dimethylformamide (DMF) in a 4 mL vial was shaken in a sand bath at 80° C. overnight. The mixture was then concentrated to give a residue which was purified via reverse-phase chromatography (Gilson) to afford (after lyophilization) 85 mg (70% yield) of 2-(4-benzyloxy-benzoyl)-4-cyclohexyl-butyric acid ethyl ester as a solid as indicated by LC-MS—calcd for $C_{26}H_{32}O_2$ $[M^+ + H]^+$: 409.23, found: 409.2.

A mixture of 71 mg (0.171 mmol) of 2-(4-benzyloxy-benzoyl)-4-cyclohexyl-butyric acid ethyl ester, 24 mg (0.171 mmol) of 5-amino-1H-pyrazole-3-carboxylic acid methyl ester, 7 mg (20 mol %) of p-toluenesulfonic acid monohydrate (PTSA), and 3 mL of chlorobenzene was heated at 120° C. overnight. The reaction mixture was then concentrated to a residue which was purified via reverse-phase chromatography (Gilson) to afford (after lyophilization) desired 5-(4-benzyloxy-phenyl)-6-(2-cyclohexyl-ethyl)-7-oxo-4,7-dihydro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid methyl ester as a solid as indicated by LC-MS—calcd for $C_{29}H_{31}N_3O_4$ $[M^+ + H]^+$: 486.23, found: 486.2. This material was then converted to 5-(4-benzyloxy-phenyl)-6-(2-cyclohexyl-ethyl)-7-oxo-4,7-dihydro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid (559) via the well known LiOH saponification protocol (10% yield over 2 steps); LC-MS—calcd for $C_{28}H_{29}N_3O_4$ $[M^+ + H]^+$: 472.22, found: 472.2.

Note that the same synthetic sequence was carried out from the commercially available 3-furan-3-yl-3-oxo-propionic acid ethyl ester as depicted above to give 6-(2-cyclohexyl-ethyl)-5-furan-3-yl-7-oxo-4,7-dihydro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid (612).

Example 37

Synthesis of 4-(3-trifluoromethyl-phenoxy)-benzoic acid



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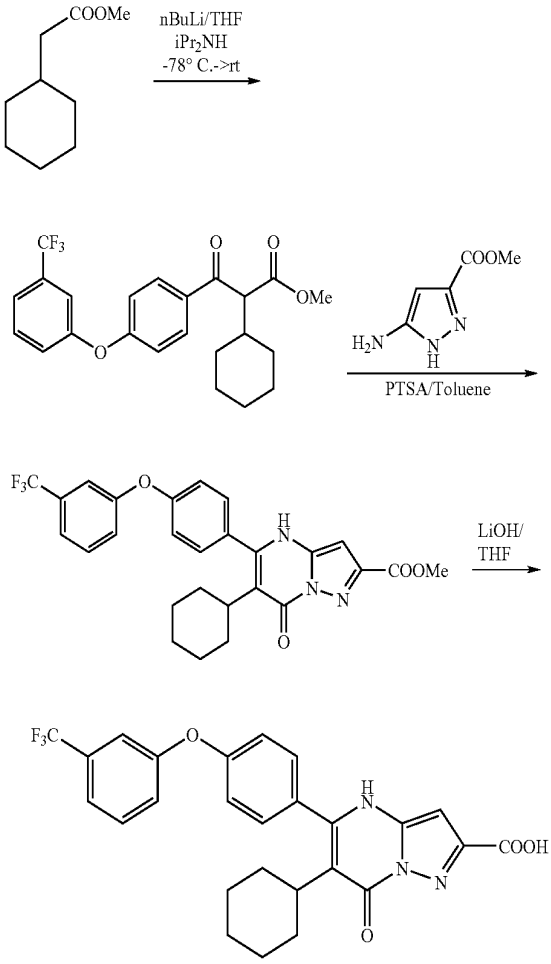


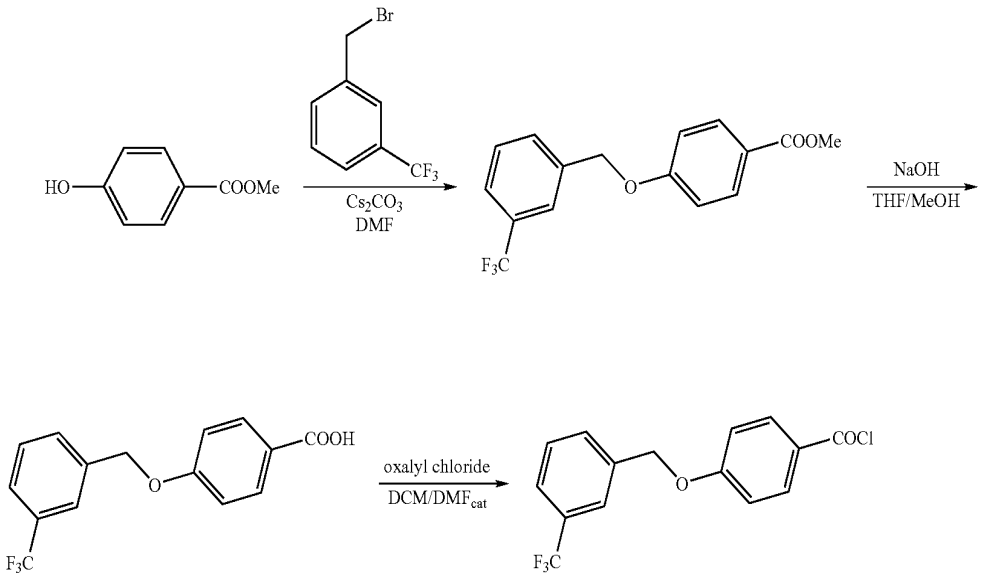
According to a modification of a literature procedure from (*J. Org. Chem.* 2002, 67, 1699–1702) an aqua-green mixture of 2.74 g (18 mmol) of 4-hydroxy-benzoic acid methyl ester, 4.9 g (27 mmol) of copper (II) acetate ($Cu(OAc)_2$), 6.84 g (36 mmol) of 3-trifluoromethyl-phenoxy-boronic acid, 2.92 mL (36 mmol) of pyridine (pyr), and 120 mL of DCM was stirred at rt for 68 h while opened to air. The reaction mixture was filtered through Celite, while rinsing the Celite pad with ethyl acetate and chloroform. The combined organic filtrates were concentrated to a green solid residue, which was partitioned between ethyl acetate and water and extracted with ethyl acetate. The combined organic extracts were washed with water (3 times), brine, dried over sodium sulfate and evaporated to give 4.6 g of a brown residue which was chromatographed on silica gel (Biotage; 1:1 hexane:DCM) to give 3.56 (67% yield) of desired 4-(3-trifluoromethyl-phenoxy)-benzoic acid methyl ester as a pale yellow oil as indicated by ^{1}H-NMR and ^{19}F-NMR; LC-MS—calcd for $C_{15}H_{11}F_3O_3$ $[M^+ + H]^+$: 297.07, found: 297.1.

A mixture of 3.56 g (12 mmol) of 4-(3-trifluoromethyl-phenoxy)-benzoic acid methyl ester, and 15 mL (60 mmol) of 4 N sodium hydroxide (NaOH) solution in 45 mL of tetrahydrofuran (THF) and 15 mL of methanol (MeOH) was heated at 50° C. for 25 h, when analysis by thin layer chromatography revealed complete conversion of starting material to product. The reaction mixture was concentrated and acidified with 2N HCl solution while keeping the flask in an ice bath, when a white precipitate formed. The solid was filtered and dried to give 3.02 g (89%) of desired 4-(3-trifluoromethyl-phenoxy)-benzoic acid as a white solid as indicated by ^{1}H NMR and ^{19}F-NMR.

Synthesis of 6-Cyclohexyl-7-oxo-5-[4-(3-trifluoromethyl-phenoxy)-phenyl]-4,7-dihydro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid (543) was accomplished as depicted in the above scheme, starting from 4-(3-trifluoromethyl-phenoxy)-benzoic acid via transformations that were described for the synthesis of 5-(4-Benzyloxy-phenyl)-6-cyclohexyl-7-oxo-4,7-dihydro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid (538). For entry 543: LC-MS—calcd for $C_{26}H_{22}F_3N_3O_4$ $[M^+ + H]^+$: 498.16, found: 498.1.

Example 38

Synthesis of 6-cyclohexyl-7-oxo-5-[4-(3-trifluoromethyl-benzyloxy)-phenyl]-4,7-dihydro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid



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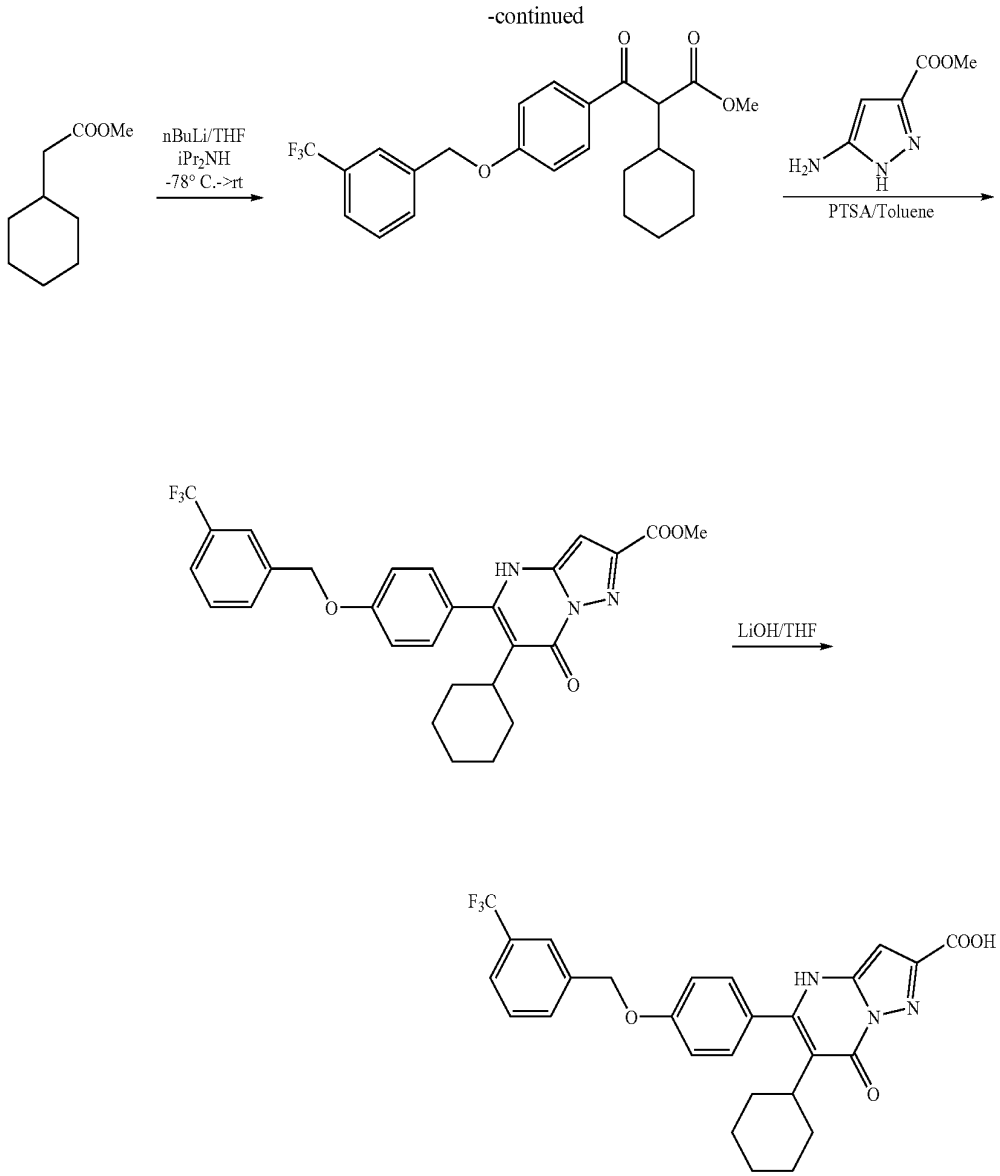
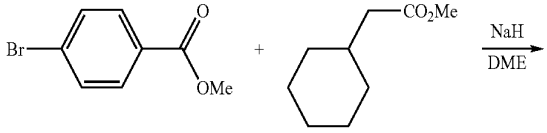


To a solution of 2.28 g (15 mmol) of 4-hydroxy-benzoic acid methyl ester in 30 mL of dimethylformamide (DMF) was added 5.38 g (16.5 mmol) of cesium carbonate (Cs_2CO_3), followed by 2.75 mL (18 mmol) of 3-(trifluoromethyl)-benzyl bromide, and the resulting heterogeneous mixture was stirred at rt overnight. The reaction mixture was filtered and concentrated, diluted with water and extracted with ethyl acetate, and the combined organic extracts were washed with water and brine, and concentrated to give 4.75 g of desired 4-(3-trifluoromethyl-benzyloxy)-benzoic acid methyl ester as indicated by ^{1}H NMR and ^{19}F-NMR (containing traces of residual 3-(trifluoromethyl)-benzyl bromide).

This product was used without any further purification in the synthesis of 6-cyclohexyl-7-oxo-5-[4-(3-trifluoromethyl-benzyloxy)-phenyl]-4,7-dihydro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid (545), which was accomplished as depicted in the above scheme, via standard transformations that were previously described for the synthesis of 5-(4-Benzyloxy-phenyl)-6-cyclohexyl-7-oxo-4,7-dihydro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid.

Example 39

Synthesis of 6-cyclohexyl-5-[4-(3,5-dimethyl-isoxazol-4-yl)-phenyl]-7-oxo-4,7-dihydro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid, 5-(4-benzyl-phenyl)-6-cyclohexyl-7-oxo-4,7-dihydro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid, and 5-(4-(3-trifluoromethoxyphenyl)-phenyl)-6-cyclohexyl-7-oxo-4,7-dihydro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid



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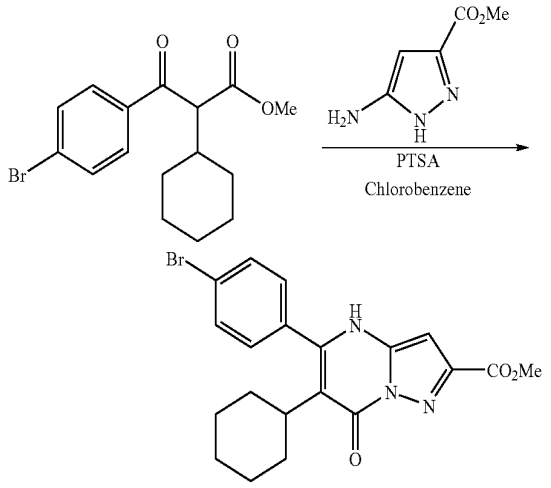
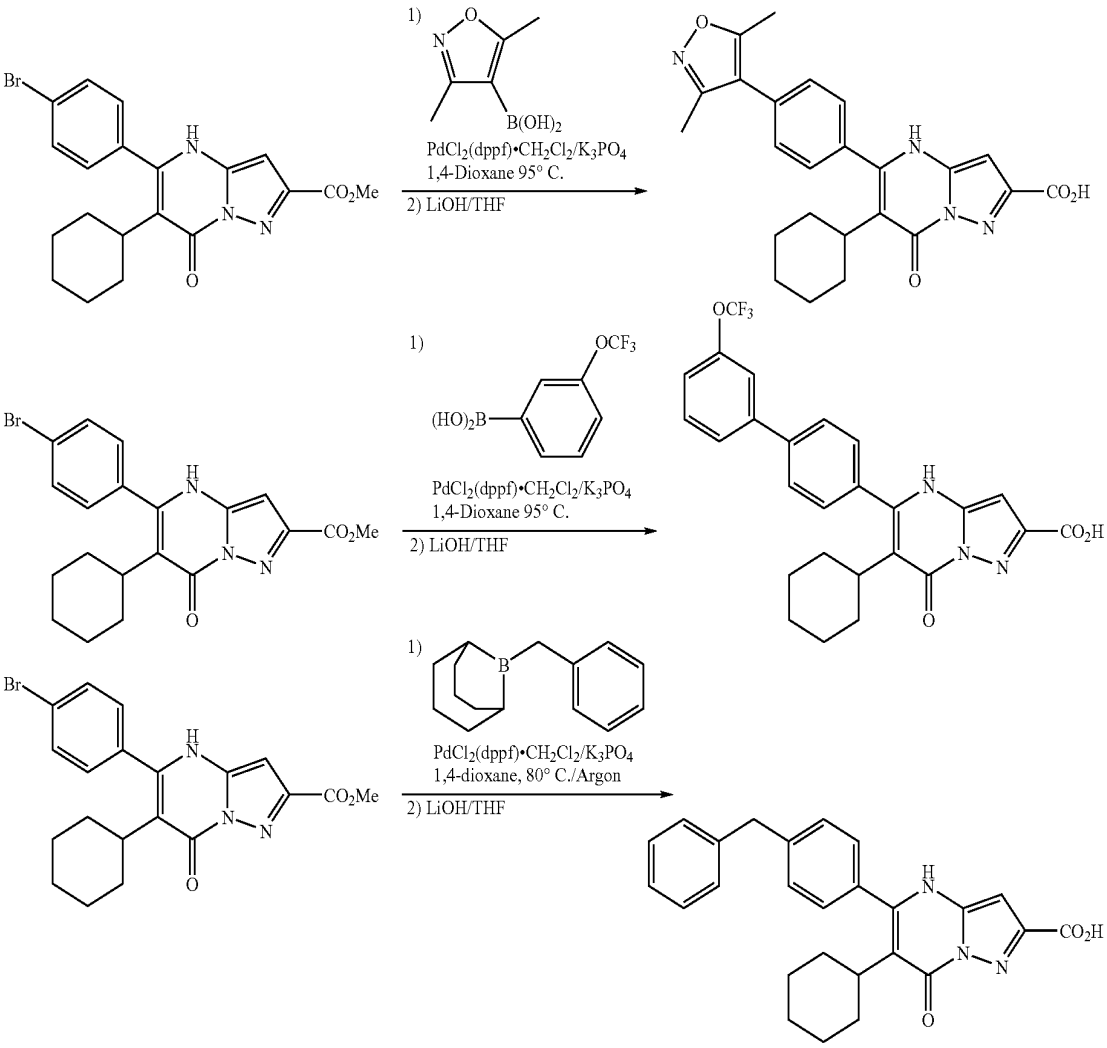


The product of the above sequence was synthesized following the same experimental procedure that was used to prepare a related intermediate where the 4-bromo-phenyl group was replaced by 2-furyl group. This aryl bromide compound was used as a synthetic intermediate, which was transformed using some of the representative reactions below.

A mixture of 42 mg (0.1 mmol) of 5-(4-bromo-phenyl)-6-cyclohexyl-7-oxo-4,7-dihydro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid methyl ester, 21 mg (0.15 mmol) of 3,5-dimethyl-isoxazoleboronic acid, 7.3 mg (0.01 mmol) of Pd catalyst, and 63 mg (0.3 mmol) of potassium phosphate in 1 mL of 1,4-dioxane was shaken at 95° C. in a sandbath overnight. The reaction mixture was then diluted with dichloromethane, filtered through a small pad of Celite, dried over sodium sulfate and evaporated to give a residue, which was purified via reverse-phase chromatography (Gilson) to afford desired 6-cyclohexyl-5-[4-(3,5-dimethyl-isoxazol-4-yl)-phenyl]-7-oxo-4,7-dihydro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid methyl ester as a solid as indicated by LC-MS—calcd for $C_{25}H_{26}N_4O_4$ $[M^+ + H]^+$: 447.19, found: 447.3. This material was then converted to 6-cyclohexyl-5-[4-(3,5-dimethyl-isoxazol-4-yl)-phenyl]-7-oxo-4,7-dihydro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid (591) via the well known LiOH saponification protocol (37% yield over 2 steps); LC-MS—calcd for $C_{24}H_{24}N_4O_4$ $[M^+ + H]^+$: 433.18, found: 433.1.

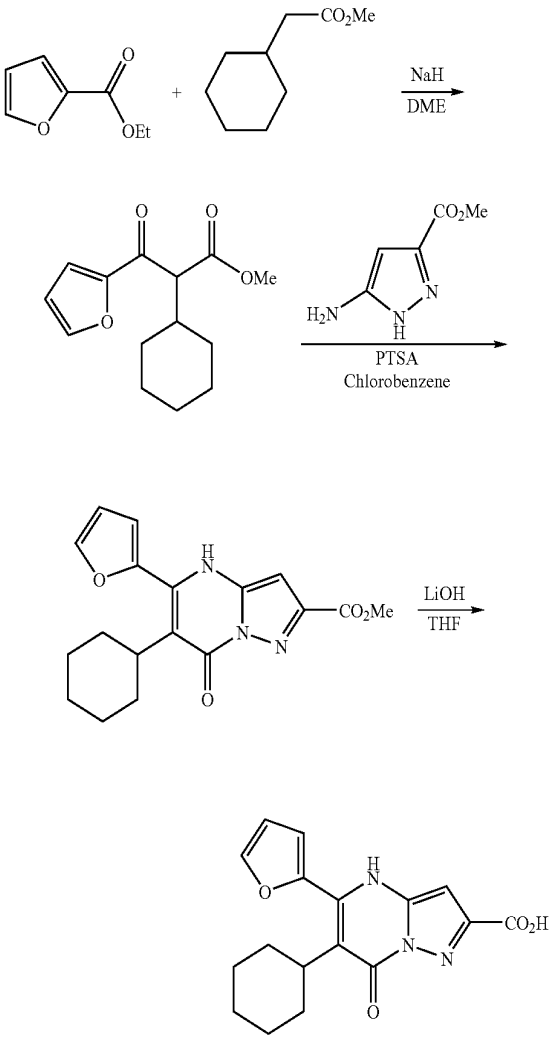
According to a modification of a literature procedure (Suzuki, A. et al *Tetrahedron Lett.* 1986, 27, 6369–6372) a mixture of 43 mg (0.1 mmol) of 5-(4-bromo-phenyl)-6-cyclohexyl-7-oxo-4,7-dihydro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid methyl ester, 7.3 mg (0.01 mmol) of Pd catalyst, 0.4 mL (0.2 mmol) of B-Benzyl-9-BBN 0.5 M solution in THF, and 63 mg (0.3 mmol) of potassium



phosphate, was purged with argon, 1 mL of 1,4-dioxane was added, and the resulting mixture was shaken at 80° C. in a sandbath overnight. The reaction mixture was then diluted with dichloromethane, filtered through a small pad of Celite, dried over sodium sulfate and evaporated to give a residue, which was purified via reverse-phase chromatography (Gilson) to afford desired 5-(4-benzyl-phenyl)-6-cyclohexyl-7-oxo-4,7-dihydro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid methyl ester as a solid as indicated by LC-MS—calcd for $C_{27}H_{27}N_3O_3$ $[M^+ + H]^+$: 442.21, found: 442.2. This material was then converted to 5-(4-benzyl-phenyl)-6-cyclohexyl-7-oxo-4,7-dihydro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid (581) via a LiOH saponification (33% yield over 2 steps); LC-MS—calcd for $C_{26}H_{25}N_3O_3$ $[M^+ + H]^+$: 428.19, found: 428.2.

Example 40

Synthesis of 6-cyclohexyl-5-furan-2-yl-7-oxo-4,7-dihydro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid and 6-cyclohexyl-5-(3-fluoro-phenyl)-7-oxo-4,7-dihydro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid



(595)

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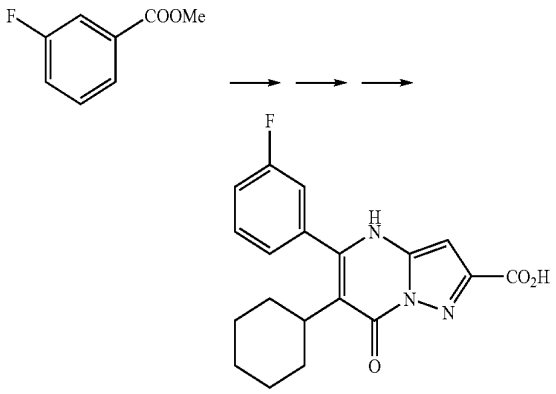


(598)

To an ice cold suspension of 0.92 g (23 mmol) of sodium hydride (NaH 60% dispersion in mineral oil) (previously washed with hexane and dried under vacuum) in 25 mL of 1,2-dimethoxyethane (DME) was added 0.9 g (5.76 mmol) of methyl cyclohexylacetate, and the resulting mixture was stirred at 0° C. for 20 min. Then 1.2 g (8.56 mmol) of ethyl 2-furoate was added, and the reaction mixture was heated at reflux overnight. The mixture was then cooled to 0° C., quenched by the addition of 1 M HCl solution to pH=3, and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over sodium sulfate and concentrated to give a brown oil which was chromatographed on silica gel (Biotage; 10% hexane in dichloromethane) to afford 1.1 g (76% yield) of desired 2-cyclohexyl-3-furan-2-yl-3-oxo-propionic acid methyl ester as indicated by ^{1}H NMR.

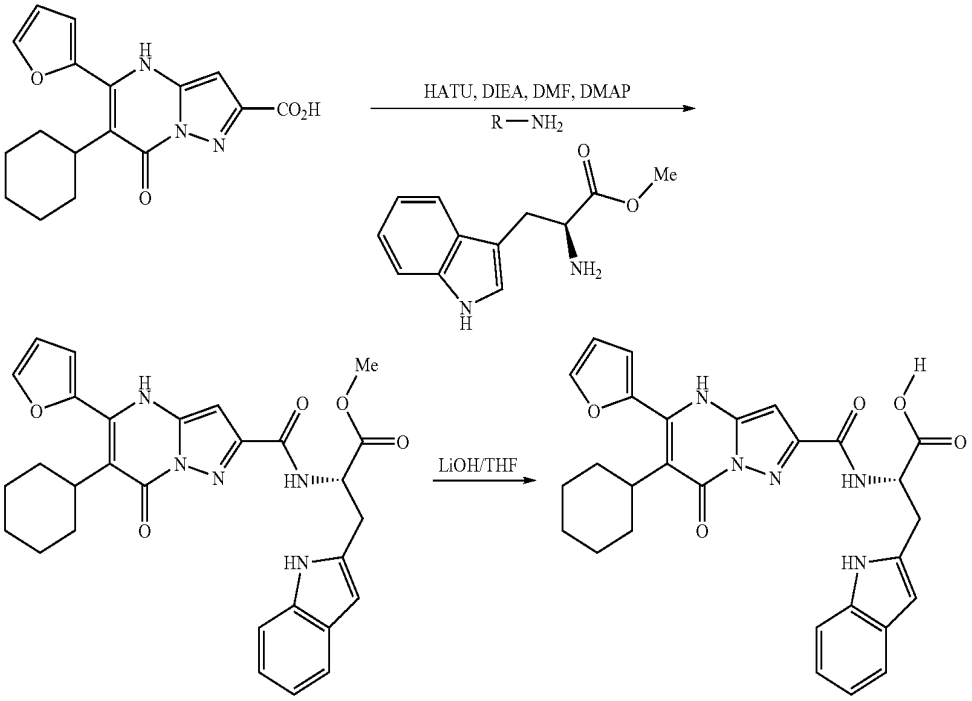
A mixture of 1.1 g (4.4 mmol) of 2-cyclohexyl-3-furan-2-yl-3-oxo-propionic acid methyl ester, 0.592 g (4.2 mmol) of 5-amino-1H-pyrazole-3-carboxylic acid methyl ester, 76 mg (0.4 mmol, 10 mol %) of p-toluenesulfonic acid monohydrate (PTSA), and 50 mL of chlorobenzene was heated at 120° C. overnight. The reaction mixture was then concentrated to a residue which was chromatographed on silica gel (7% methanol in dichloromethane) to afford 0.46 g (32% yield) of desired 6-cyclohexyl-5-furan-2-yl-7-oxo-4,7-dihydro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid methyl ester as indicated by ^{1}H NMR; LC-MS—calcd for $C_{18}H_{19}N_3O_4$ $[M^+ + H]^+$: 342.14, found: 342.3.

Conversion of 6-cyclohexyl-5-furan-2-yl-7-oxo-4,7-dihydro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid methyl ester to 6-cyclohexyl-5-furan-2-yl-7-oxo-4,7-dihydro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid (595) was accomplished via the well known LiOH saponification protocol where the yield was 77%. LC-MS—calcd for $C_{17}H_{17}N_3O_4$ $[M^+ + H]^+$: 328.13, found: 328.1. ^{1}H NMR (DMSO-d_6) δ 8.06–8.05 (d, J=2 Hz, 1H), 6.99–6.98 (d, J=3.6 Hz, 1H), 6.80–6.78 (d of d, J=3.6 Hz, J=2 Hz, 1H), 6.39 (s, 1H), 2.79–2.71 (m, 1H), 2.25–2.16 (m, 2H), 1.77–1.75 (m, 2H), 1.66–1.65 (m, 1H), 1.59–1.55 (m, 2H), 1.25–1.20 (m, 3H).

Note that the same synthetic scheme was carried out for 3-fluoro-benzoic acid methyl ester as depicted above to afford 6-cyclohexyl-5-(3-fluoro-phenyl)-7-oxo-4,7-dihydro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid (598); the cyclization yield was slightly improved (54%).

Example 41

Synthesis of 2-[(6-cyclohexyl-5-furan-2-yl-7-oxo-4,7-dihydro-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-amino]-3-(1H-indol-2-yl)-propionic acid



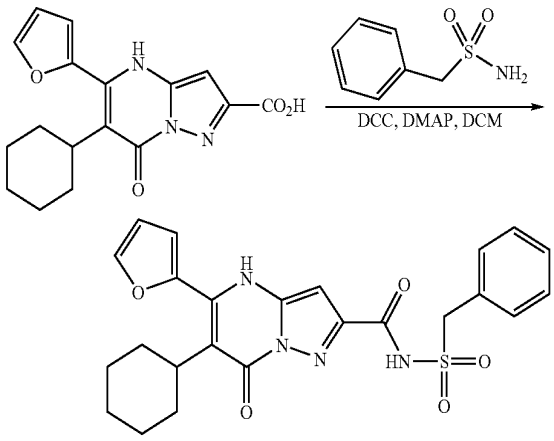
To a solution of 8.2 mg (0.025 mmol) of 6-cyclohexyl-5-furan-2-yl-7-oxo-4,7-dihydro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid in 2 mL of dimethylformamide (DMF) was added 0.009 mL (0.05 mmol) of diisopropylethylamine (DIEA), a few crystals of dimethylaminopyridine (DMAP cat), 7 mg (0.027 mmol) of L-tryptophan methyl ester hydrochloride, followed by 11 mg (0.03 mmol) of HATU, and the resulting mixture was stirred at rt overnight. The reaction mixture was diluted with ethyl acetate, washed with 0.1 N sodium hydroxide solution (2 times) and brine. The separated organic layer was dried over sodium sulfate and concentrated to give a residue which was purified via reverse-phase chromatography (Gilson) to afford desired 2-[(6-cyclohexyl-5-furan-2-yl-7-oxo-4,7-dihydro-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-amino]-3-(1H-indol-2-yl)-propionic acid methyl ester (606). This compound was then converted to 2-[(6-cyclohexyl-5-furan-2-yl-7-oxo-4,7-dihydro-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-amino]-3-(1H-indol-2-yl)-propionic acid (599) via the well known LiOH saponification protocol (39% yield over 2 steps); LC-MS calcd. for $C_{28}H_{27}N_5O_5$ $[M^+ + H]^+$: 514.2; found: 514.2.

Note that this protocol was used for most of the amides in this series, however for expediency in some cases a different amidation protocol was utilized as follows: To a solution of the acid in tetrahydrofuran (THF) was added 4 equiv of amine (R—NH_2), followed by 2 equiv of 1-hydroxybenzotriazole (HOBt) and 4 equiv of PS-carbodiimide resin, and the resulting mixture was stirred at rt overnight. The reaction mixture was then treated with 4 equiv of MP-carbonate resin and 4.8 equiv of PS-TsOH resin, and stirring was continued at rt for 4 h. The mixture was then filtered and washed with THF, and the combined THF extracts were concentrated to afford the crude coupling product.

In the second (deprotection) step, a typical aqueous LiOH mediated saponification was employed for those amine building blocks containing methyl or ethyl esters, and for those amine building blocks containing t-butyl esters or ethers a typical 95:5 TFA:water deprotection protocol was carried out.

Example 42

Synthesis of N-(6-cyclohexyl-5-furan-2-yl-7-oxo-4,7-dihydro-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-C-phenyl-methanesulfonamide



To a solution of 20 mg (0.06 mmol) of 6-cyclohexyl-5-furan-2-yl-7-oxo-4,7-dihydro-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid in 2 mL of dichloromethane (DCM) was a few crystals of DMAP (cat), 12 mg (0.071 mmol) of toluenesulfonamide, followed by 0.071 mL (0.071 mmol) of 1 M dicyclohexylcarbodiimide (DCC) solution in DCM.

The reaction mixture was stirred at rt overnight, concentrated, and the resulting residue was purified by reverse-phase chromatography (Gilson) to afford (after lyophilization) 5 mg (17% yield) of desired N-(6-cyclohexyl-5-furan-2-yl-7-oxo-4,7-dihydro-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-C-phenyl-methanesulfonamide (616) as a solid as indicated by LC-MS calcd. for $C_{24}H_{24}N_4O_5S$ $[M^+ + H]^+$: 481.15; found: 481.1.

Note that N-(6-Cyclohexyl-5-furan-2-yl-7-oxo-4,7-dihydro-pyrazolo[1,5-a]pyrimidine-2-carbonyl)-C,C,C-trifluoro-methanesulfonamide (617) was also synthesized using this protocol.

Example 43

Assay for HCV RNA-dependent RNA Polymerase Activity

Overview

HCV RNA-dependent RNA polymerase (RdRp) was assayed by scintillation proximity assay (SPA), using an RNA homopolymer (polyC) complexed with a biotinylated oligoG_{12} primer. The primer can be added directly to the template without a denaturing and annealing process. The assay specifically measures the incorporation of [^{3}H] labeled GTP into PolyG. The biotinylated G_{12} enables the capture of the [^{3}H] labeled products by streptavidin-coated SPA beads.

The HCV NS5B RdRp used in this assay was modified by the removal of a 55 amino acid portion from the C-terminus, which contains a hydrophobic domain of 21 amino acids. The HCV NS5B RdRp protein was purified as a polyhistidine (His_6) fusion protein expressed in *E. coli,* and the His-tag was then removed by specific proteolysis.

The assay was carried out at room temperature (~22° C.) in a 96-well plate for 50 minutes. No preincubation was required. The reaction was initiated by adding the enzyme to the RNA substrate in the presence or absence of test compounds. To stop the reaction, 50 µl of 10 mg/mL streptavidin-coated SPA beads supplemented with 100 mM EDTA was added to each well, and the plate was incubated by shaking at room temperature for 15 minutes. After harvesting and a wash by filtration, the radioactivity in each well was counted using a TopCount Scintillation/Luminescence Counter.

The assay conditions are: 50 µl reaction volume incubated at room temperature for 50 minutes in 20 mM Hepes pH 7.3, 7.5 mM DTT, 20 units/mL RNasin, 0.5 ug/mL oligo $(G)_{12}$, 5 µg/mL Poly (C), 0.5 µM GTP, 1 µCi/mL 3H-GTP, 10 mM $MgCl_2$, 60 mM NaCl, 100 µg/mL BSA, 6 nM NS5B CT55 enzyme.

MATERIALS Buffer:	1 X	1 Liter
Hepes (pH 7.3),	20 mM	20 mLs 1 M
$MgCl_2$	10 mM	10 mLs 1 M
NaCl	60 mM	12 mLs 5 M
BSA	100 µg/mL	100 mgs
RNAse-free H20		to 1 Liter

Sterile filter. Store buffer at 4° C.

RNA Template:

A stock solution of 5 mgs/mL was prepared in 20 mM Hepes pH 7.3. Buffer (4 mL) was added to 5 mg of polycytidylic acid [Sigma, #P4903], and the solution was checked for absorbance at OD_{260}, and quantitated using the conversion: OD_{260} of 1=40 µg/mL. The solution was then corrected to 5 mg/mL in buffer, aliquoted, and stored at −80° C.

RNA Primer:

A stock solution of 0.5 mg/mL of the primer was prepared in 20 mM Hepes pH 7.3. The solution was checked for absorbance at OD_{260}, and quantitated using the conversion: OD_{260} of 1=32 µg/mL, then aliquoted and stored at −80° C.

GTP Substrate:

A stock solution (2 mM) was prepared in 20 mM Hepes pH 7.3, and then aliquoted and stored at −80° C.

NS5BΔCT55 RdRp:

HCV NS5BΔCT55 (from 1b BK strain) was purified as a polyhistidine (His_6) fusion protein expressed in *E. coli.* The protein was modified by removing a 55 amino acid portion from the C-terminus containing a hydrophobic domain of 21 amino acids and a His_6-tag was fused to the protein at the C-terminus. After purification, the His-tag was removed by specific proteolysis. The M.W. of the protein is 60323. For a working stock the enzyme was diluted 1:10 from 53 µM down to 5.4 µM, then aliquoted and stored at −80° C. 6 nM of the enzyme was required for each reaction.

Enzyme Storage Buffer:

25 mM Hepes (pH7.5), 5 mM DTT, 0.6 M NaCl, 15% Glycerol, 0.1% Octylglucoside, 2 mg/L Leupeptin, 100 µM PMSF.

The buffer was stored at −20° C.

Zinc Acetate Control Inhibitor:

50× stock solutions of zinc acetate were made up at 16, 8, 4 and 2 mM in 100% DMSO. Stocks were stored at 4° C.

Filter Plate Wash Buffer:

200 mL of 20×SSC Buffer and 80 mLs of 1M Hepes pH 7.3 were brought up to 4 Liters in milli-Q^R water. The solution was stored at room temperature.

INSTRUMENTS AND SUPPLIES	
TopCount.NXT Microplate Reader	[Packard, A991200]
Mach 3U Harvester 96	[TomTec, 96–3]
Microtest U Bottom Tissue Culture Plate	[Falcon, 353077]
Unifilter-96, GF/B white microplate	[Packard, 6005177]
Nunc Polypropylene Microplate	[Nunc, 442587]
TopSeal-A:96-well Microplate sealing film	[Packard, 6005185]
Mini Orbital Shaker	[Bellco, 7744–08096]
CHEMICALS	
RNA homopolymer/Poly(C)	[Sigma, #P4903]
Biotin-Oligo$(G)_{12}$	[Oligo, Etc., EO-1/22/98]
Unlabeled GTP	[Novagen, 69176-1]
[^{3}H] labeled GTP	[Amersham, TRK314]
1 M Hepes (pH 7.3)	[USB, 16924]
0.5 M EDTA (pH 8.0)	[GibcoBRL, 15575–012]
DTT [dithiothreitol]	[GibcoBRL, 15508–013]
$MgCl_2$	[Sigma, M1028]
BSA (Fraction V)	[Boehringer Mannheim, 100350]
RNaseIN	[Promega, N2515]
Leupeptin	[Sigma, L9783]
n-Octylglucoside	[Boehringer Mannheim, 1359088]
PMSF	[Sigma, 7626]
5M NaCl	[GibcoBRL, 24740–011]
Glycerol	[GibcoBRL, 15514–011]
Streptavidin-coated SPA beads	[Amersham, RPNQ0007]

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PBS (w/o Mg^{++} and Ca^{++})	[GibcoBRL, 14190–144]
DMSO	[Sigma, D5879]
ZnOAc	[Sigma, Z0625]
Rnase-free Water	[USB, US70783]
20 X SSC Buffer	[GibcoBRL, 15557–044]

Assay Procedures

Dilution of Test Compounds

Stock solutions were prepared at a concentration of 1 mg/mL in 100% DMSO. Compounds were serially diluted in a 96-well polypropylene microplate [Nunc] using a multichannel pipetter as follows:

(1) To Rows B, E and H were added 15 μl DMSO; to Rows C, D, F, and G were added 20 μl DMSO. 12 Compounds were added undiluted across Row A, and then 5 μl of each compound was transferred from Row A to Row B, triturating 10–12 times to mix. Another 5 μl was then transferred from Row B to Row C and so on to Row H, producing 7 serial dilutions of the stock.

(2) 1 μl of each dilution (50×) was transferred to assay plates as described below, producing final concentrations of 20, 5, 1, 0.2, 0.05, 0.01, 0.002, and 0.0005 μg/mL.

Assay Set Up: 1 Plate

Enzyme/RNA Mixture (700 μl Total, 5 μl/Reaction)

660 μl of 1× Buffer

7 μl	5 mg/mL template polyC
7 μl	0.5 mg/L primer oligorG_{12}
3.5 μl	40 U/μl RNAsin
10 μl	1 M DTT

8 μl of 5.3 μM enzyme (10× for 6 nM final)

Nucleotide Mixture (2 mL Total, 20 μl/Reaction):

2.0 mL of 1× Buffer

30 μl of 1M DTT

5 μl of 1 mCi/mL [3H]-GTP

1.3 μl of 2 mM cold GTP

Reaction Mixture:

24 μl of 1× Buffer

20 μl of Nucleotide mixture

1 μl of Compound

5 μl of Enzyme

Protocol

(1) 24 μl of 1× buffer was placed in each well on a 96-well Plate (Microtest U Bottom Tissue Culture Plate from Falcon).

(2) In order of addition, 1× Buffer, DTT, unlabeled GTP, and ^{3}H-GTP were mixed. 20 μl of this nucleotide mixture in 1× Buffer was added to each well.

(3) 1 μl of each test compound dilution was added in triplicate to each well except for the Enzyme/RNA and RNA alone control wells. The control wells received 1 μl of 100% DMSO.

(4) 1 μl of each stock solution of zinc acetate control inhibitor was added to wells in duplicate. 50× zinc acetate stock solutions used were 16, 8, 4 and 2 mM for final concentrations of 320, 160, 80, and 40 μM.

(5) In order of addition, 1× Buffer, DTT, RNasin, Biotin-Oligo$(G)_{12}$, and polyC were mixed and incubated at room temperature for 15 minutes. Enzyme was added, mixed, and 5 μl of the Enzyme/RNA/Buffer Mix was added to each well except for the RNA alone control wells. 5 μl of RNA/1× Buffer Mix was added to the RNA alone control wells.

(6) The plate was shaken for 1 min on a mini-orbital shaker (Bellco) to mix the reaction components thoroughly. Plate was incubated at room temperature (~22° C.) for 50 minutes.

(7) The reaction was stopped by adding 50 μl of streptavidin SPA beads (10 mg/mL in PBS w/o Mg^{++} and Ca^{++} supplemented with 100 mM EDTA) to each well. The plate was then shaken again for 15 minutes at room temperature as in (5) to mix the beads.

(8) The plate was then harvested and washed with Filter Plate Wash Buffer by transferring to a filter plate (Unifilter-96 GF/B white microplate from Packard) using a harvester (Tomtec). Plate was allowed to dry for 30 minutes at 37° C. After drying, the adhesive backing tape (supplied by manufacturer) was applied to the bottom of the Unifilter plate. The top was covered with TopSeal microplate sealing film.

(9) The radioactivity in each well was counted using a TopCount Scintillation/Luminescence Counter.

Representative date for HCV RdRp inhibitors of the invention are shown in Table 1.

Example 43

High Throughput Assay for HCV NS5B RNA-dependent RNA Polymerase

The Scintillation Proximity Assay (SPA) for HCV NS5B RdRp we developed uses an RNA homopolymer (polyc) complexed with a biotinylated oligoG12 primer. The primer can be added directly to the template without a denaturing and annealing process. The assay specifically measures the incorporation of [3H] labeled GMP into PolyG. The biotinylated G12 enables the capture of the [3H] labeled products by streptavidin-coated SPA beads.

The NS5B enzymes, NS5BCT21-His and NS5BCT55, used in this assay were purified as polyhistidine (His6) fusion proteins expressed in *E. coli*. The NS5BCT21-His protein has been modified by removing a 21 amino acid hydrophobic domain from the C-terminus. A His6-tag was fused to the protein at the C-terminus, replacing the deleted hydrophobic domain. The NS5BCT55 protein has been modified by removing a 55 amino acid portion from the C-terminus containing the hydrophobic domain of 21 amino acids and a His6-tag was fused to the protein at the N-terminus. After purification, the His-tag was removed by specific proteolysis.

The substrate of this assay is a RNA homopolymer template (polyC) complexed with a biotinylated primer (oligoG12). [3H]-GTPs are polymerized into polyG complementing the PolyC template.

The assay is carried out at room temperature (~22° C.) in a 96-well plate for three hours. No preincubation is required. The reaction is initiated by mixing the RNA substrate and the enzyme in the presence or absence of test compounds. EDTA is added to a final concentration of 50 mM to stop the reaction. Streptavidin-coated SPA beads (0.5 mg) are then added to each well. After harvesting and a wash by filtration, the radioactivity in each well was counted using a TopCount Scintillation/Luminescence Counter.

The assay conditions were: 50 μl reaction volume at room temperature for three hours in: 20 mM Hepes (pH7.3), 7.5 mM DTT, 10 mM MgCl2, 121 mM NaCl, 100 μg/ml BSA, 2% DMSO, 0.05% glycerol, 5 μM GTP, 1.0 μCi [3H]-GTP, 0.25 μg poly(C)/0.025 μg oligo(G)12, 1 unit of RNaseIN and 0.05 μM NS5BDCT21-His or NS5BDCT55.

MATERIALS			
	1 X	1.25 X	5 X Stock
Enzyme buffers:			
Hepes (pH 7.3),	20 mM	25 mM	100 mM
$MgCl_2$	10 mM	12.5 mM	50 mM
NaCl 120 mM	150 mM	600 mM	
Reaction buffers:			
Hepes (pH 7.3),	20 mM	25 mM	100 mM
$MgCl_2$	10 mM	12.5 mM	50 mM
BSA	100 μg/ml	125 μg/mM	500 μg/ml

Store buffers at 4° C.

Store substrates and enzyme at −80° C.

NS5BCT21-His Enzyme Storage Buffer:

50 mM Hepes (pH7.3), 5 mM DTT, 0.5 M NaCl, 20% Glycerol, 200 ng/ml Antipain, 100 ng/ml Leupeptin, 50 μM PMSF.

Store buffer at −20° C.

NS5BCT55 Enzyme Storage Buffer:

25 mM Hepes (pH7.5), 10 mM β-Mercaptoethanol, 0.6 M NaCl, 15% Glycerol, 0.1% Octyl-glucaside, 2 mg/L Leupeptin, 100 μM PMSF.

Store buffer at −20° C.

Assay Procedures

(1) 9 μl of Rnase-free water is placed in each well on a 96-well Plate (Microtest U Bottom Tissue Culture Plate from Falcon).

(2) In order of addition, Rnase-free H_2O, 5× reaction buffer (with BSA), DTT, cold GTP, and ^{3}H-GTP are mixed. 20 μl of this nucleotide mixture in 1.25× Reaction buffer is added to each well.

(3) In order of addition, Rnase-free H_2O, 5× enzyme buffer (with NaCl), DTT, RNaseIN, Oligo$(G)_{12}$, and polyC are mixed and incubated at room temperature for 15 minutes. Enzyme is added, mixed, and 20 μl of the Enzyme/RNA mixture in 1.25× Enzyme buffer is added to each well except for the RNA alone control wells. 20 ul of Enzyme storage buffer/RNA mixture in 1.25× Enzyme buffer is added to the RNA alone control wells.

(4) 1 μl of each test compound [100% DMSO, 100 μg/ml] is added to each well except for the Enzyme/RNA and RNA alone control wells. The control wells received 1 μl of 100% DMSO.

(5) The plate is shaken gently for 1 min on a mini-orbital shaker (Bellco) to mix the reaction components thoroughly and then incubated at room temperature for 3 hours.

(6) The reaction is stopped by adding 50 μl of streptavidin SPA beads (0.5 mg, resuspended in PBS w/o Mg^{++} and Ca^{++} supplement with 100 mM EDTA to each well. The plate is shaken again as above to mix the beads and incubated at room temperature for 15 minutes.

(7) The plate is then harvested, washed, and transferred to a filter plate using a harvester (Tomtec). The radioactivity in each well is counted using a TopCount Scintillation/Luminescence Counter.

TABLE 1

Inhibition of HCV RdRp[1]
A = >10 μM, B = 1–10 μM, C = <1 μM

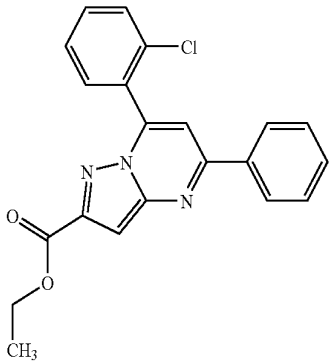
Compound	MOLSTRUCTURE	Δ-55 Activity	Δ-21 Activity
1		A	

TABLE 1-continued

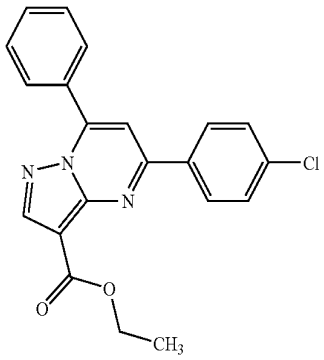
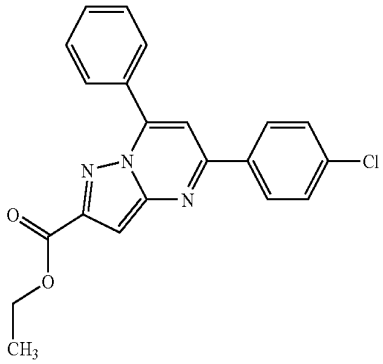
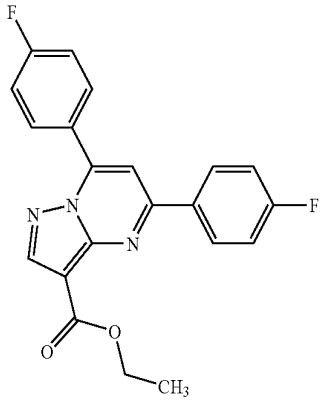
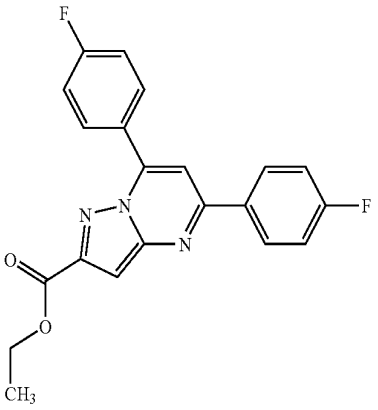
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
2		A	
3		A	
4		A	
5		A	

TABLE 1-continued

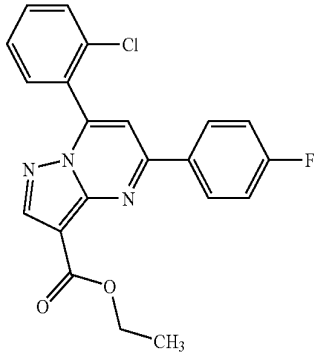
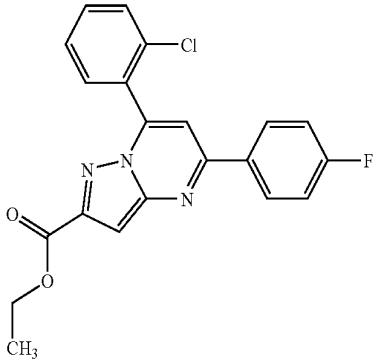
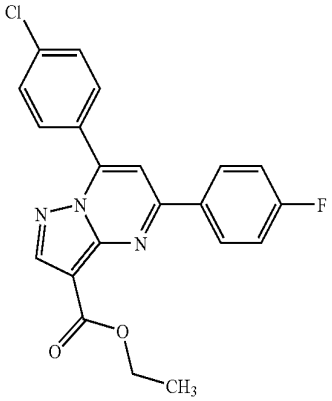
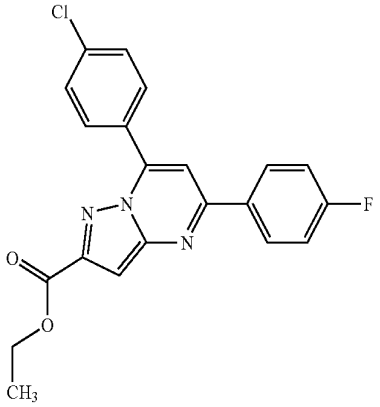
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
6		A	
7		A	
8		A	
9		A	

TABLE 1-continued

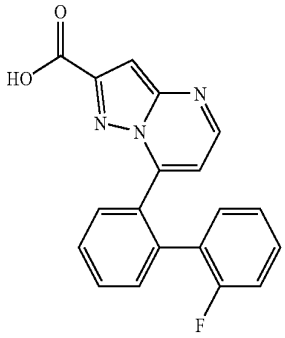
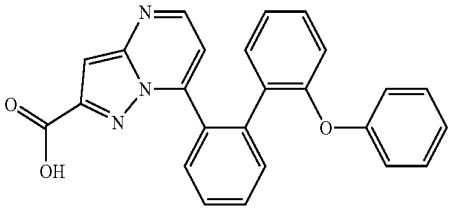
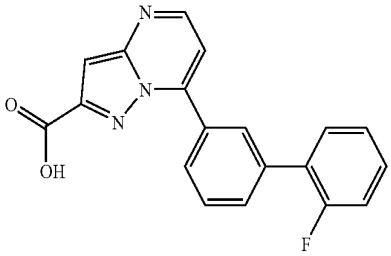
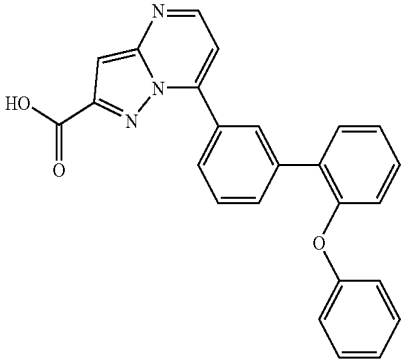
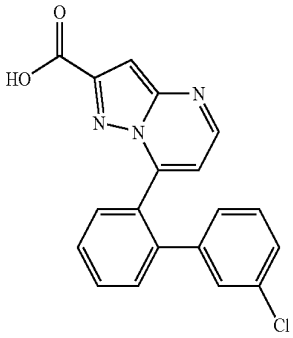
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
10		A	
11		A	
12		A	
13		A	
14		A	

TABLE 1-continued

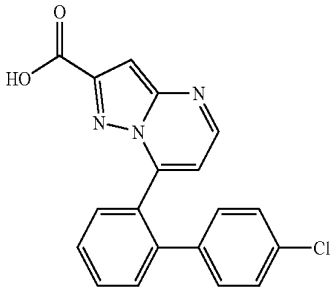
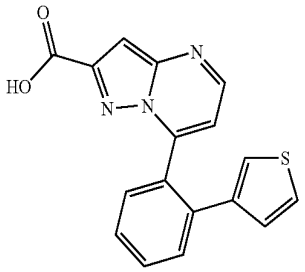
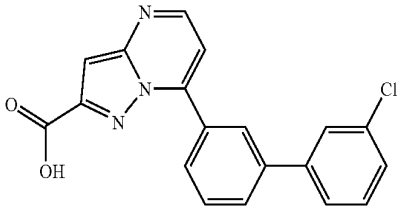
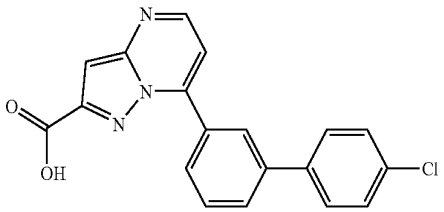
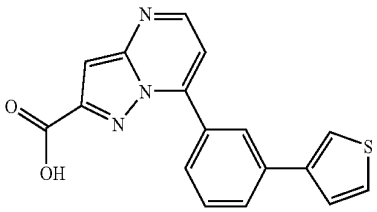
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
15		B	
16		B	
17		A	
18		B	
19		A	

TABLE 1-continued

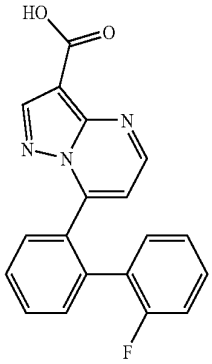
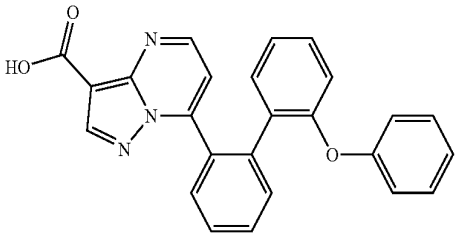
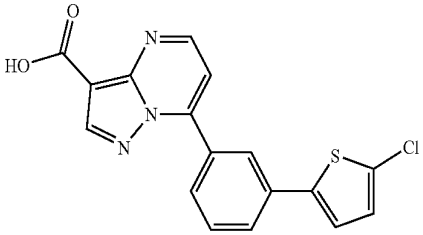
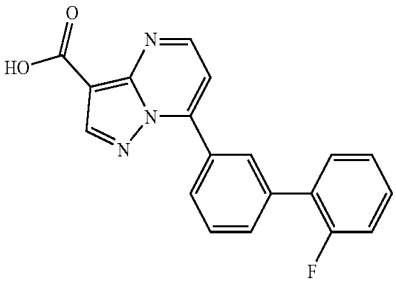
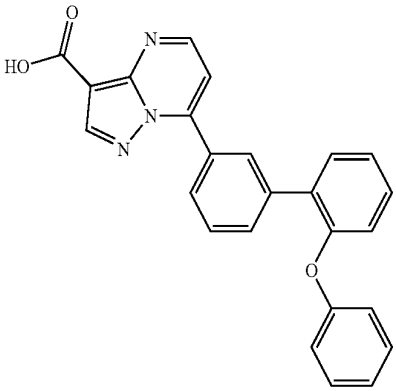
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
20		A	
21		A	
22		A	
23		A	
24		B	

TABLE 1-continued

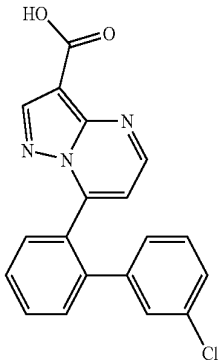
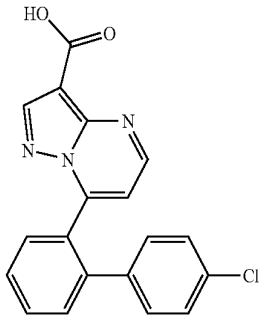
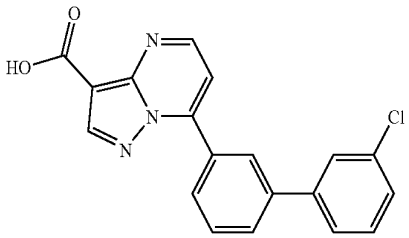
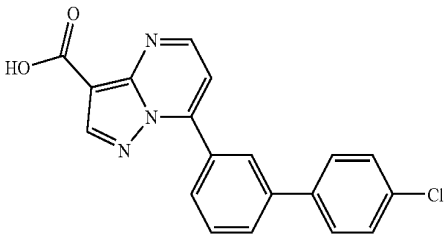
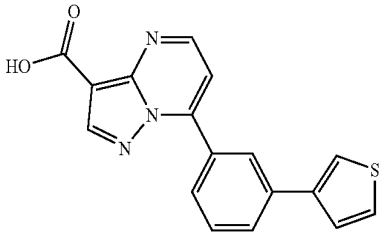
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
25		A	
26		A	
27		B	
28		A	
29		A	

TABLE 1-continued

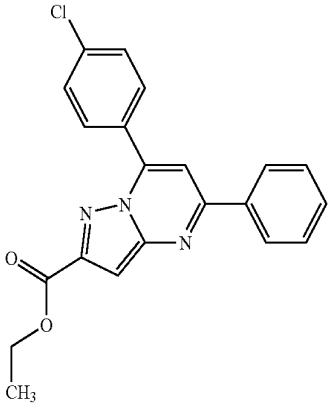
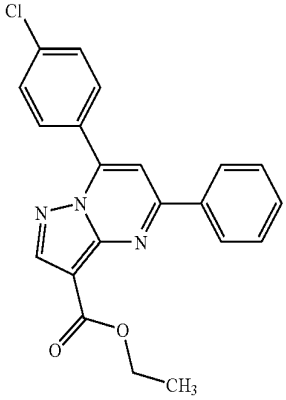
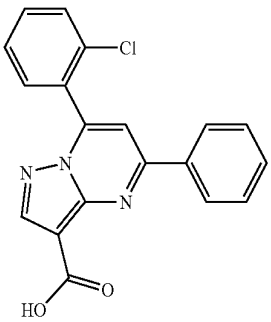
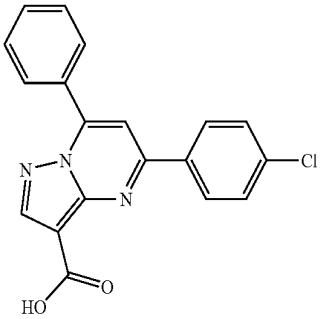
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
30		A	
31		A	
32		A	
33		A	

TABLE 1-continued

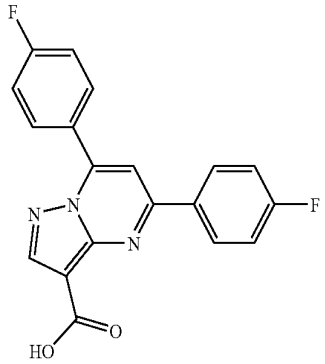
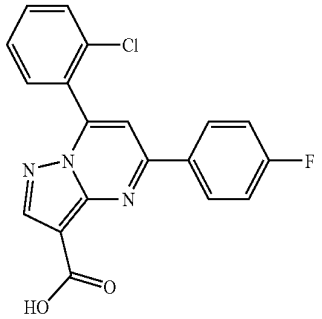
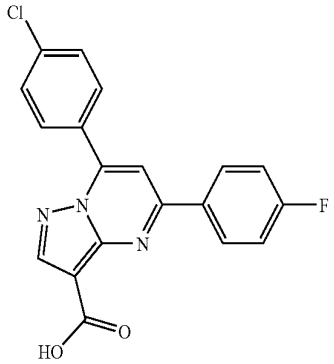
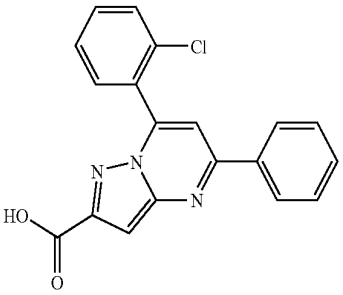
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
34		A	
35		A	
36		A	
37		A	

TABLE 1-continued

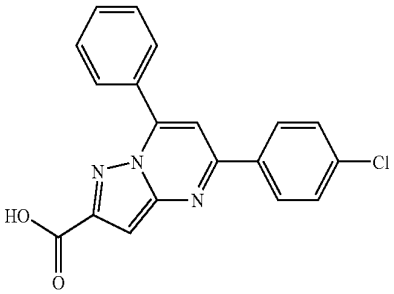
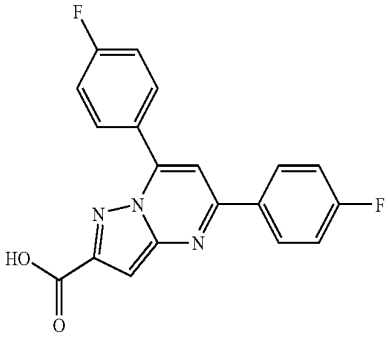
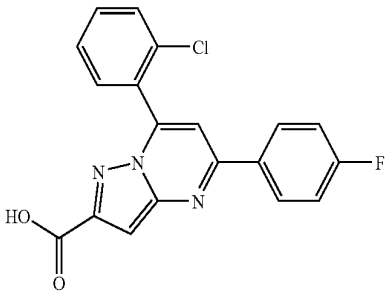
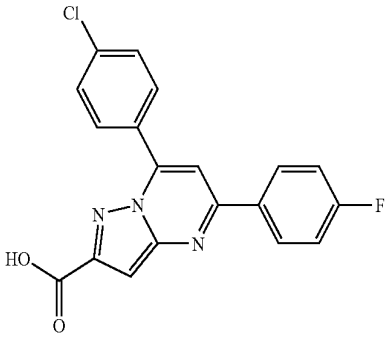
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
38		A	
39		A	
40		A	
41		A	

TABLE 1-continued

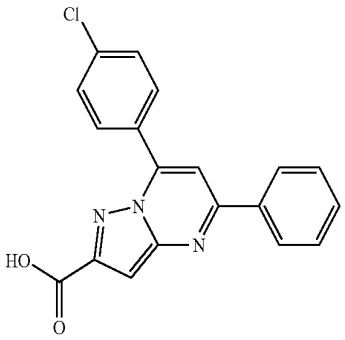
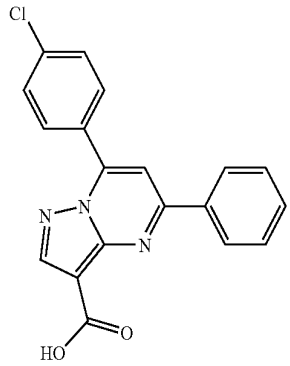
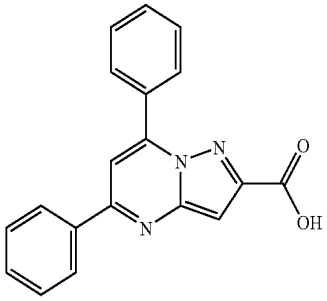
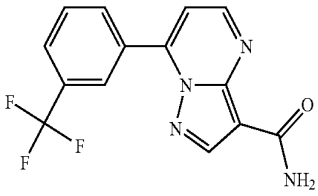
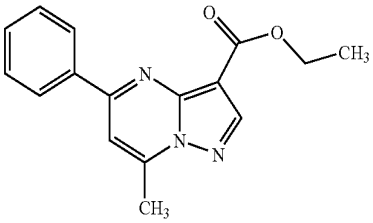
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
42		A	
43		A	
44		A	
45		A	
46		A	

TABLE 1-continued

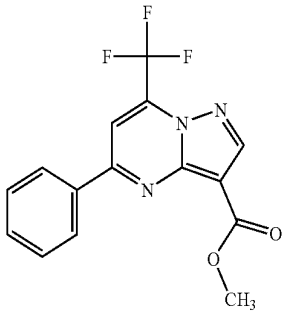
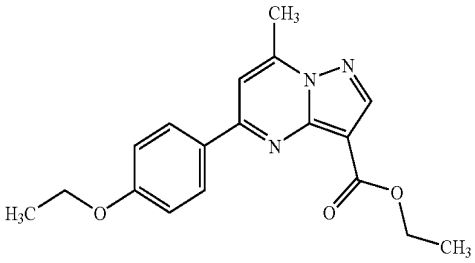
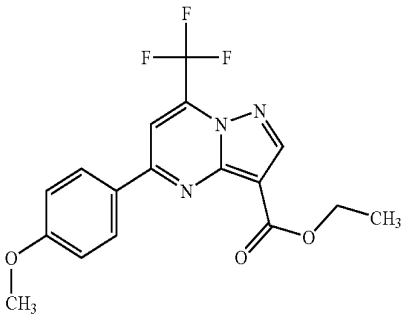
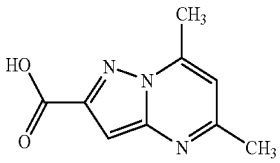
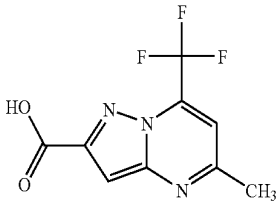
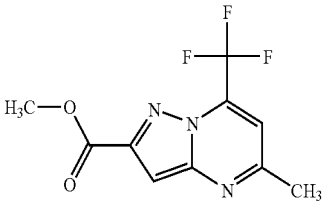
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
47		A	
48		A	
49		A	
50		A	
51		A	
52		A	

TABLE 1-continued

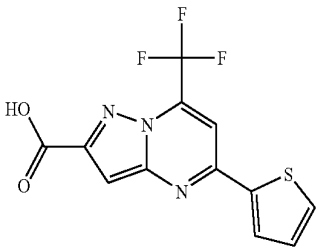
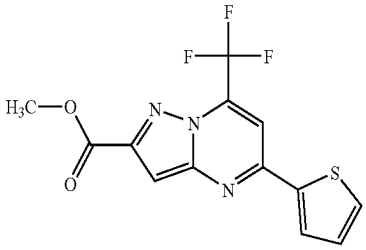
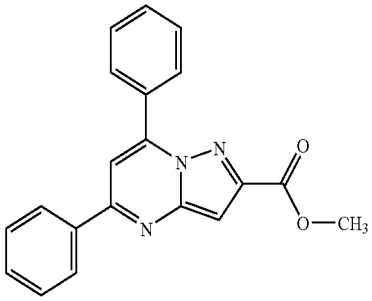
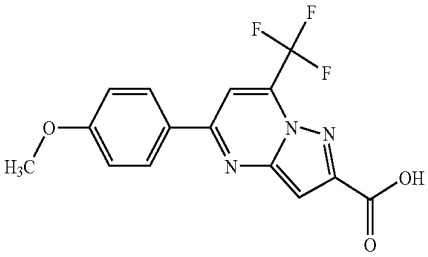
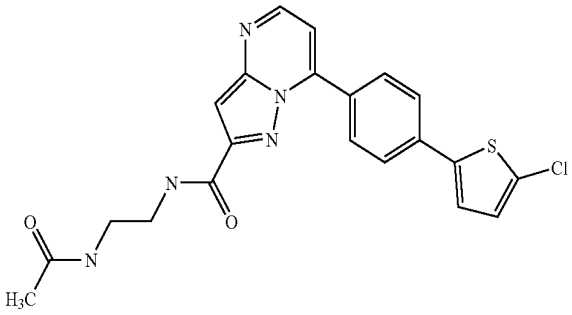
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
53		A	
54		A	
55		A	
56		A	
57		A	

TABLE 1-continued

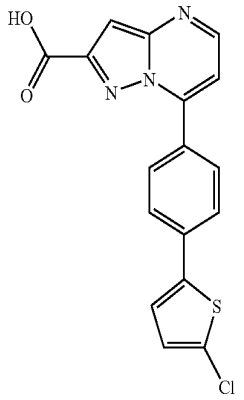
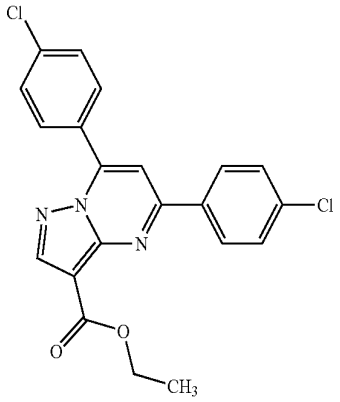
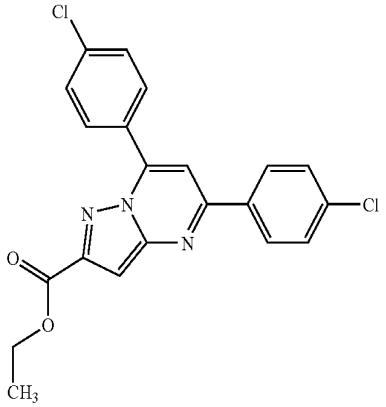
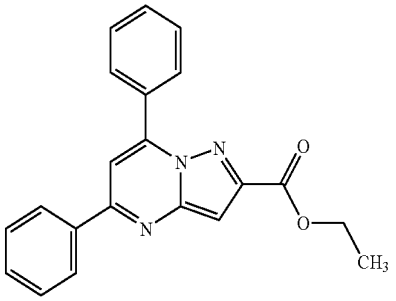
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
58		A	
59		A	
60		A	
61		A	

TABLE 1-continued

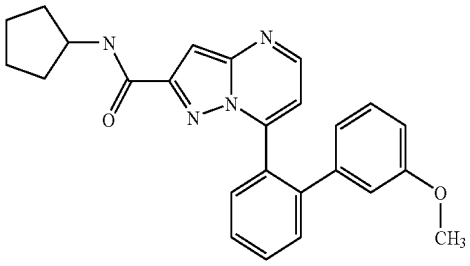
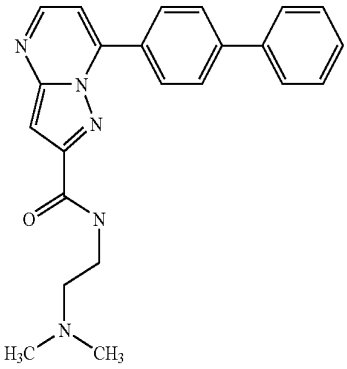
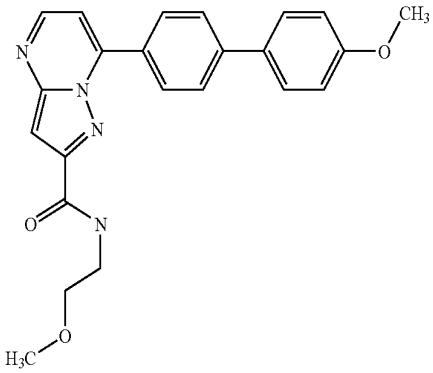
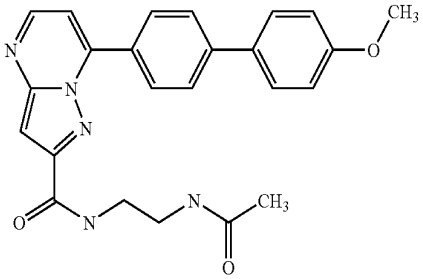
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
62		A	
63		A	
64		B	
65		A	

TABLE 1-continued

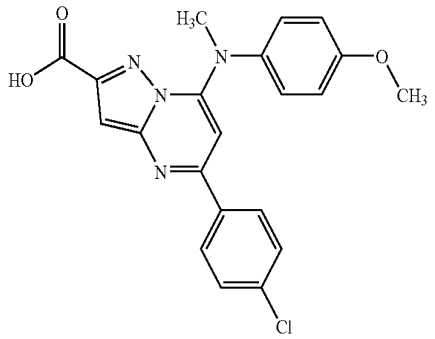
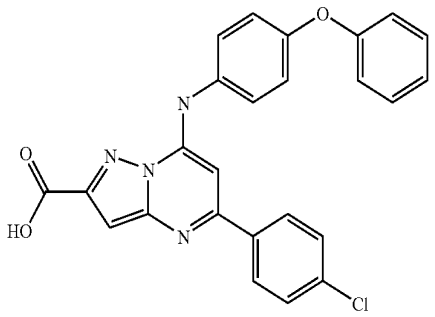
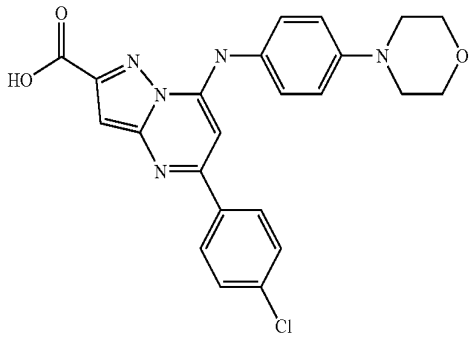
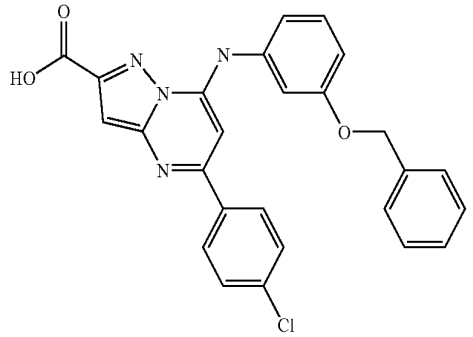
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
66		A	
67		A	
68		A	
69		A	

TABLE 1-continued

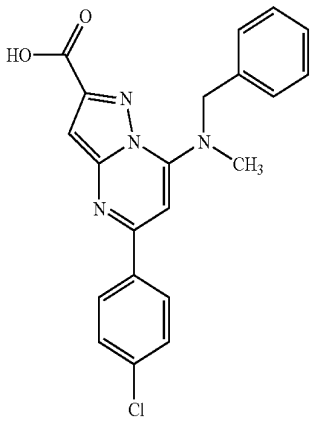
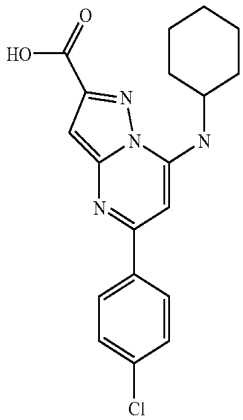
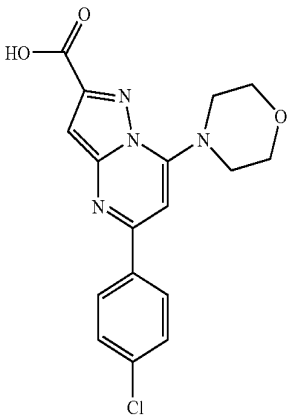
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
70		A	
71		A	
72		A	

TABLE 1-continued

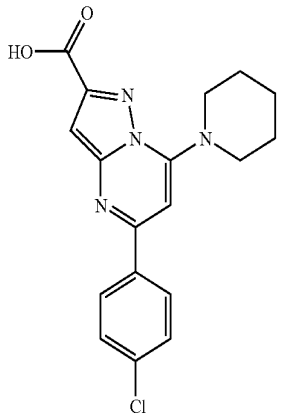
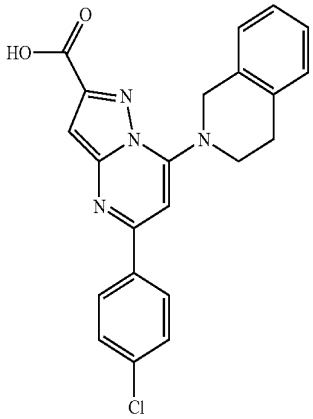
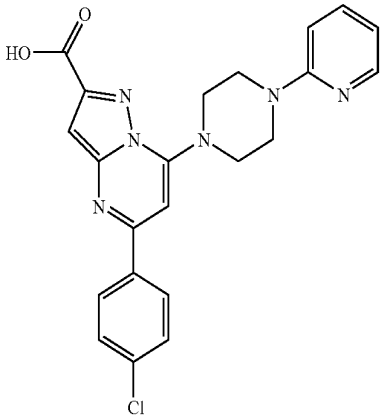
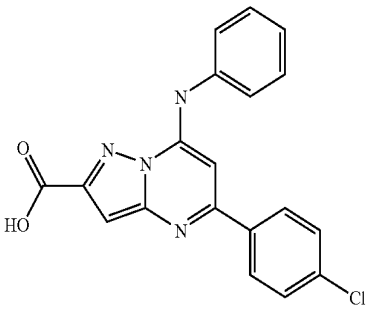
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
73		A	
74		A	
75		A	
76		A	

TABLE 1-continued

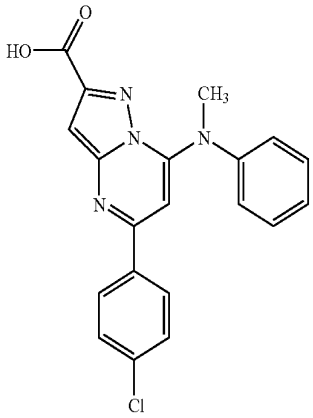
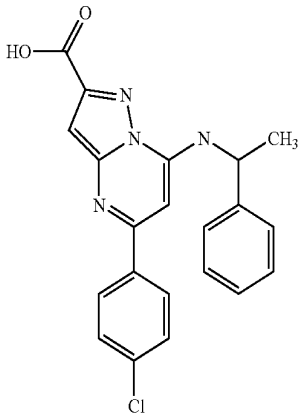
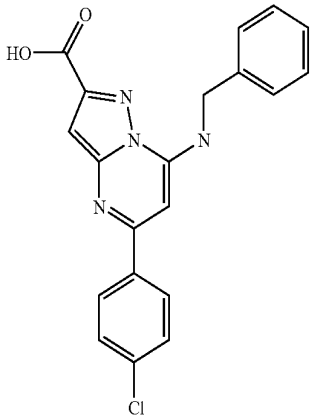
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
77		A	
78		A	
79		A	

TABLE 1-continued

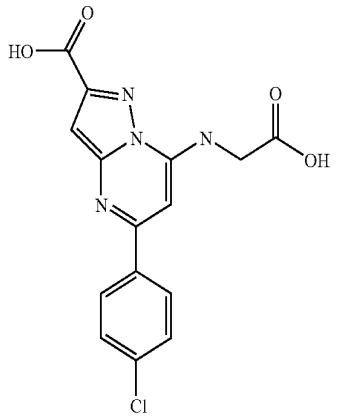
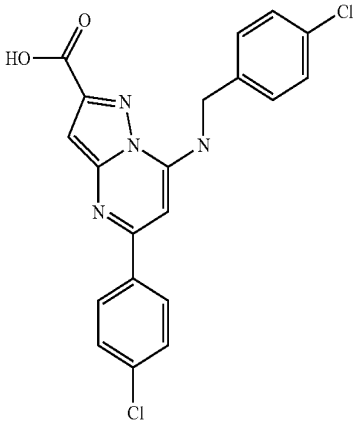
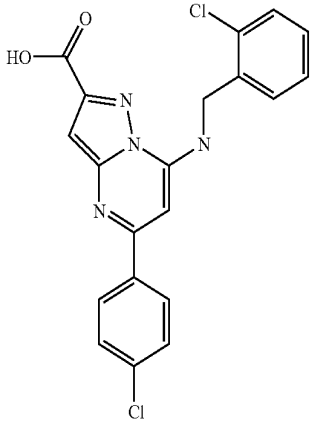
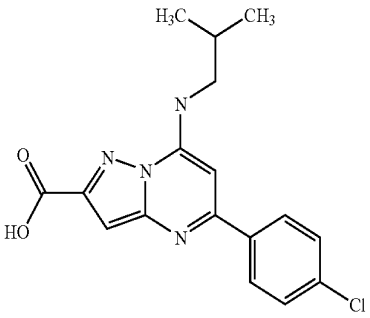
Compound	MOLSTRUCTURE	Δ-55 Activity	Δ-21 Activity
	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM		
80		A	
81		A	
82		A	
83		A	

TABLE 1-continued

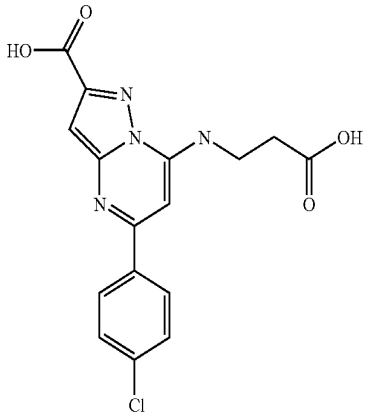
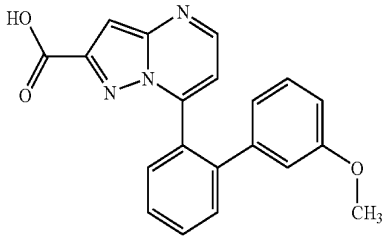
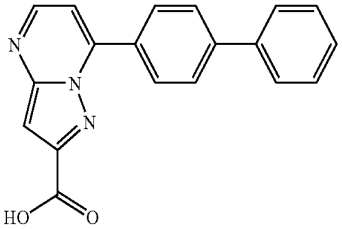
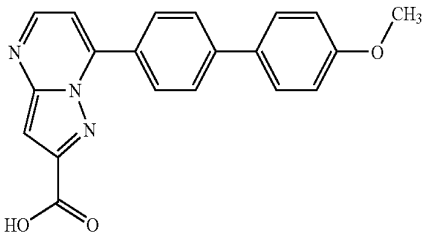
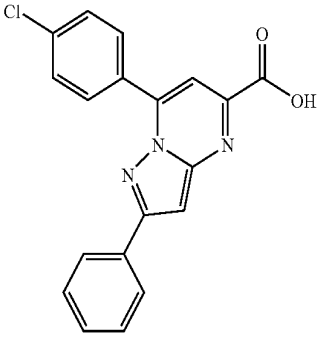
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
84		A	
85		A	
86		A	
87		A	
88		A	

TABLE 1-continued

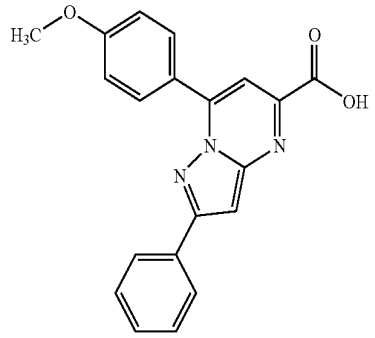
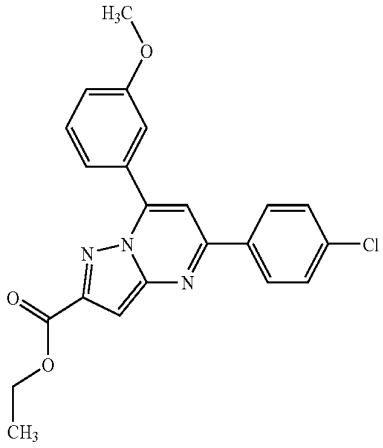
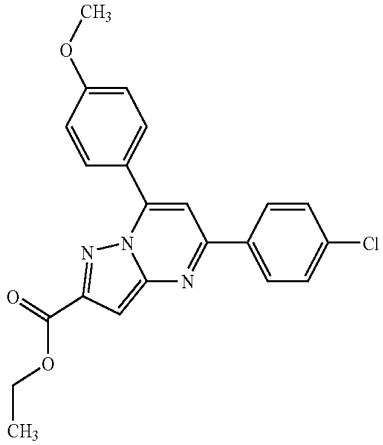
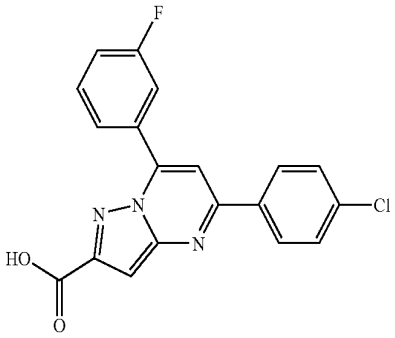
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
89		A	
90		A	
91		A	
92		A	

TABLE 1-continued

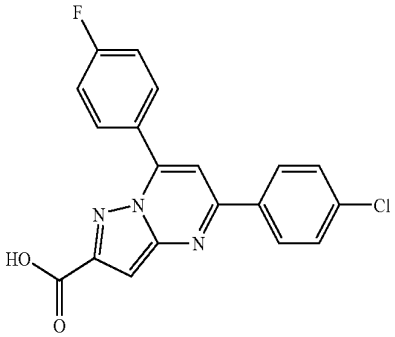
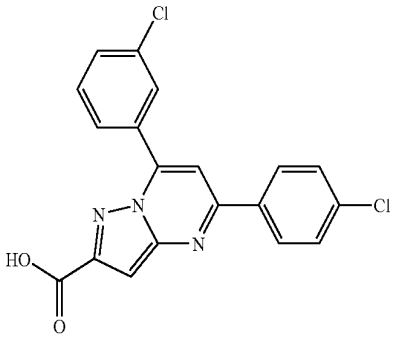
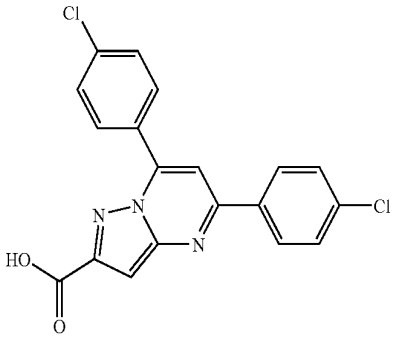
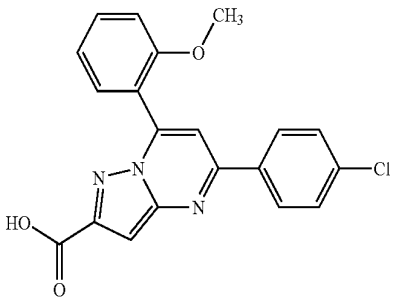
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
93		A	
94		A	
95		A	
96		A	

TABLE 1-continued

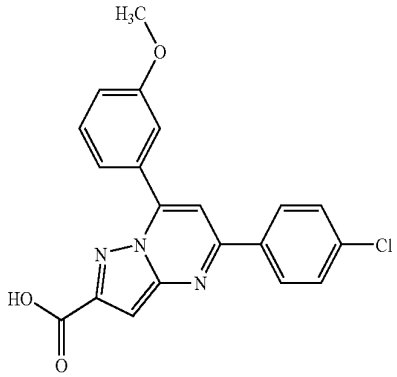
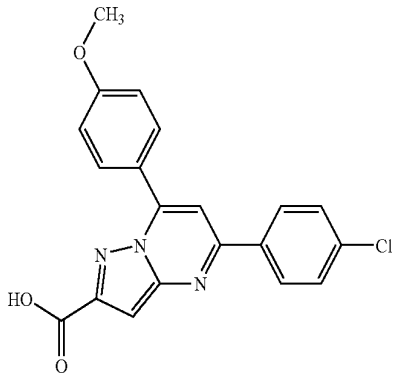
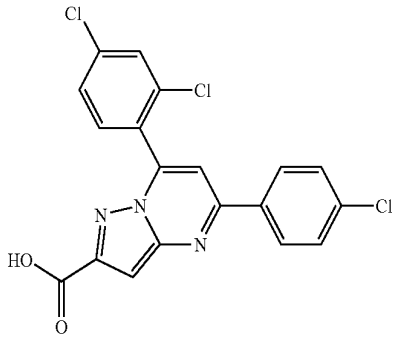
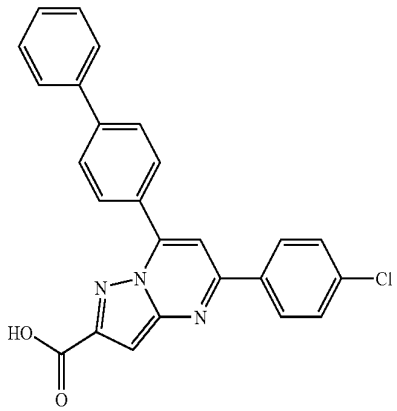
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
97		A	
98		A	
99		A	
100		B	B

TABLE 1-continued

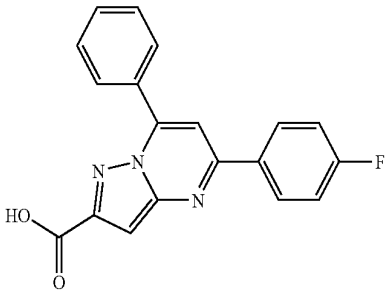
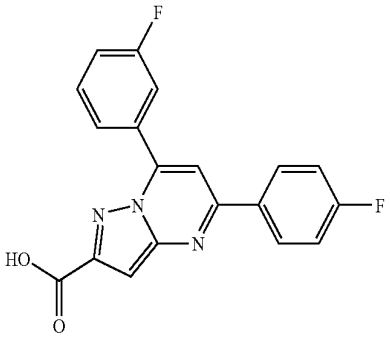
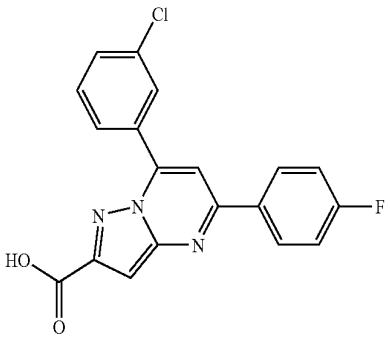
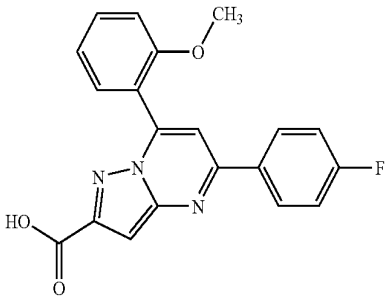
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
101		A	
102		A	
103		A	
104		A	

TABLE 1-continued

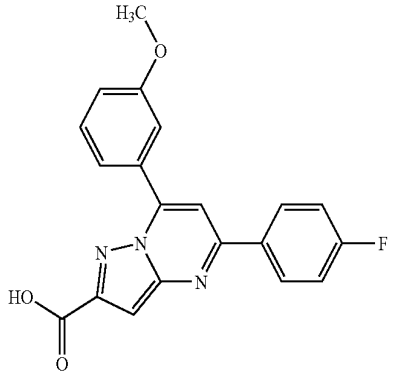
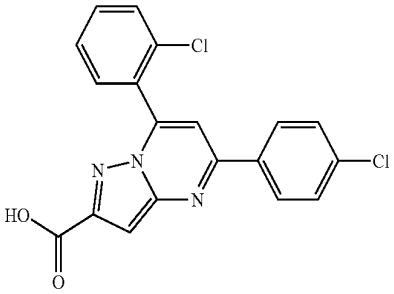
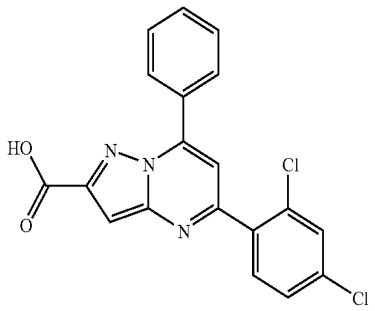
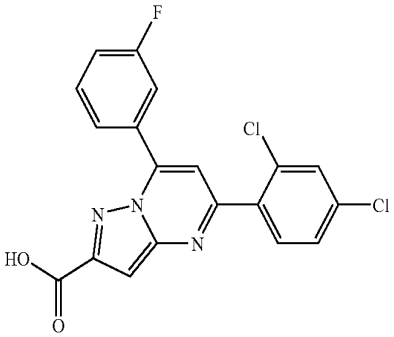
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
105		A	
106		A	
107		A	
108		A	

TABLE 1-continued

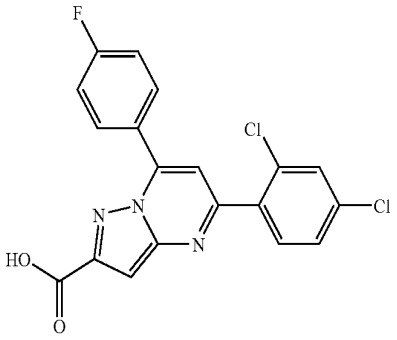
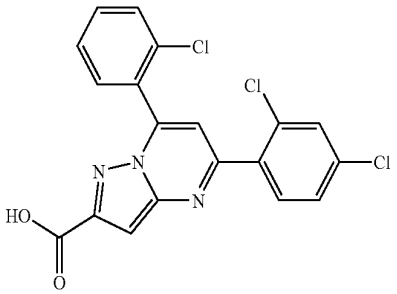
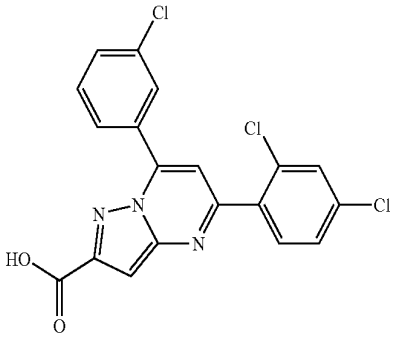
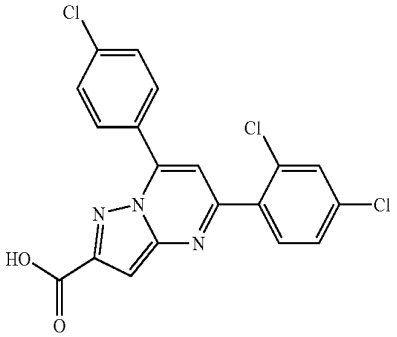
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
109		A	
110		A	
111		A	
112		A	

TABLE 1-continued

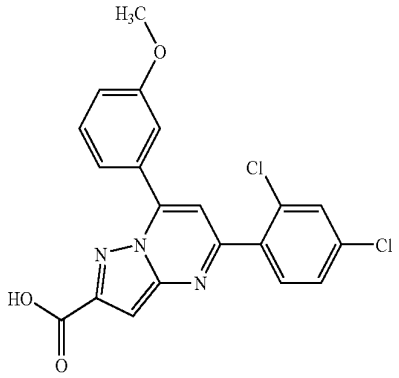
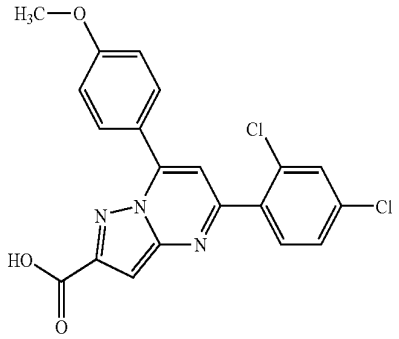
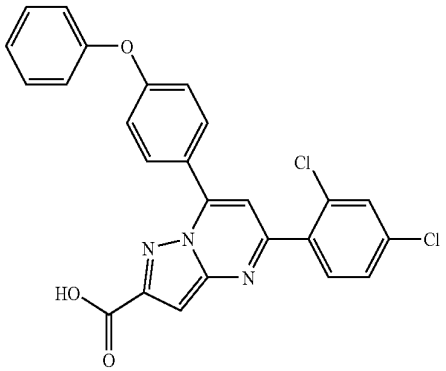
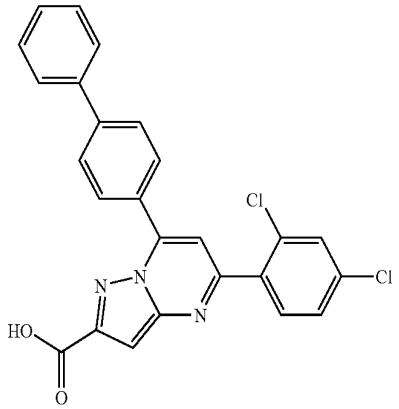
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
113		A	
114		A	
115		A	
116		B	B

TABLE 1-continued

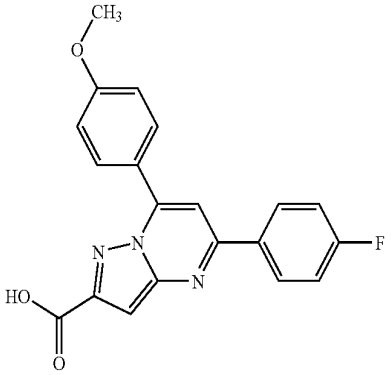
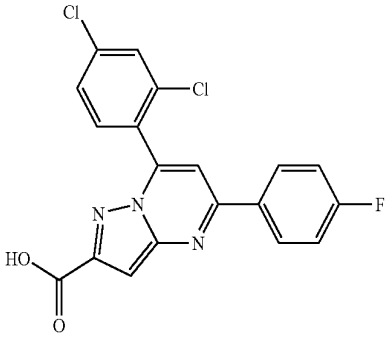
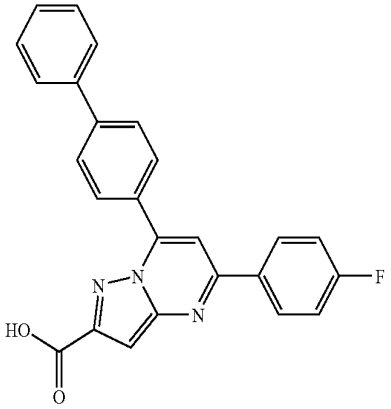
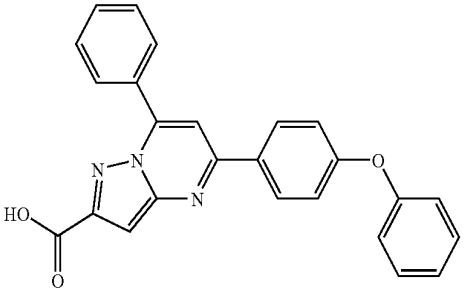
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
117		A	
118		A	
119		B	B
120		A	

TABLE 1-continued

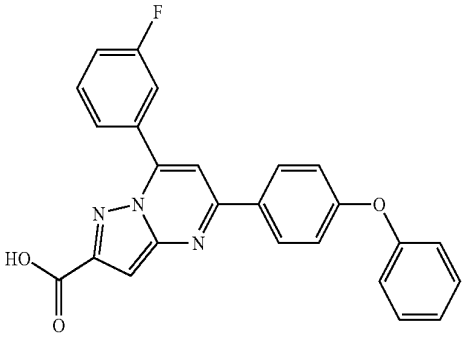
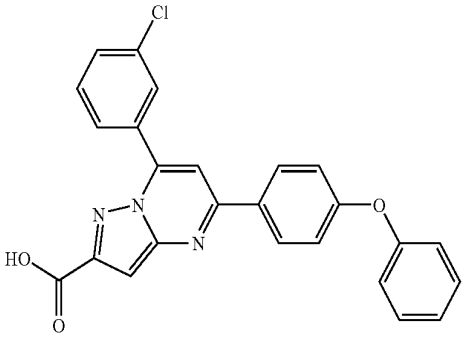
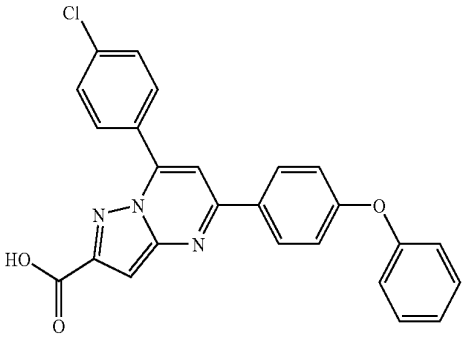
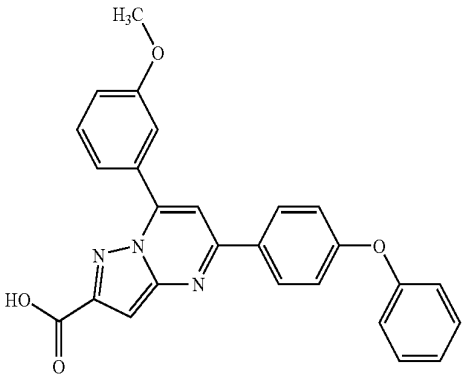
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM	
		Δ-55 Activity	Δ-21 Activity
121		A	
122		B	B
123		B	B
124		B	B

TABLE 1-continued

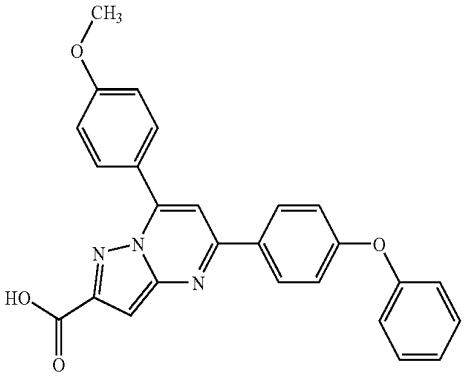
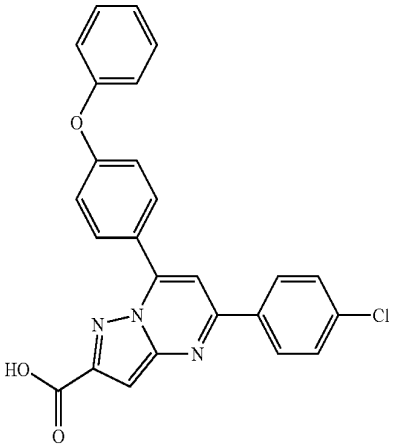
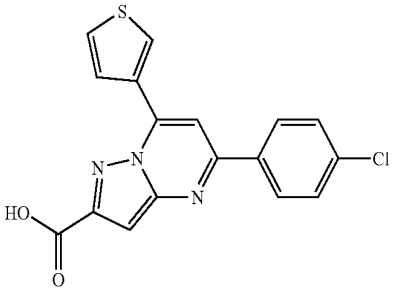
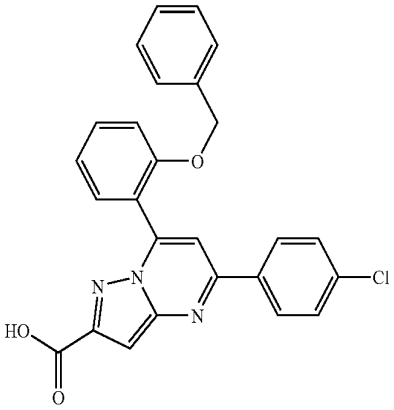
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
125		B	B
126		B	B
127		A	
128		B	B

TABLE 1-continued

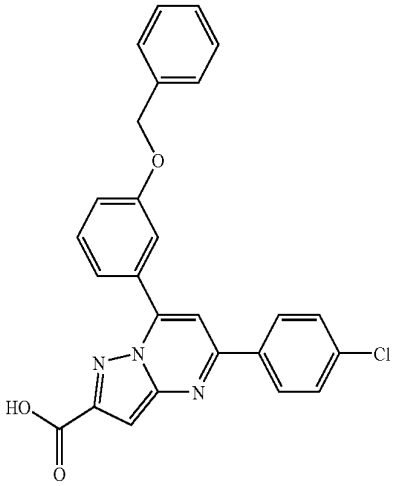
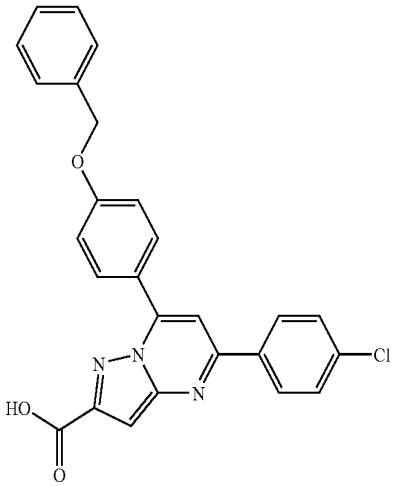
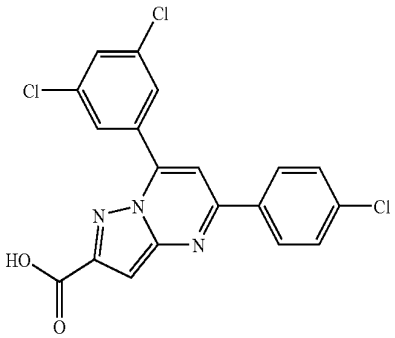
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM	
		Δ-55 Activity	Δ-21 Activity
129		B	B
130		B	B
131		A	

TABLE 1-continued

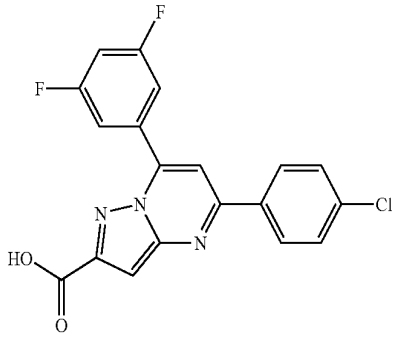
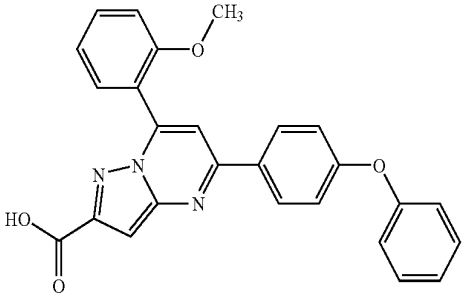
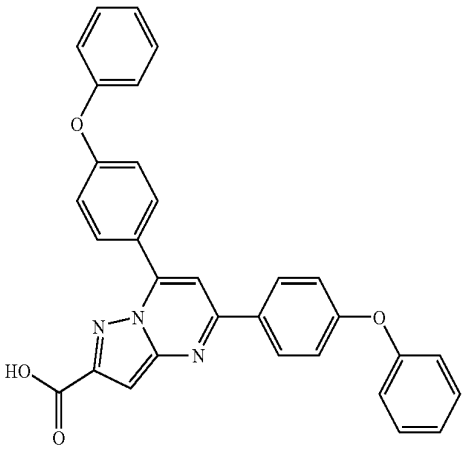
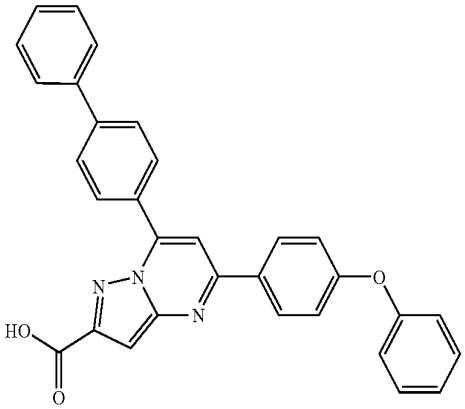
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
132		A	
133		B	B
134		B	B
135		B	B

TABLE 1-continued

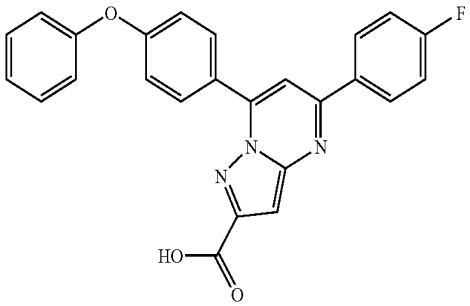
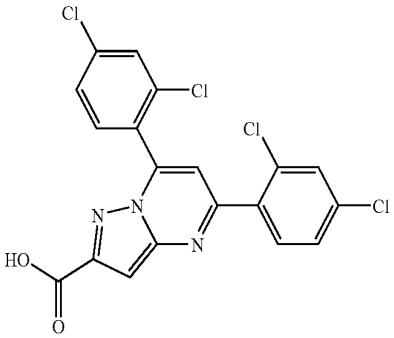
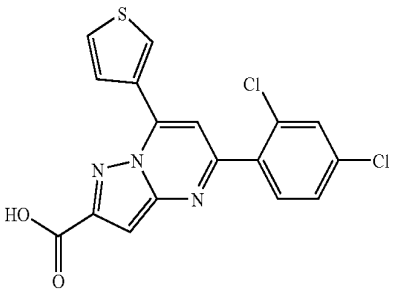
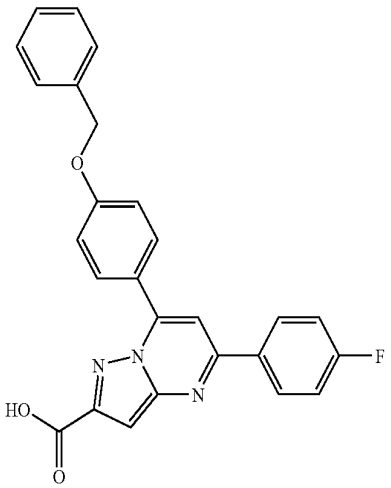
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
136		A	
137		B	
138		A	
139		A	

TABLE 1-continued

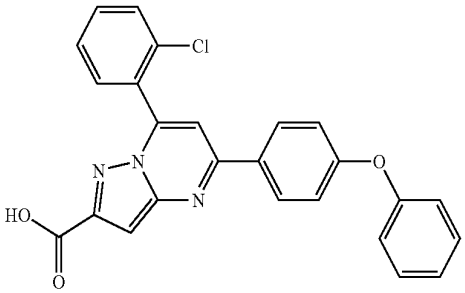
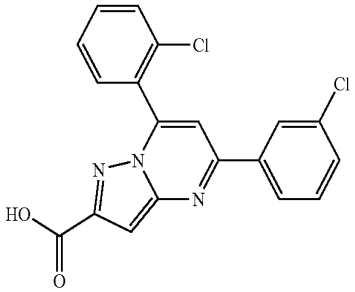
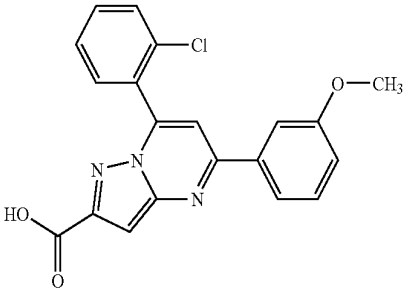
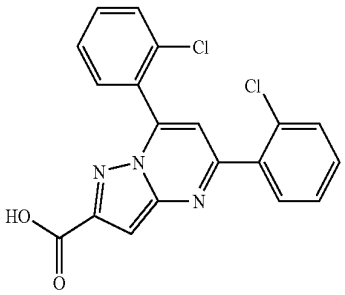
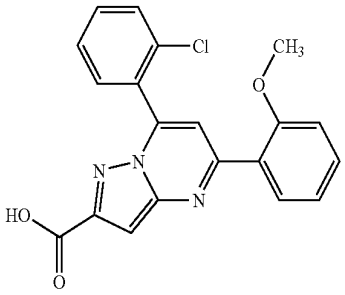
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
140		B	B
141		A	
142		A	
143		A	
144		A	

TABLE 1-continued

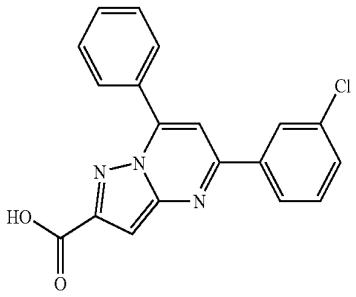
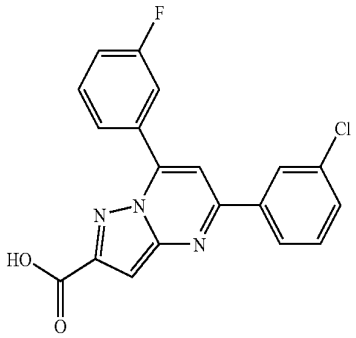
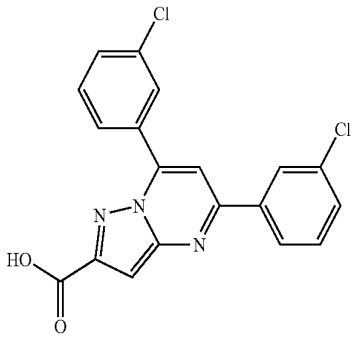
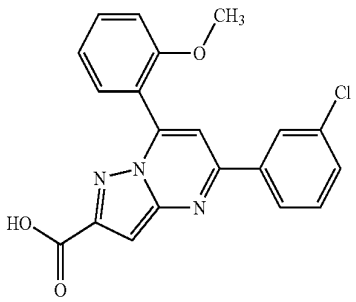
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
145		A	
146		A	
147		A	
148		A	

TABLE 1-continued

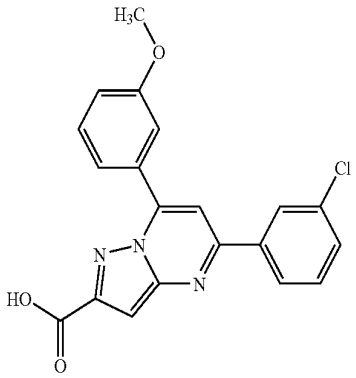
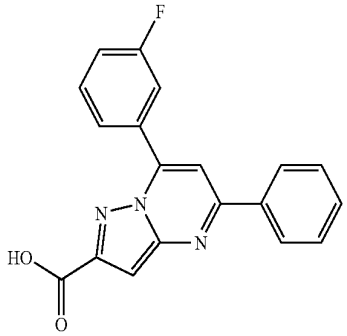
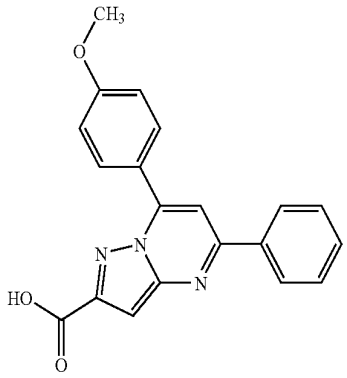
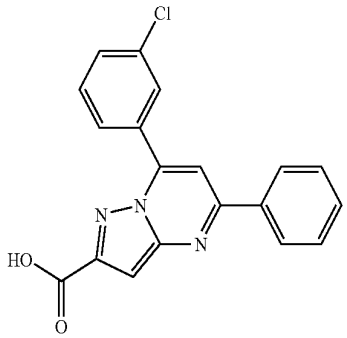
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
149		A	
150		A	
151		A	
152		A	

TABLE 1-continued

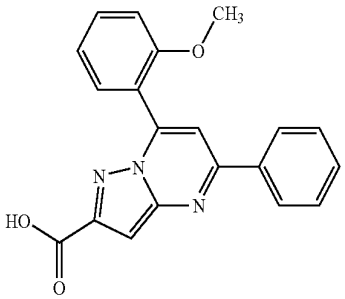
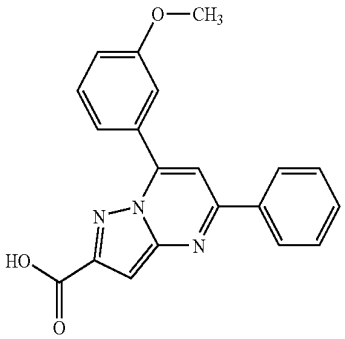
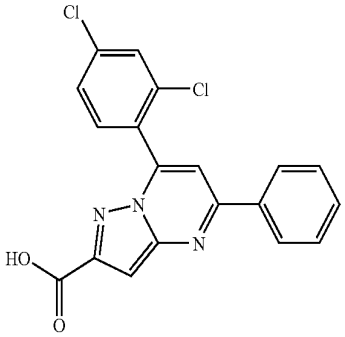
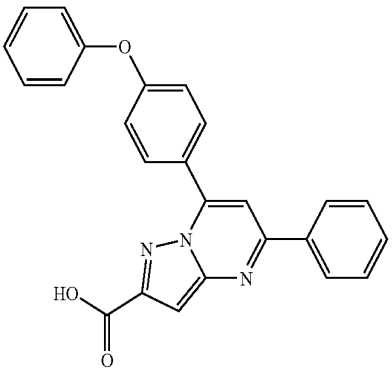
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
153		A	
154		A	
155		A	
156		A	

TABLE 1-continued

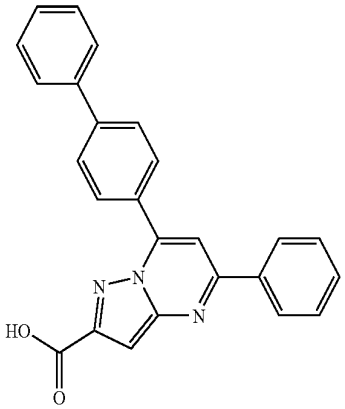
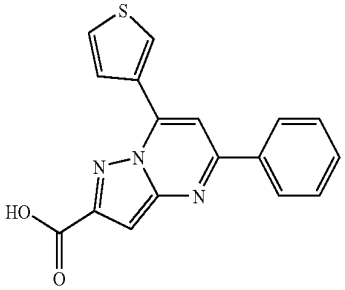
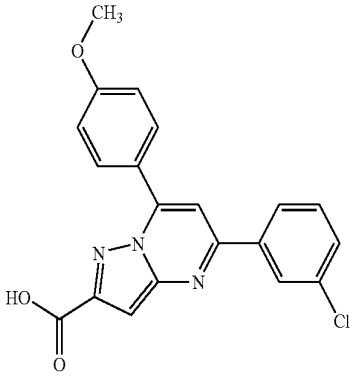
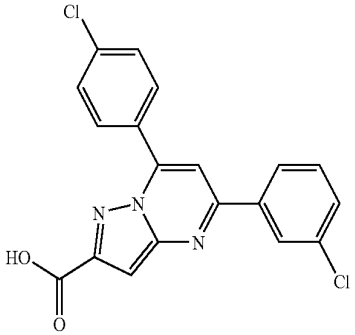
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
157		B	B
158			A
159			A
160			A

TABLE 1-continued

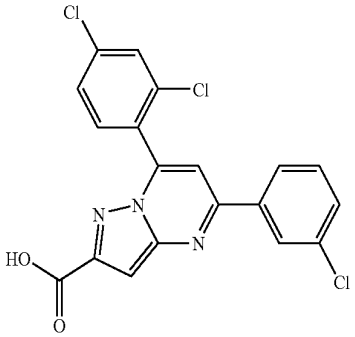
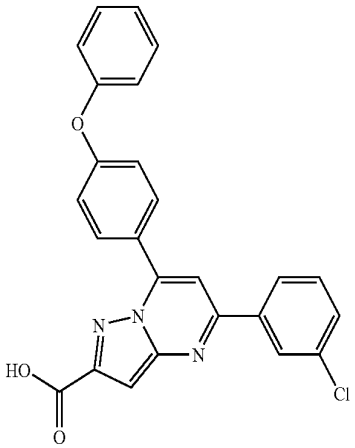
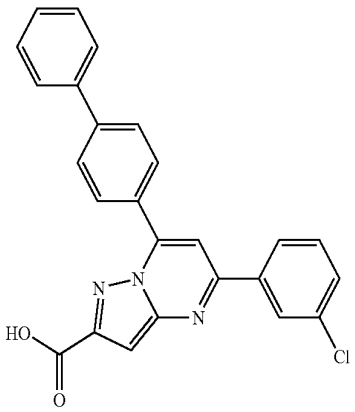
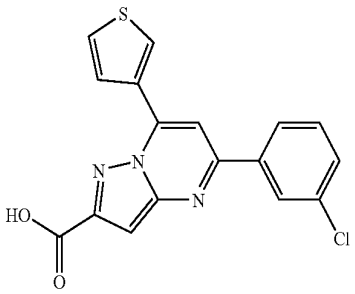
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
161		A	
162		B	B
163		B	B
164		A	

TABLE 1-continued

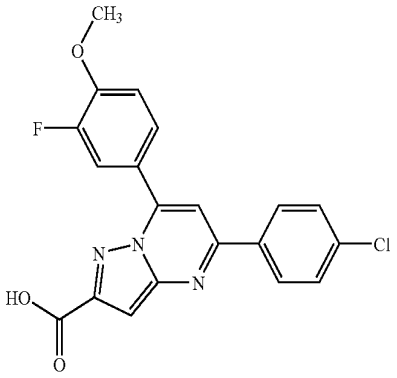
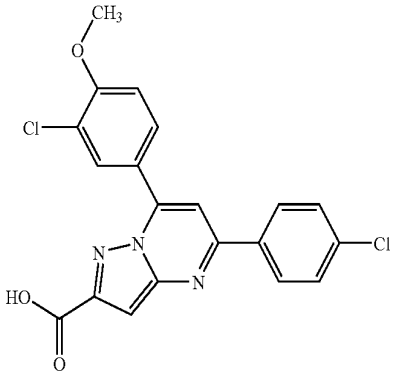
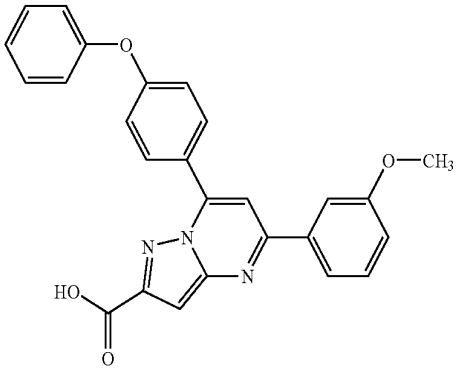
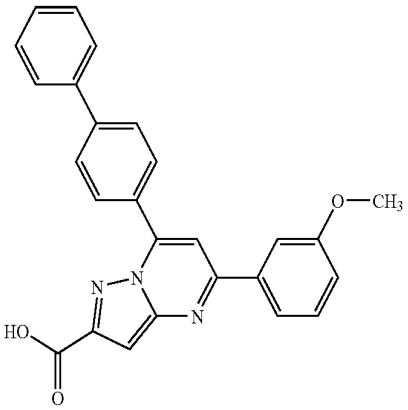
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
165		A	B
166		A	
167		A	
168		B	

TABLE 1-continued

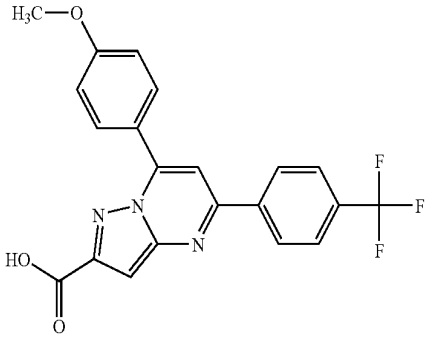
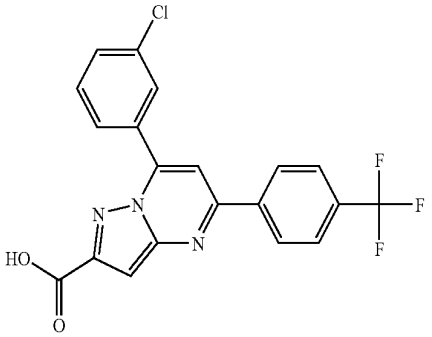
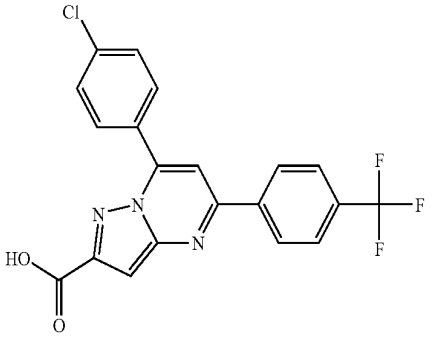
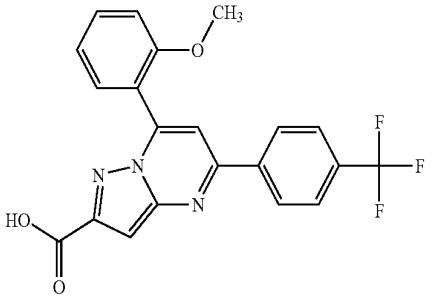
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
169		A	
170		A	
171		A	
172		A	

TABLE 1-continued

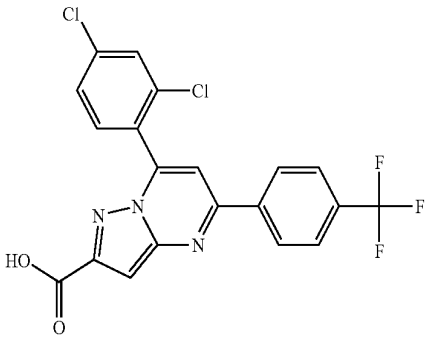
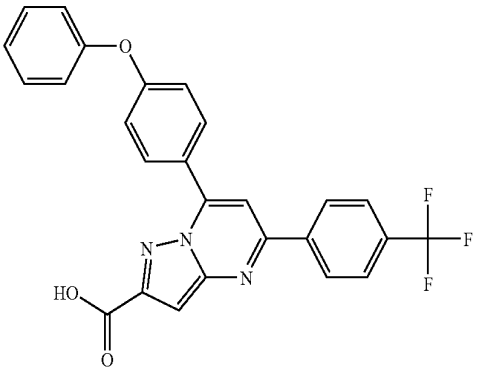
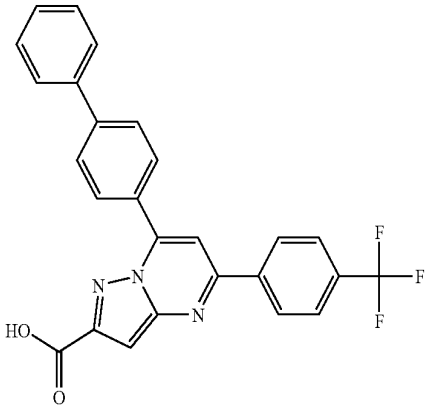
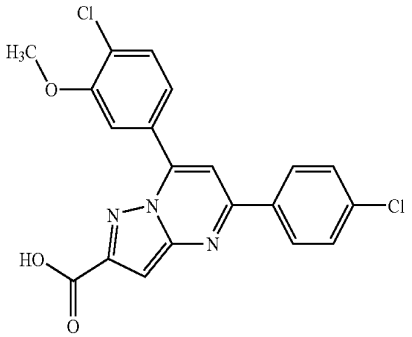
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
173		A	
174		B	
175		B	
176		A	

TABLE 1-continued

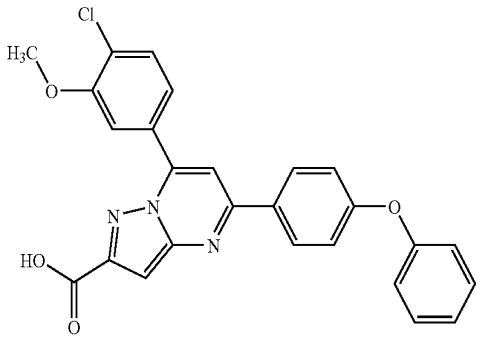
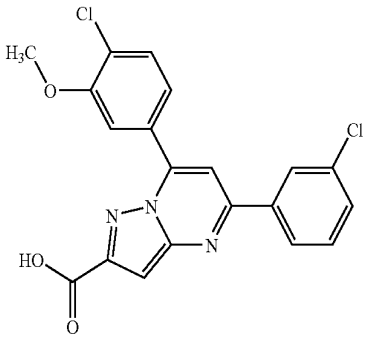
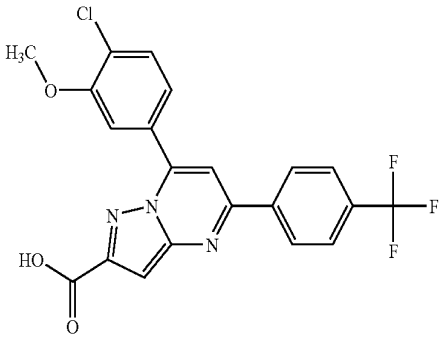
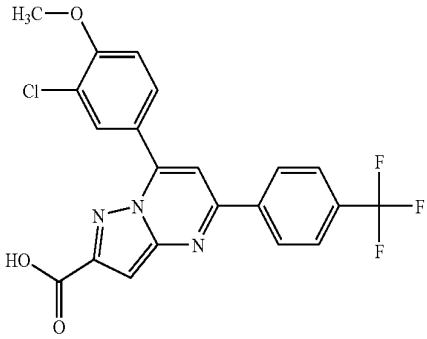
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
177		B	
178		A	
179		A	
180		B	

TABLE 1-continued

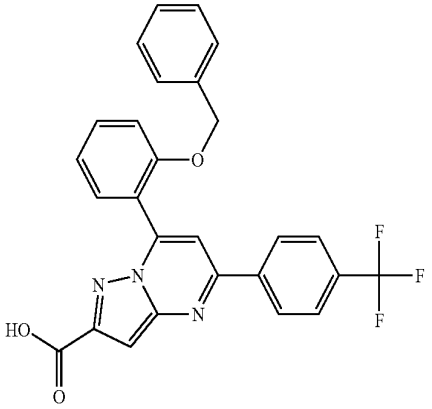
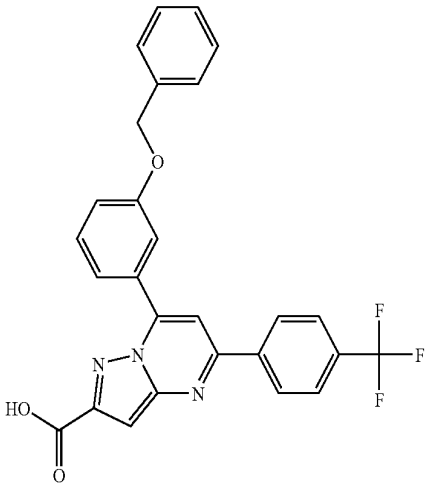
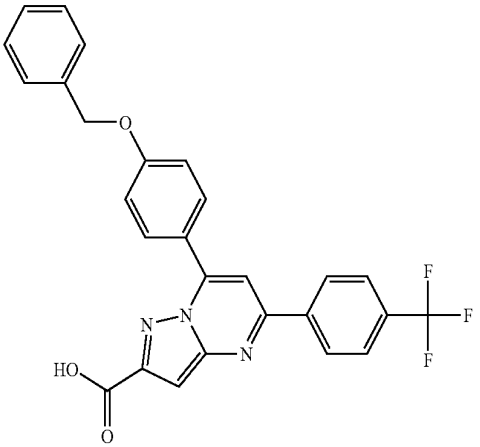
Compound	MOLSTRUCTURE	Δ-55 Activity	Δ-21 Activity
	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM		
181		B	
182		A	
183		B	

TABLE 1-continued

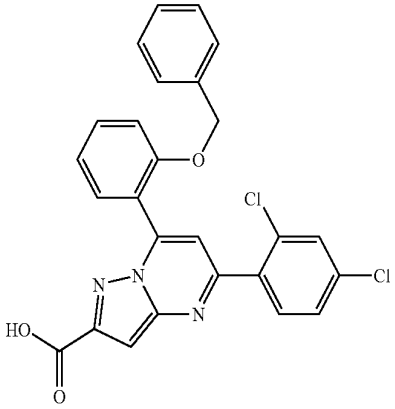
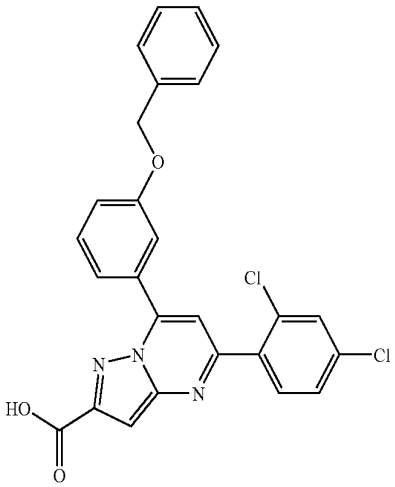
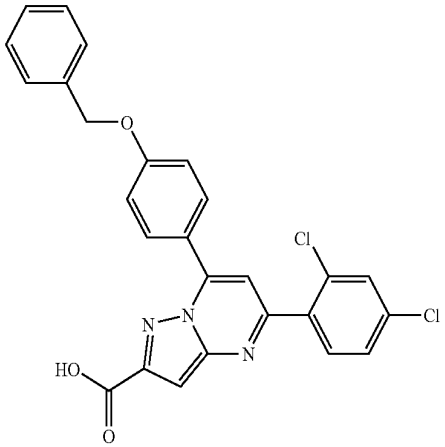
Compound	MOLSTRUCTURE	Δ-55 Activity	Δ-21 Activity
	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM		
184		B	
185		B	
186		B	

TABLE 1-continued

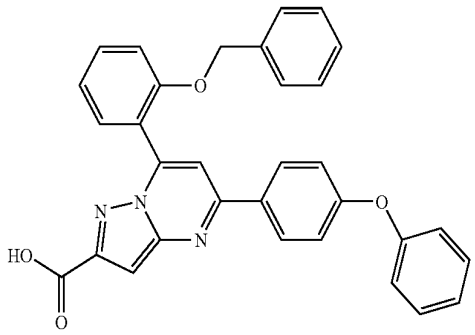
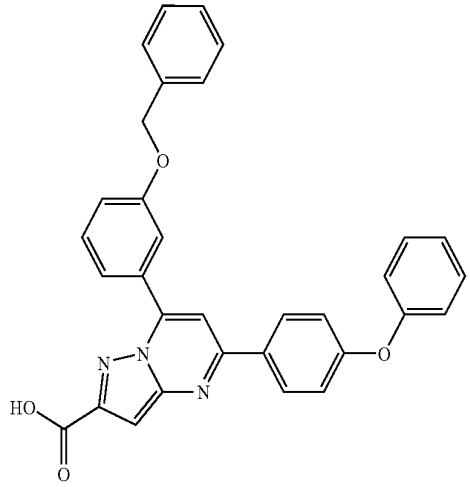
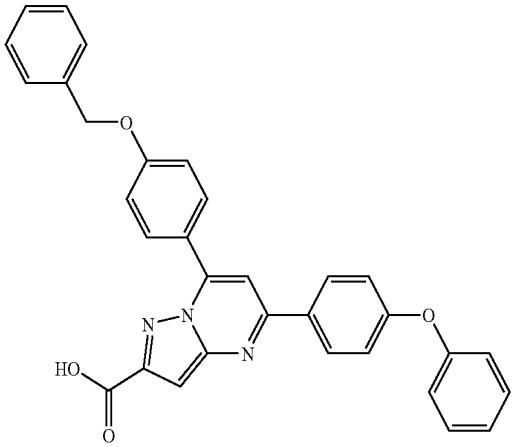
Compound	MOLSTRUCTURE	Δ-55 Activity	Δ-21 Activity
	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM		
187		B	B
188		B	B
189		A	

TABLE 1-continued

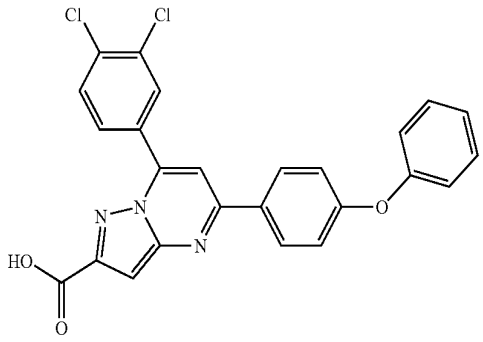
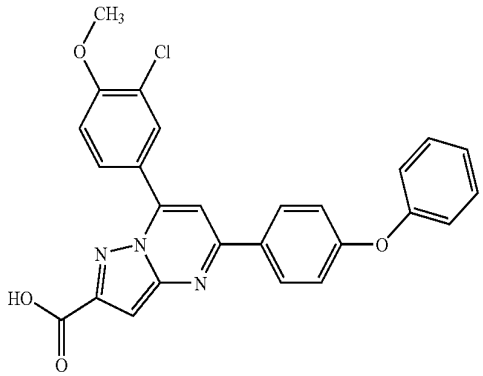
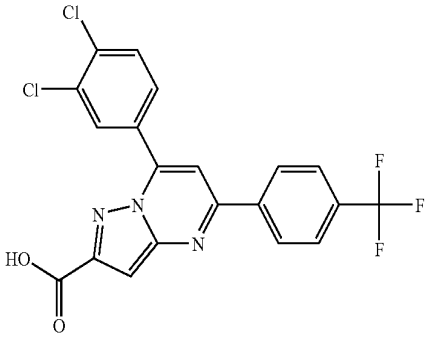
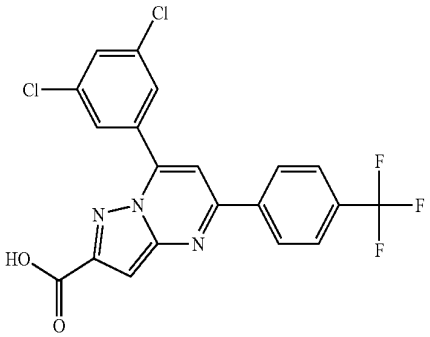
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
190		B	B
191		B	B
192		A	
193		A	

TABLE 1-continued

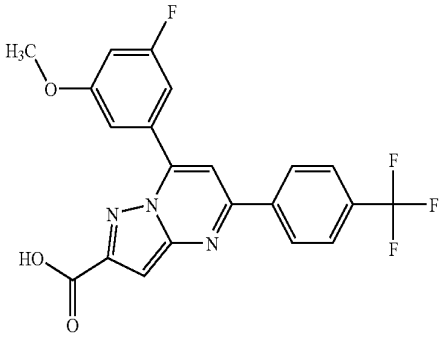
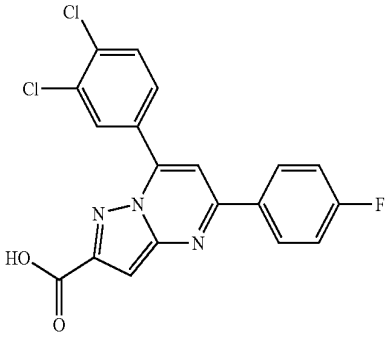
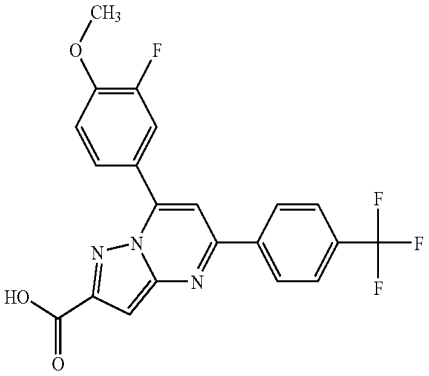
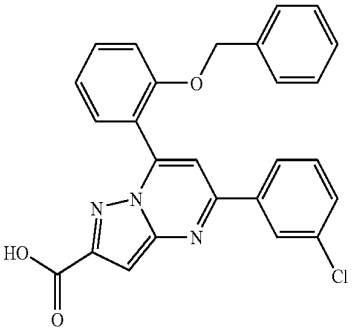
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
194		A	
195		B	
196		A	
197		B	B

TABLE 1-continued

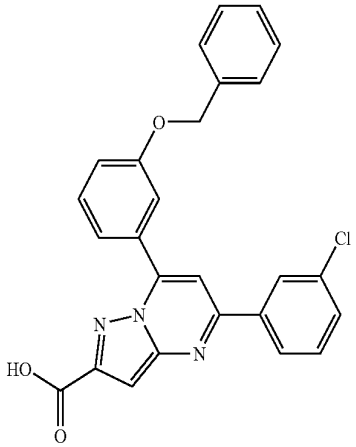
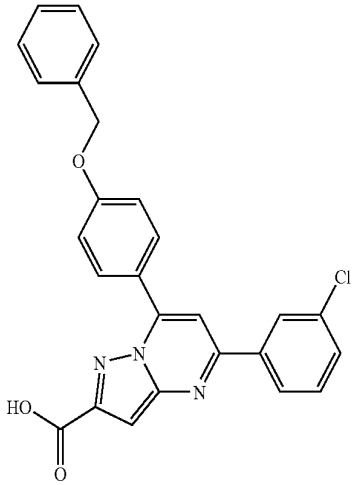
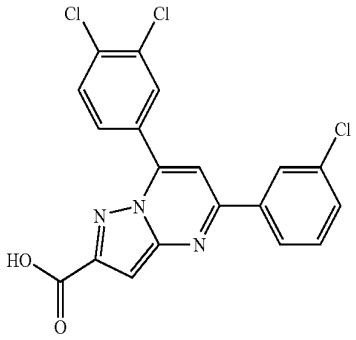
Compound	MOLSTRUCTURE	Δ-55 Activity	Δ-21 Activity
	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM		
198		B	B
199		B	B
200		B	A

TABLE 1-continued

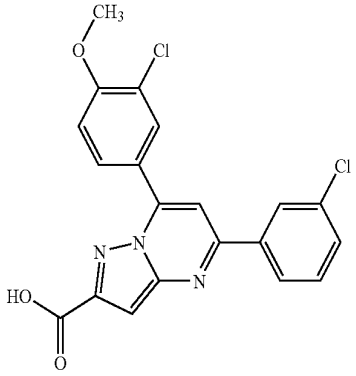
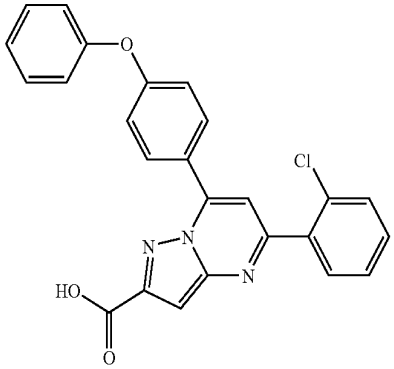
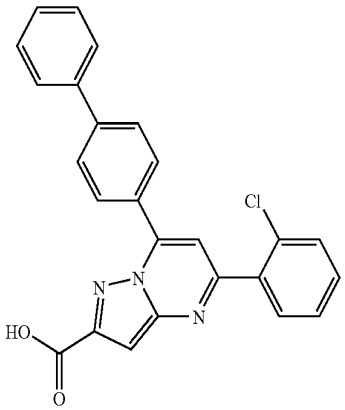
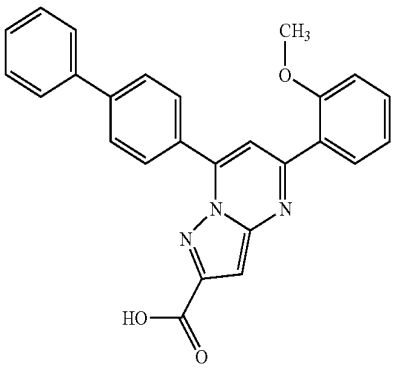
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
201		A	
202		B	B
203		B	
204		A	

TABLE 1-continued

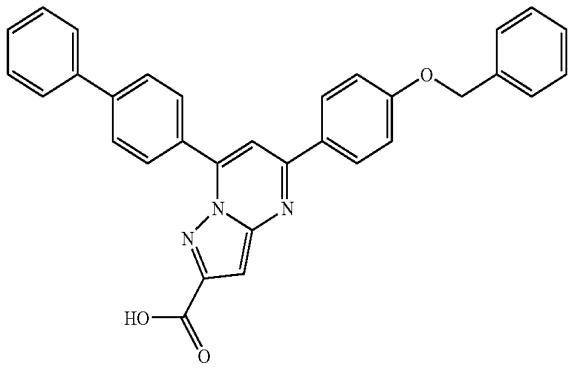
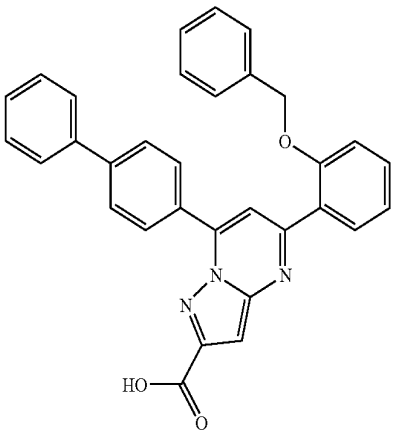
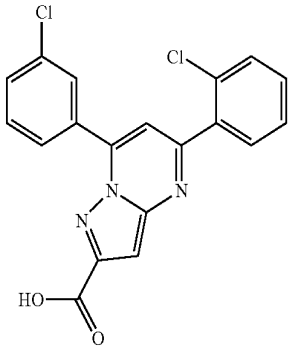
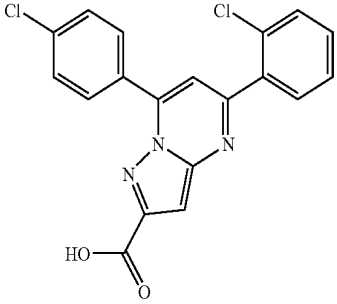
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
205		B	B
206		B	B
207		A	
208		A	

TABLE 1-continued

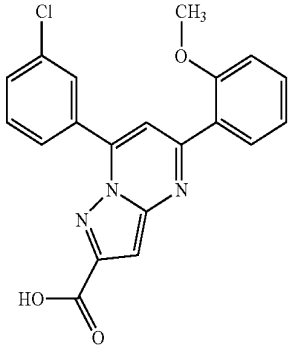
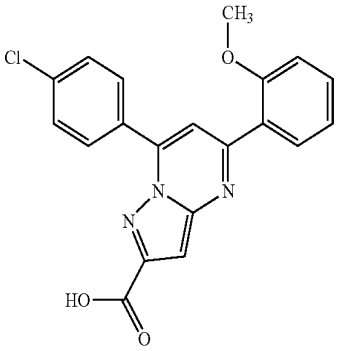
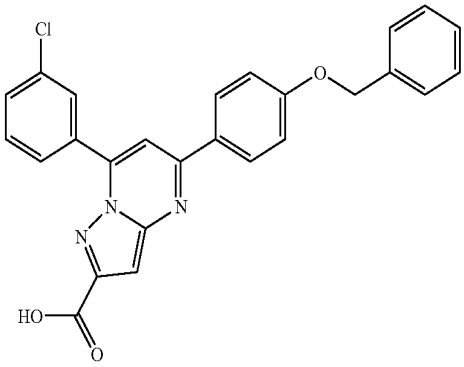
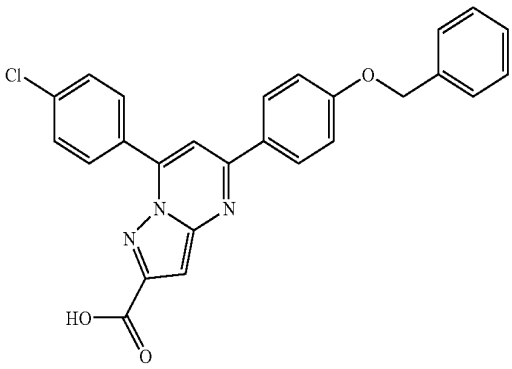
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM	
		Δ-55 Activity	Δ-21 Activity
209		A	
210		A	
211		B	B
212		B	B

TABLE 1-continued

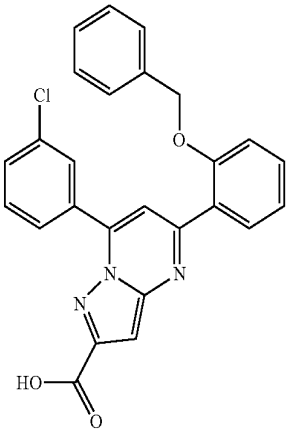
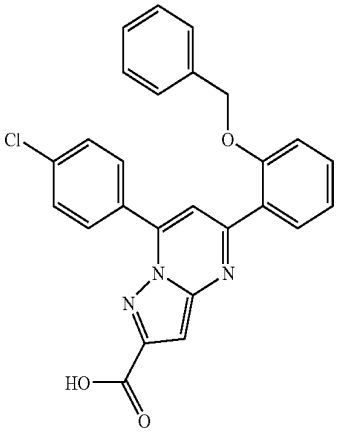
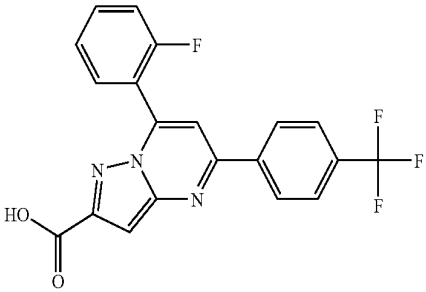
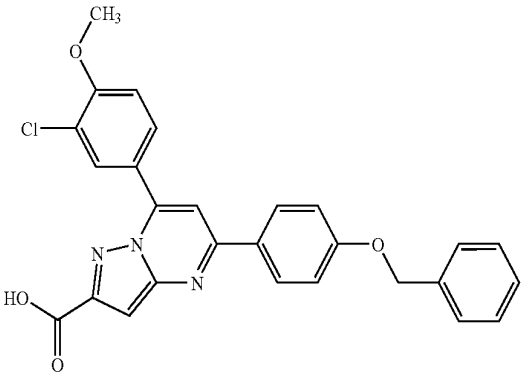
Compound	MOLSTRUCTURE	Δ-55 Activity	Δ-21 Activity
	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM		
213		A	
214		B	B
215		A	
216		B	

TABLE 1-continued

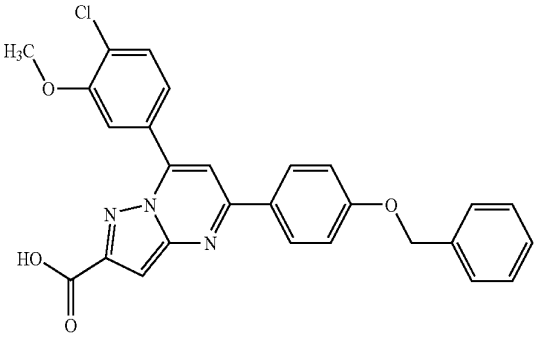
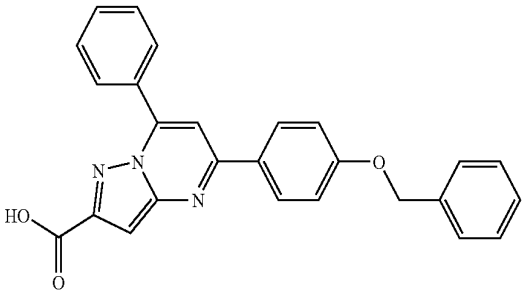
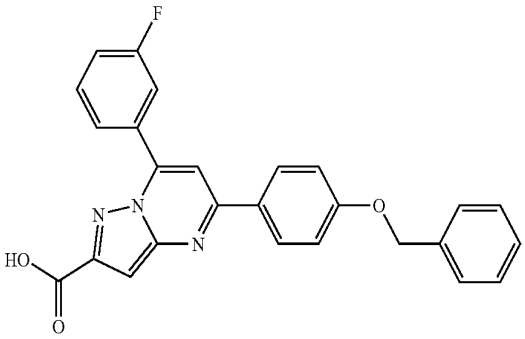
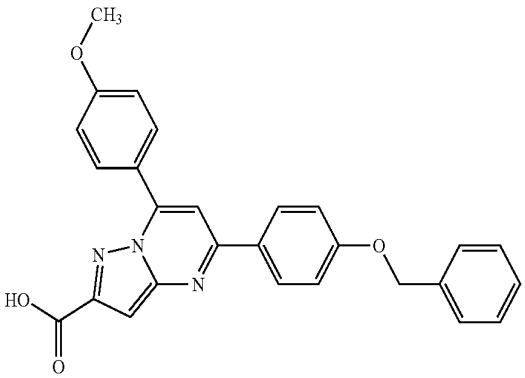
Compound	MOLSTRUCTURE	Δ-55 Activity	Δ-21 Activity
	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM		
217		B	B
218		A	
219		A	
220		B	B

TABLE 1-continued

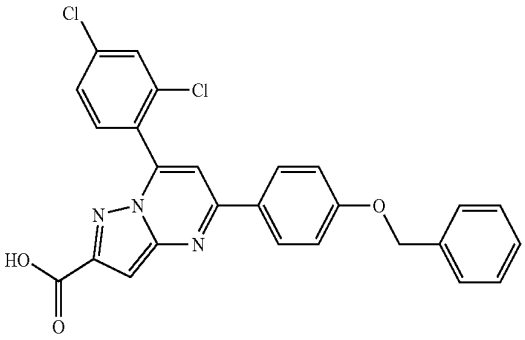
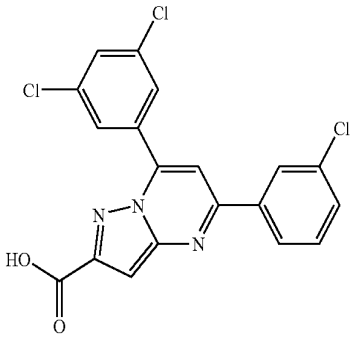
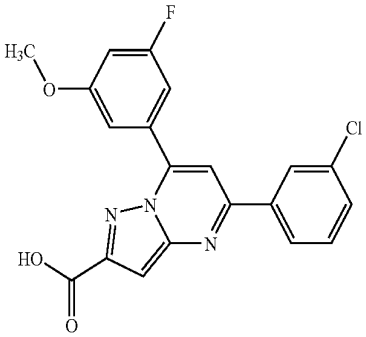
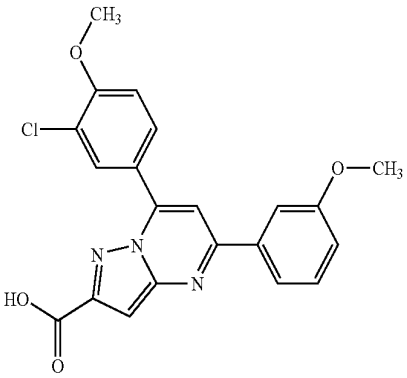
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
221		A	
222		A	
223		B	
224		A	

TABLE 1-continued

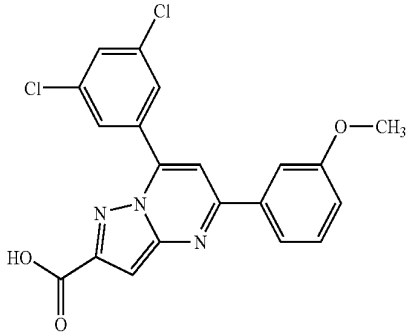
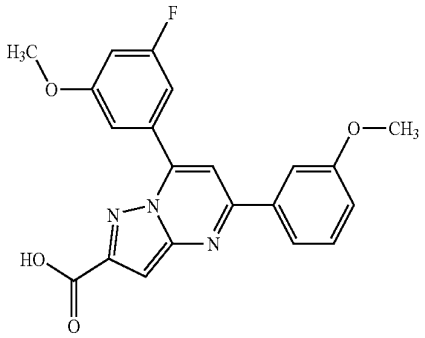
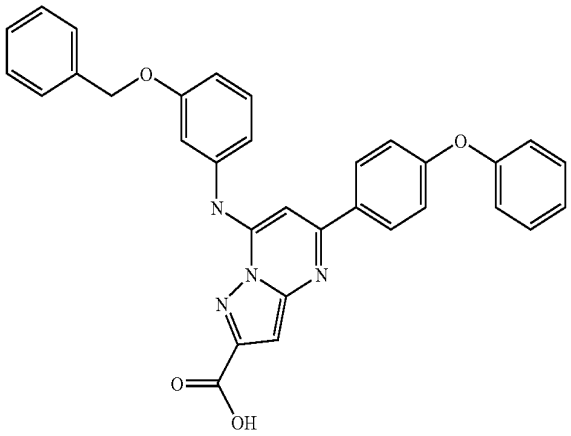
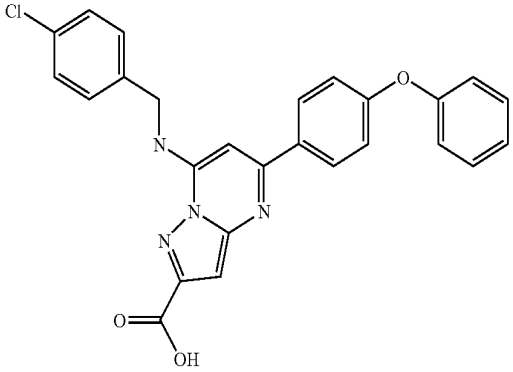
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
225		A	
226		A	
227		B	
228		B	

TABLE 1-continued

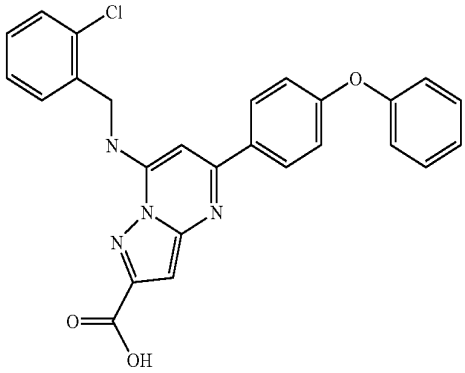
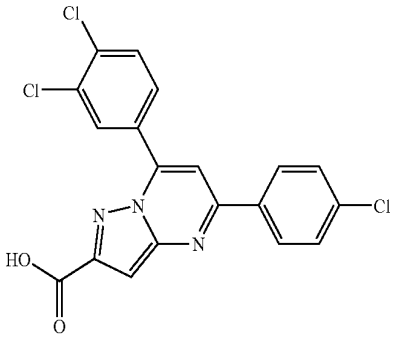
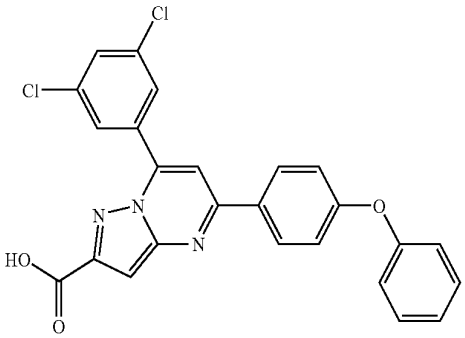
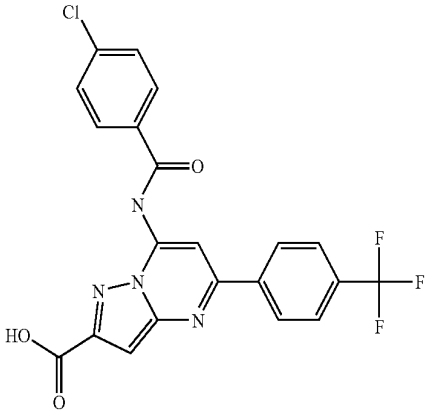
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
229		B	
230		A	
231		A	
232		A	

TABLE 1-continued

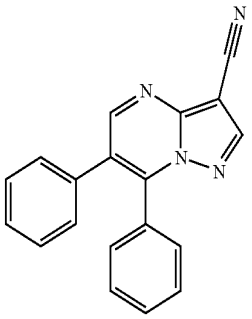
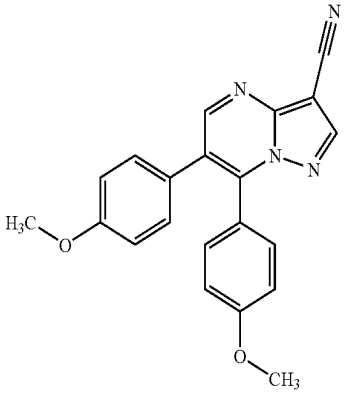
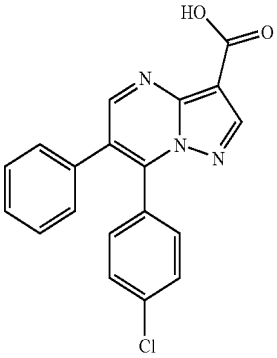
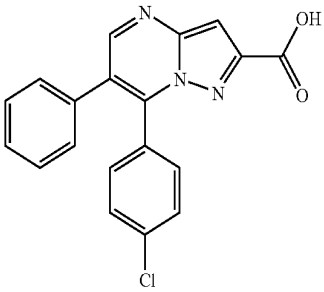
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
233		A	
234		A	
235		A	
236		A	

TABLE 1-continued

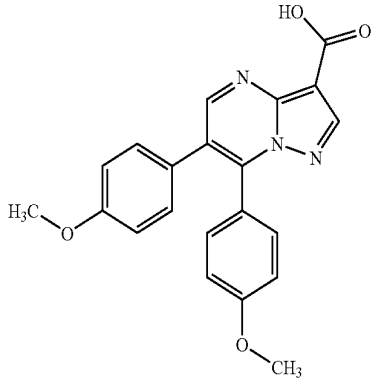
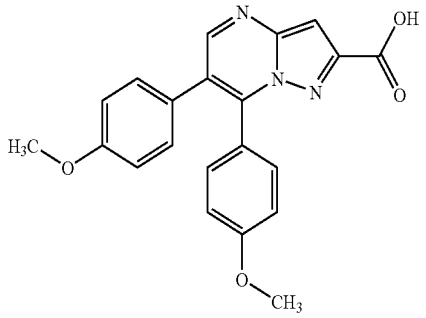
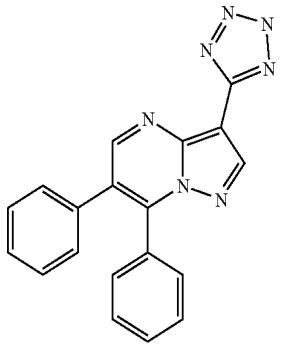
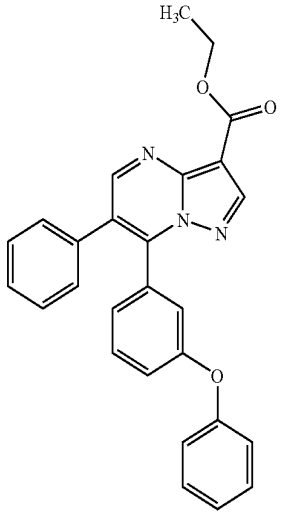
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
237		A	
238		A	
239		A	
240		A	

TABLE 1-continued

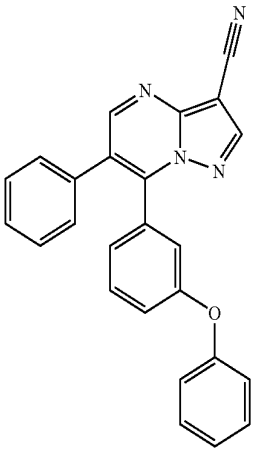
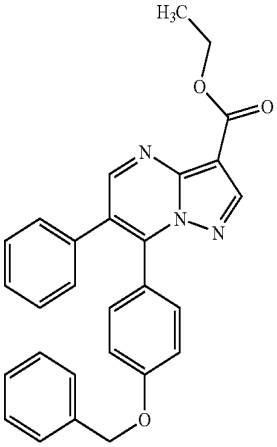
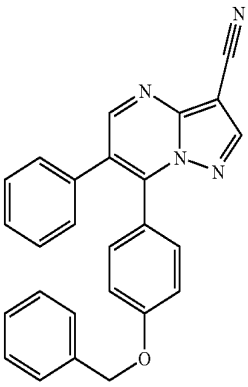
Compound	MOLSTRUCTURE	Δ-55 Activity	Δ-21 Activity
	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM		
241		A	
242		A	
243		A	

TABLE 1-continued

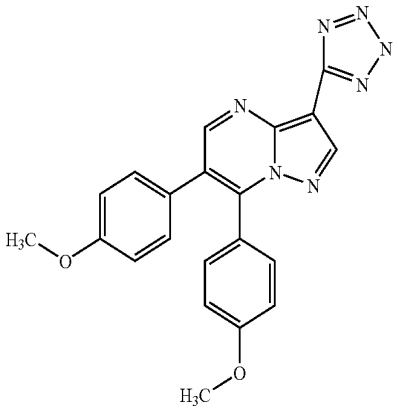
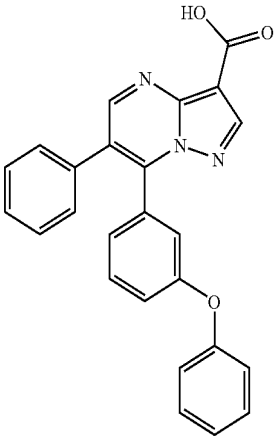
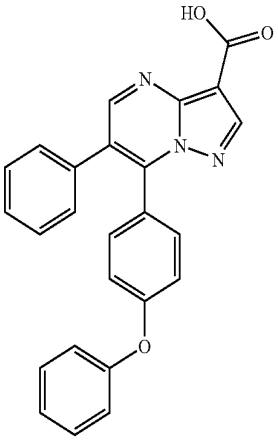
Compound	MOLSTRUCTURE	Δ-55 Activity	Δ-21 Activity
	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM		
244		A	
245		A	
246		A	

TABLE 1-continued

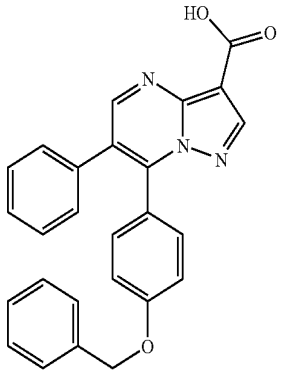
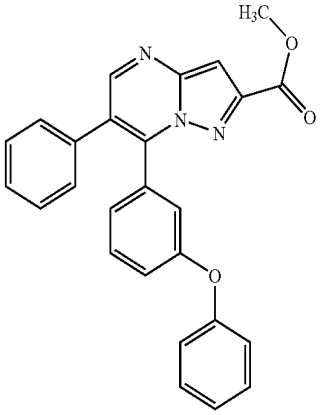
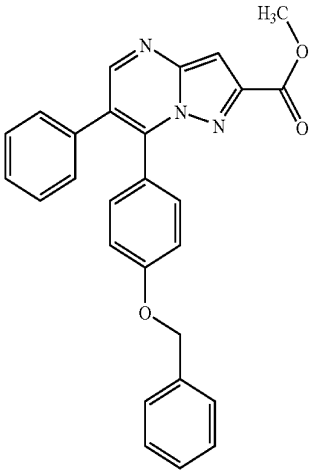
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
247		A	
248		A	
249		A	

TABLE 1-continued

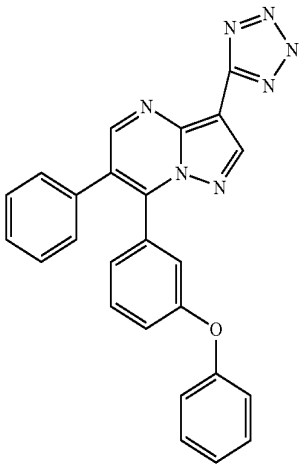
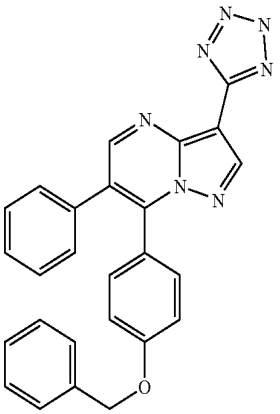
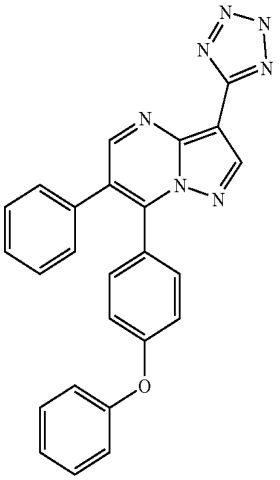
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM	
		Δ-55 Activity	Δ-21 Activity
250		A	
251		A	
252		A	

TABLE 1-continued

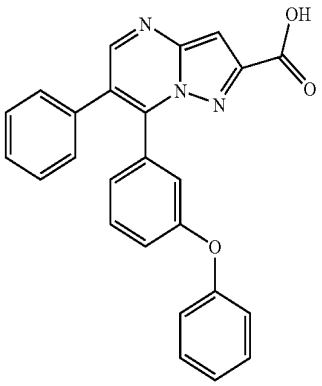
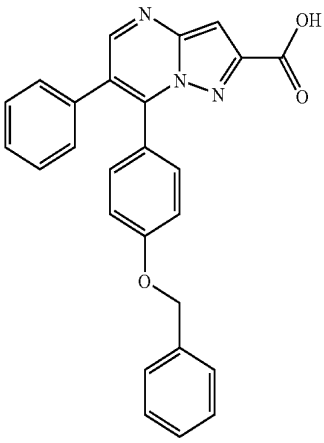
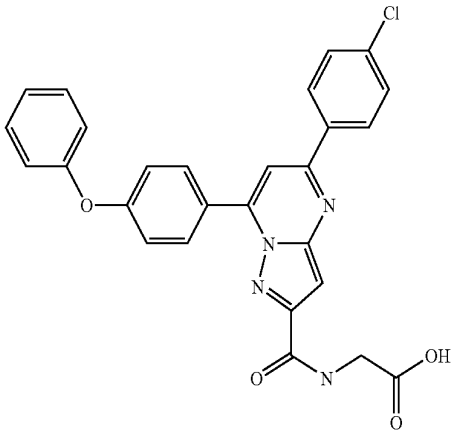
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
253		A	
254		A	
255		B	

TABLE 1-continued

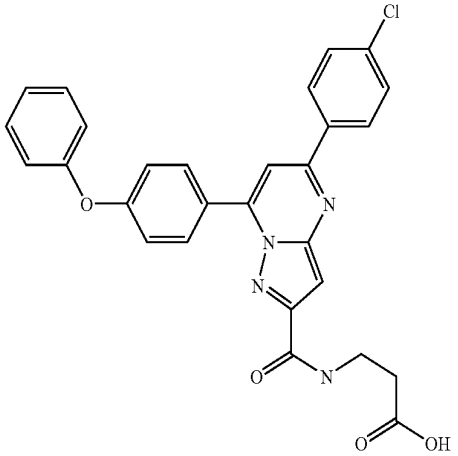
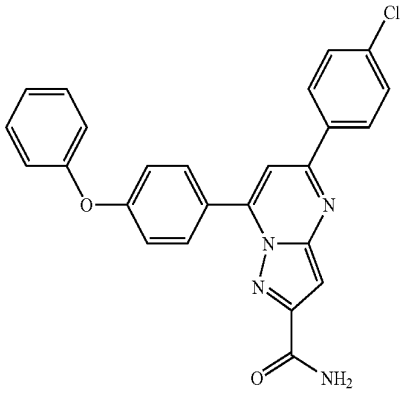
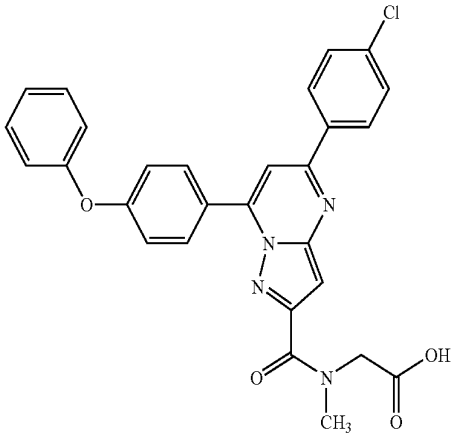
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
256		B	
257		A	
258		B	

TABLE 1-continued

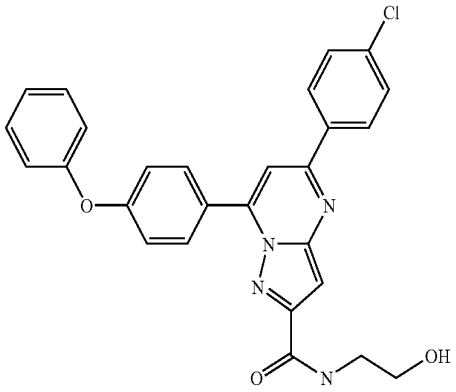
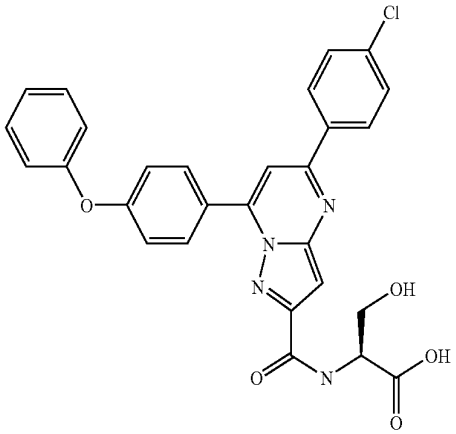
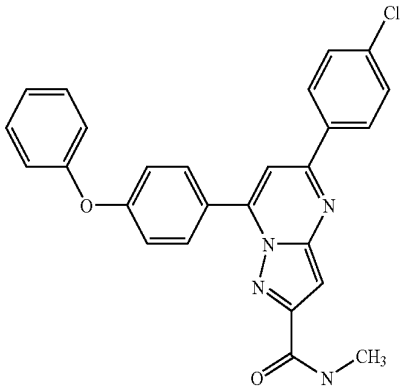
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
259		A	
260		B	
261		A	

TABLE 1-continued

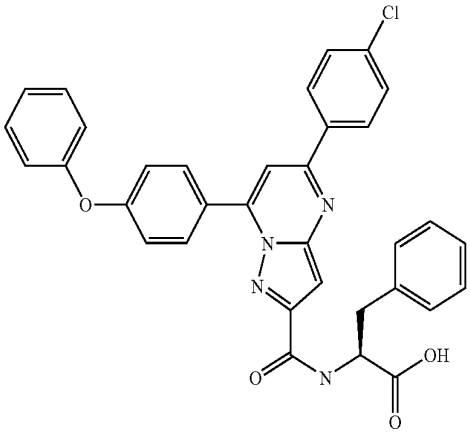
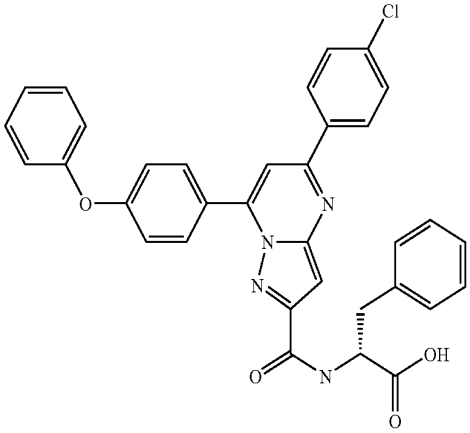
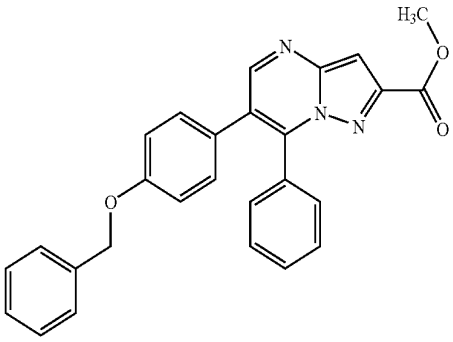
Compound	MOLSTRUCTURE	Δ-55 Activity	Δ-21 Activity
	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM		
262		A	
263		B	
264		A	

TABLE 1-continued

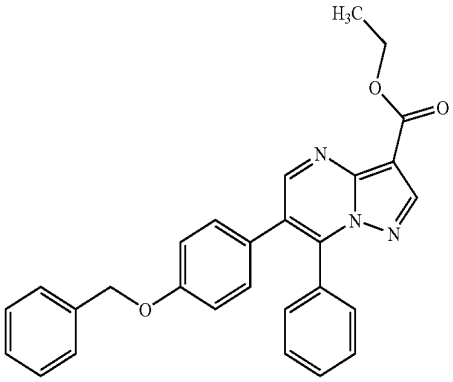
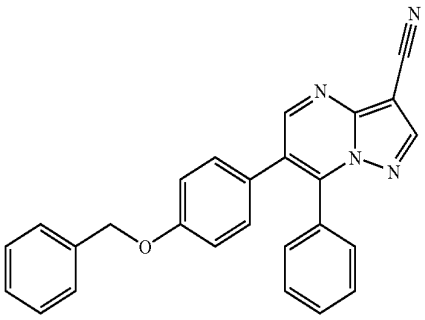
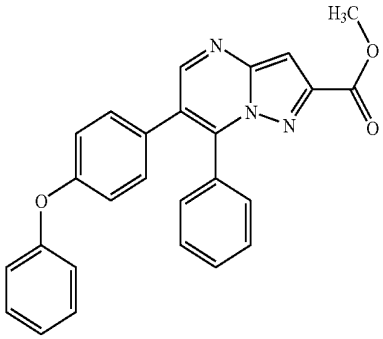
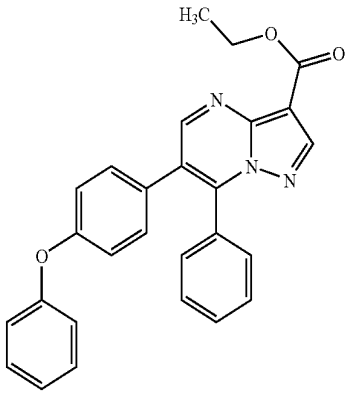
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
265		A	
266		A	
267		A	
268		A	

TABLE 1-continued

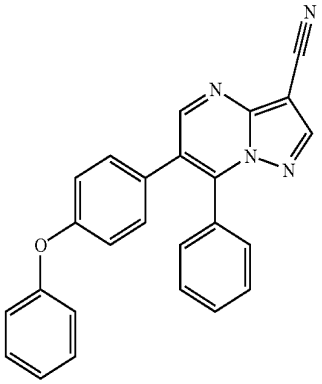
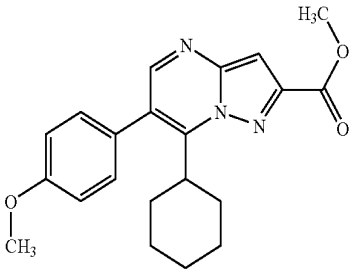
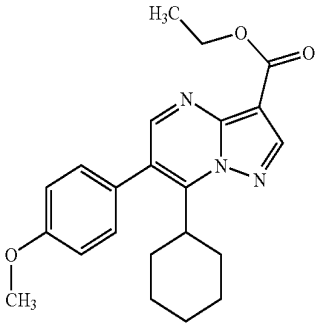
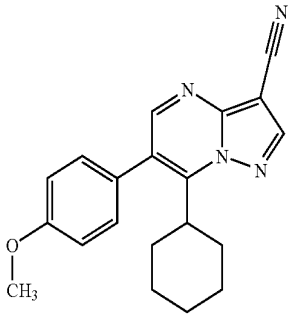
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
269		A	
270		A	
271		A	
272		A	

TABLE 1-continued

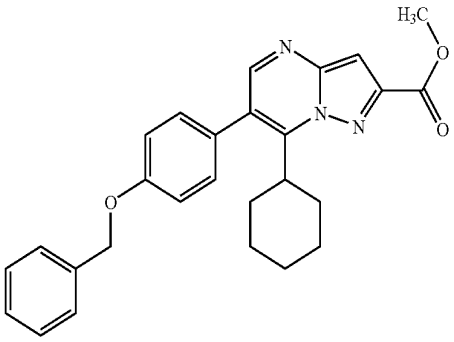
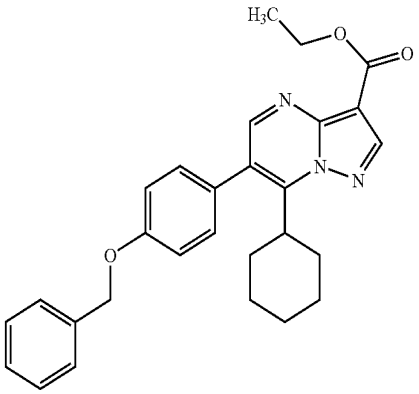
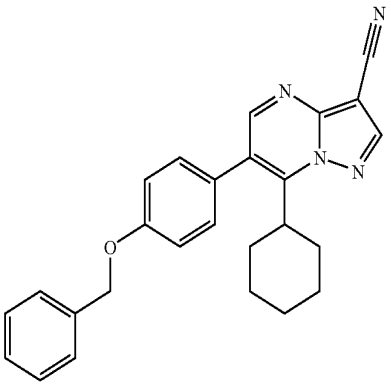
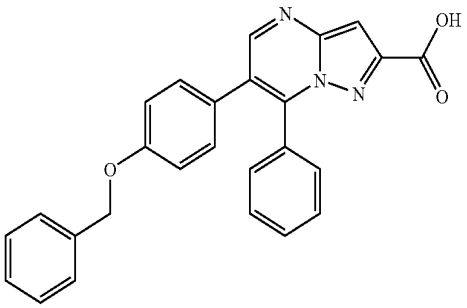
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
273		A	
274		A	
275		A	
276		B	

TABLE 1-continued

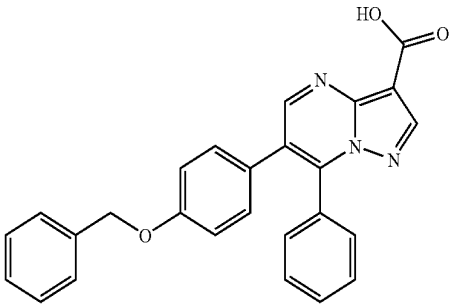
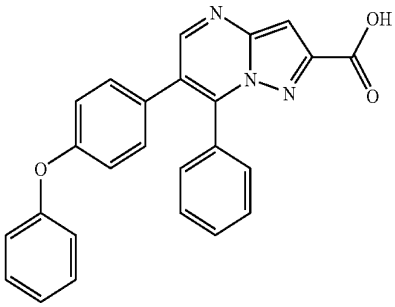
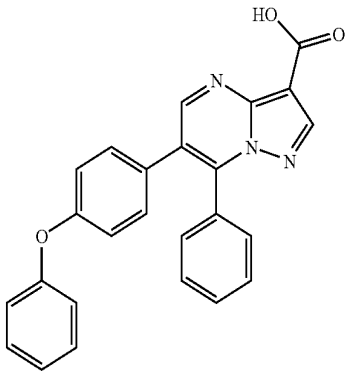
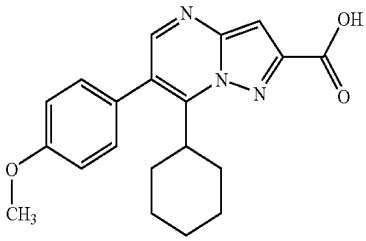
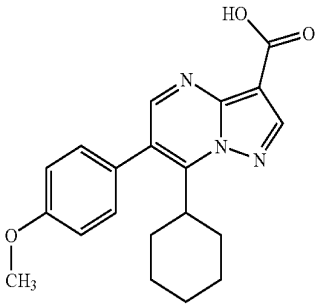
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
277		A	
278		A	
279		A	
280		A	
281		B	

TABLE 1-continued

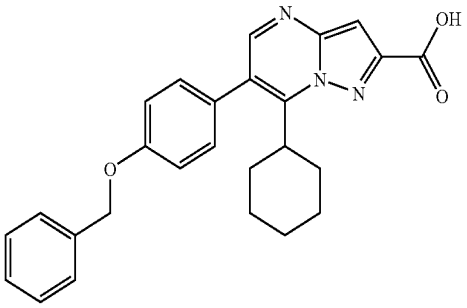
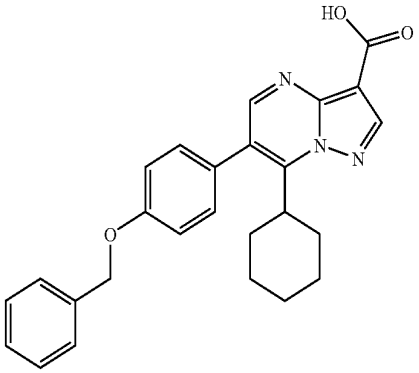
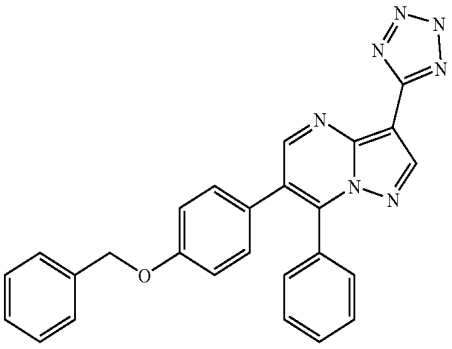
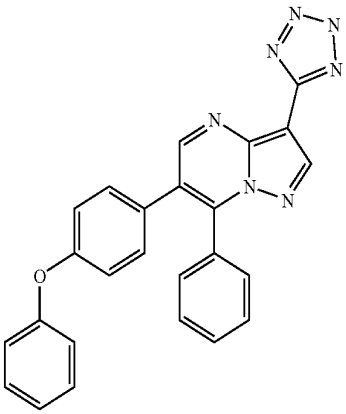
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
282		B	
283		B	
284		A	
285		A	

TABLE 1-continued

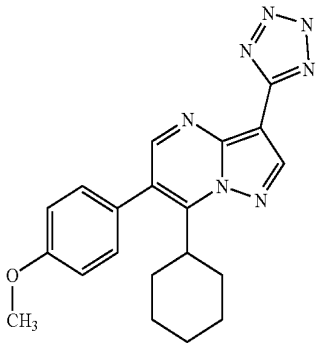
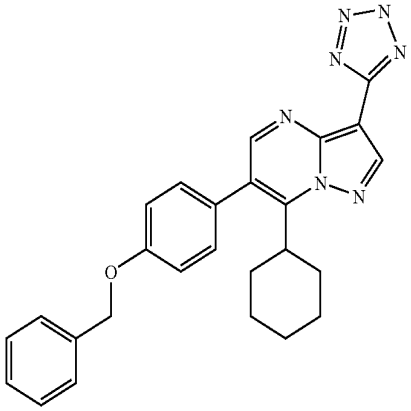
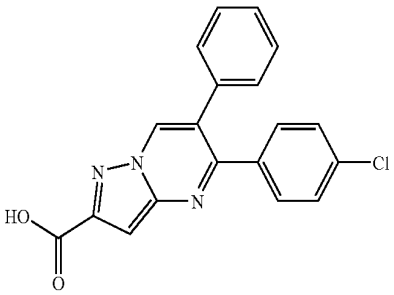
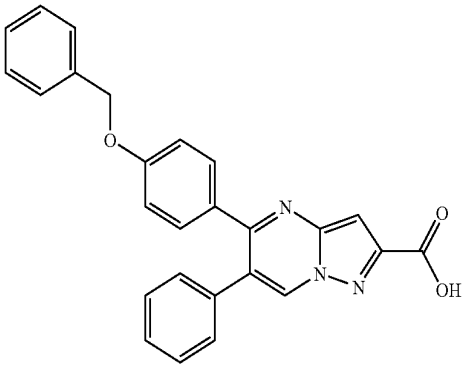
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM	
		Δ-55 Activity	Δ-21 Activity
286		B	
287		C	C
288		A	
289		A	

TABLE 1-continued

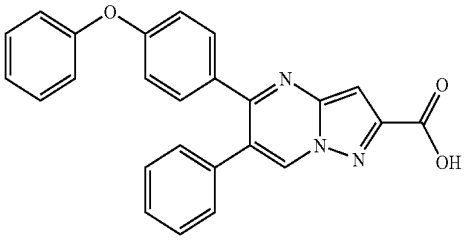
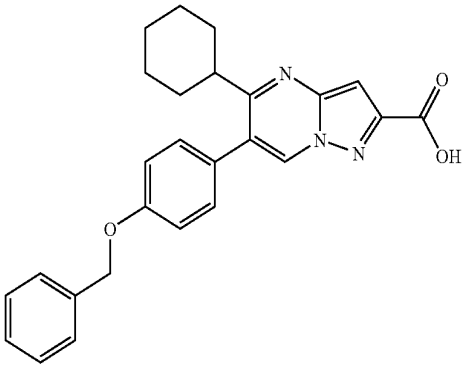
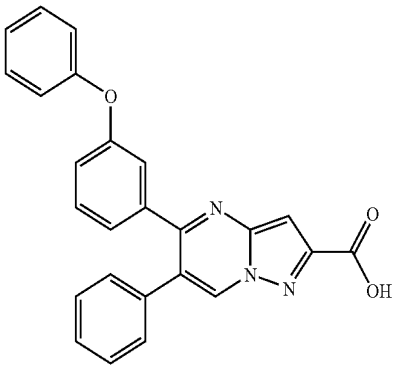
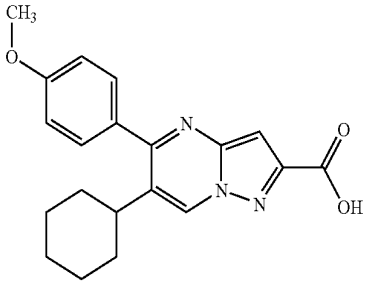
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
290		B	
291		B	
292		A	
293		A	

TABLE 1-continued

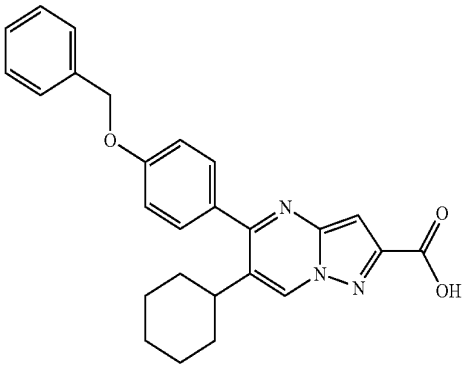
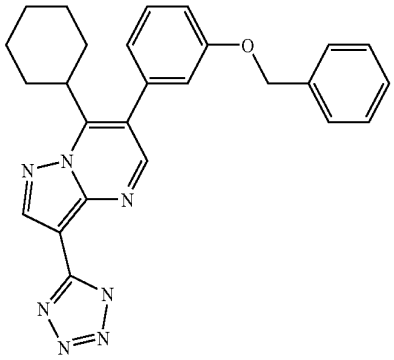
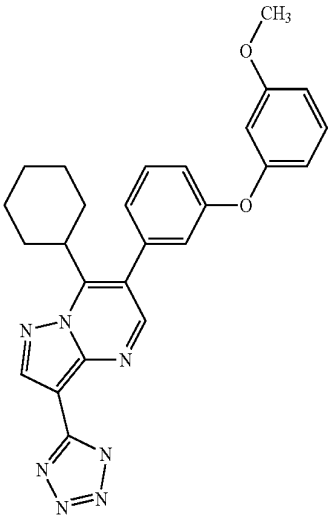
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
294		B	
295		B	
296		B	

TABLE 1-continued

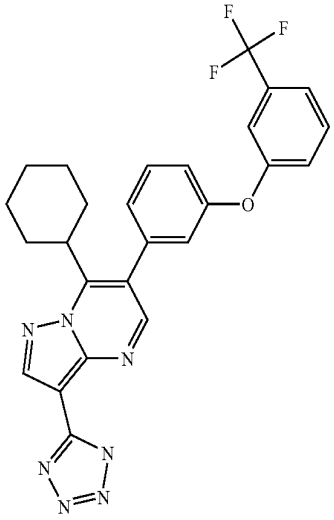
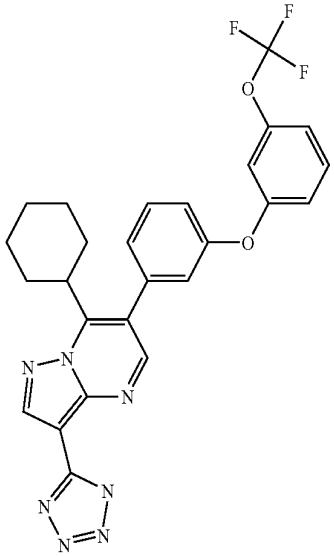
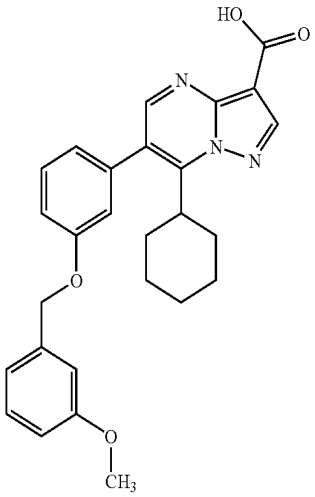
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
297		B	
298		B	
299		B	

TABLE 1-continued

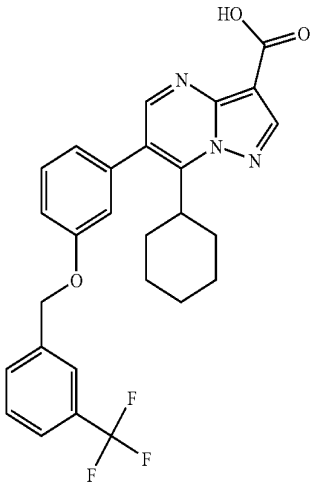
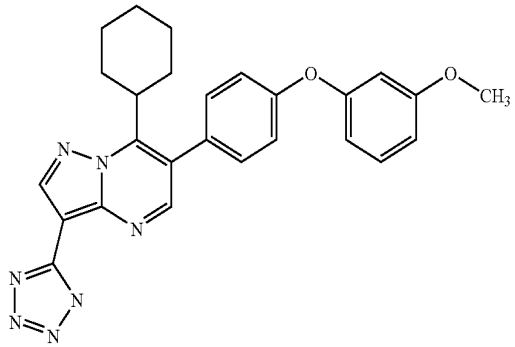
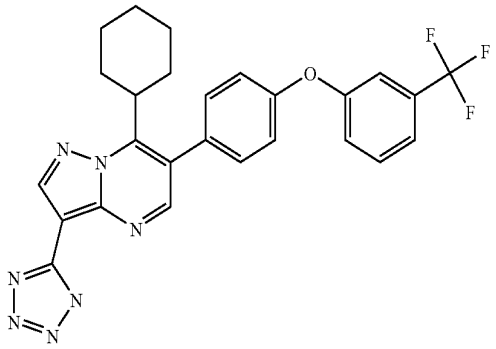
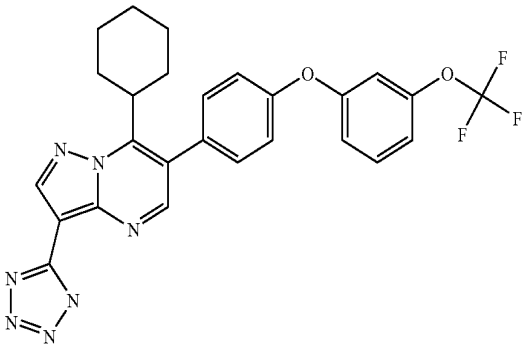
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
300		A	
301		C	C
302		B	B
303		B	B

TABLE 1-continued

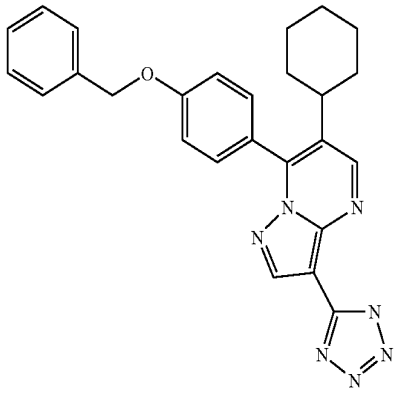
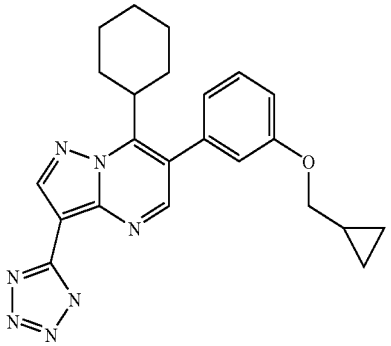
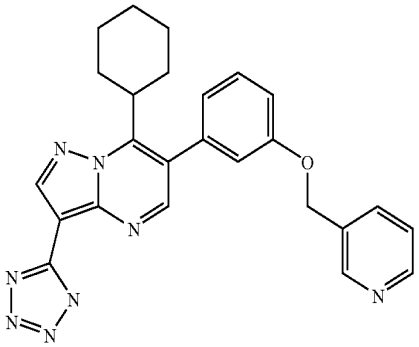
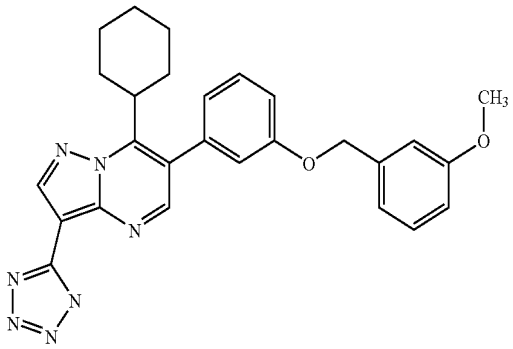
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM	
		Δ-55 Activity	Δ-21 Activity
304		B	
305		B	
306		B	
307		B	B

TABLE 1-continued

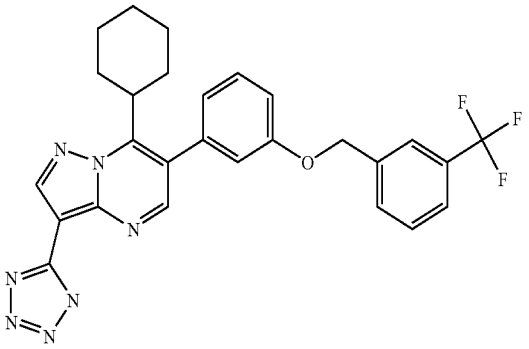
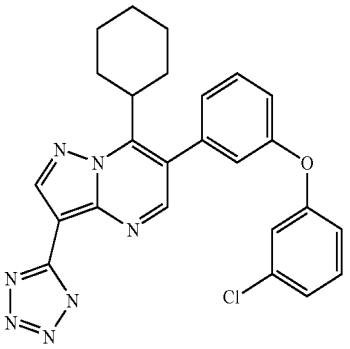
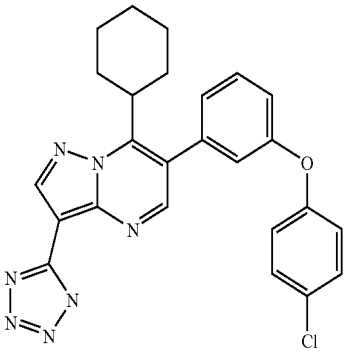
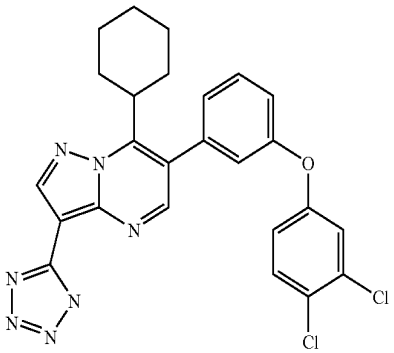
Compound	MOLSTRUCTURE	Δ-55 Activity	Δ-21 Activity
	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM		
308		B	B
309		B	
310		B	
311		B	

TABLE 1-continued

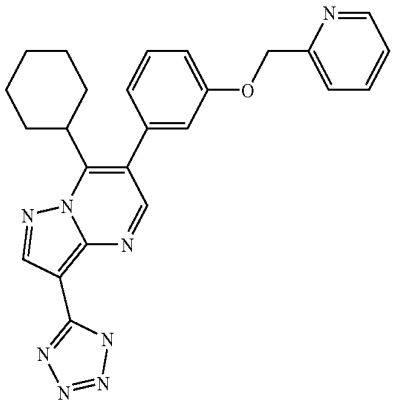
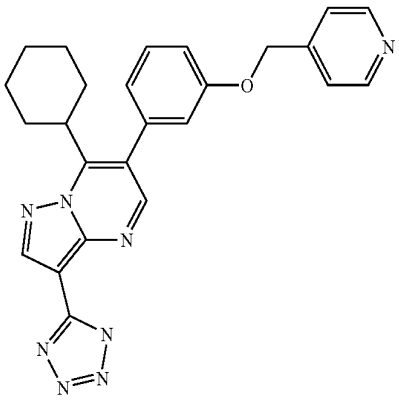
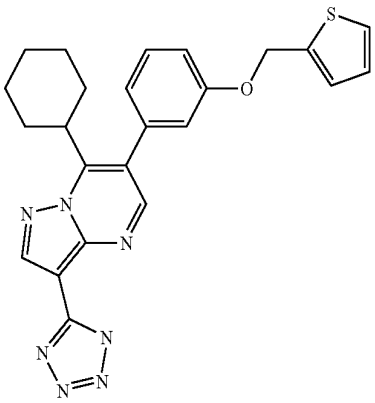
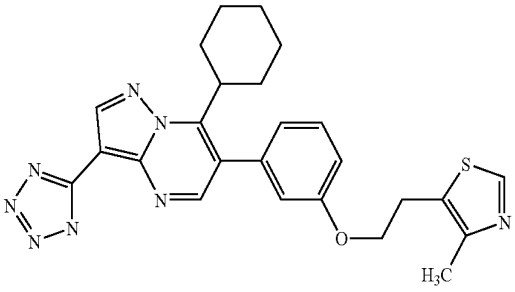
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
312		B	
313		B	
314		B	
315		B	

TABLE 1-continued

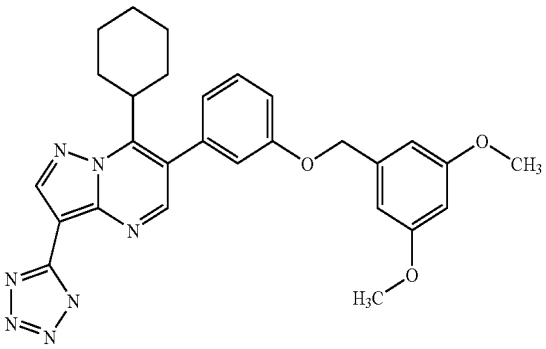
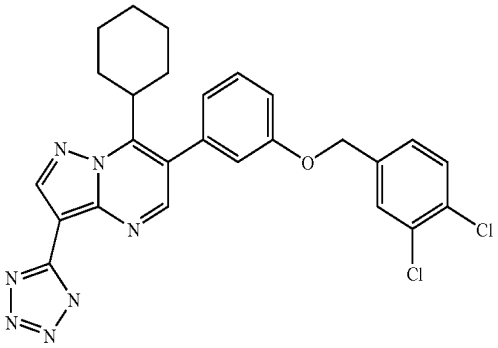
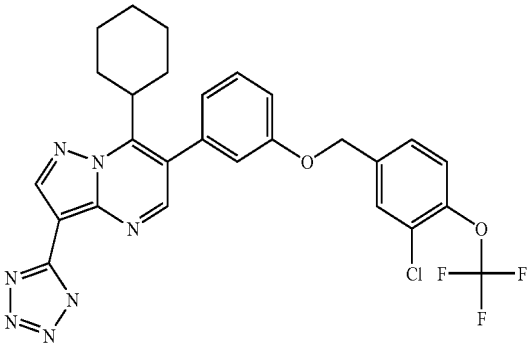
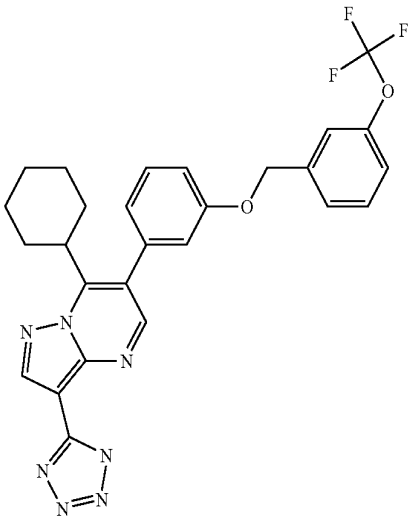
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
316		B	
317		B	
318		B	
319		B	

TABLE 1-continued

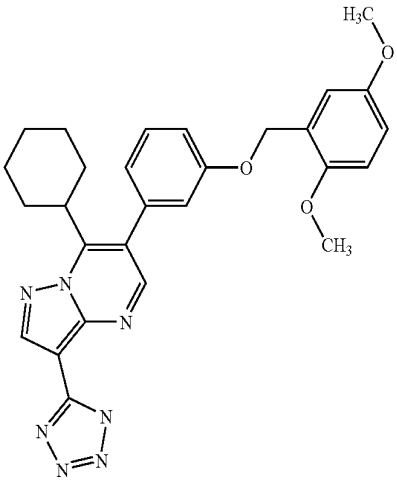
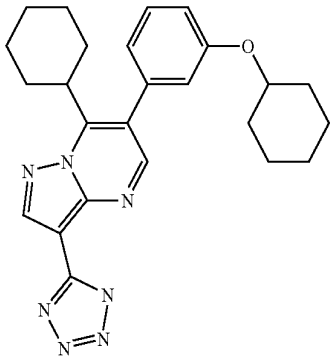
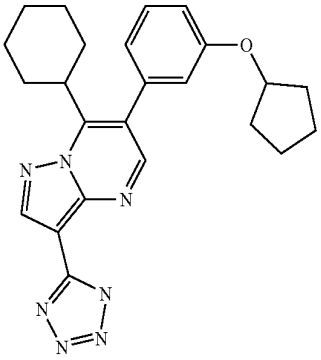
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
320		B	
321		B	
322		B	

TABLE 1-continued

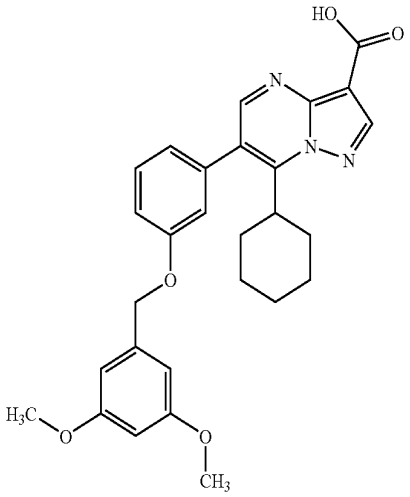
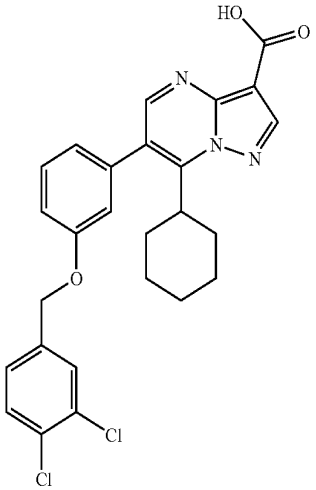
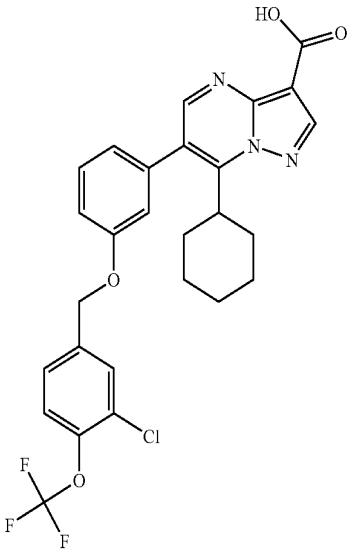
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
323		B	
324		B	
325		A	

TABLE 1-continued

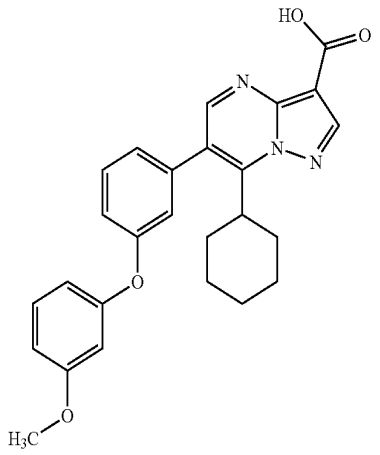
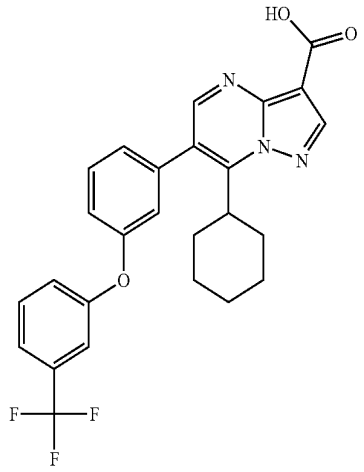
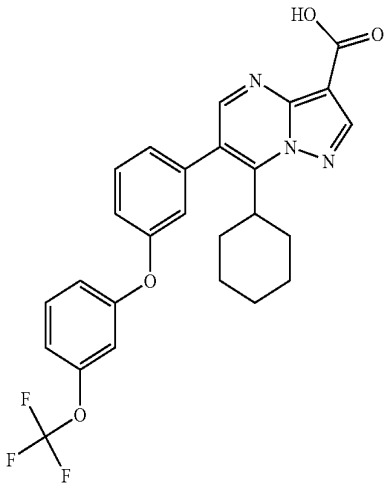
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
326		B	
327		B	
328		A	

TABLE 1-continued

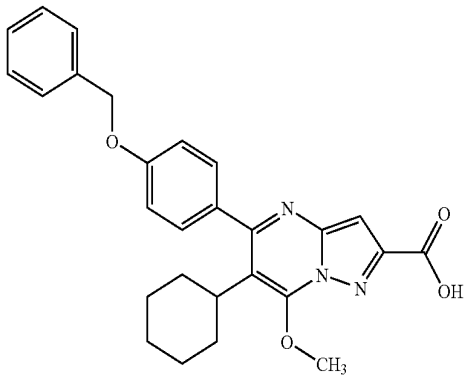
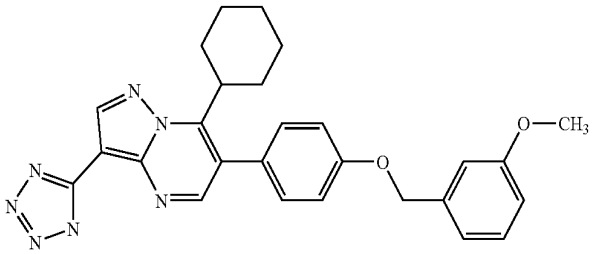
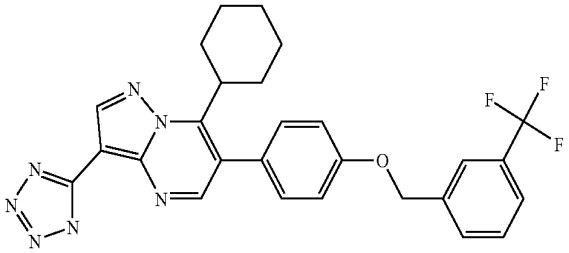
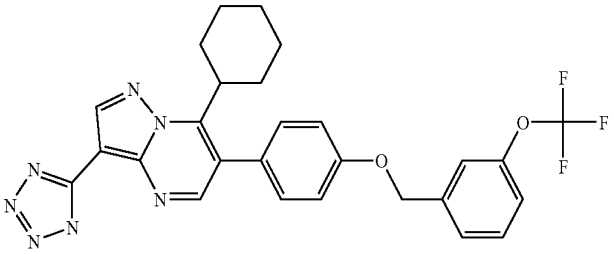
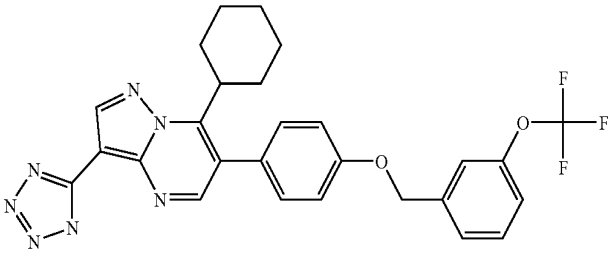
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM	
		Δ-55 Activity	Δ-21 Activity
329		A	
330		B	C
331		B	C
332		B	
333		B	

TABLE 1-continued

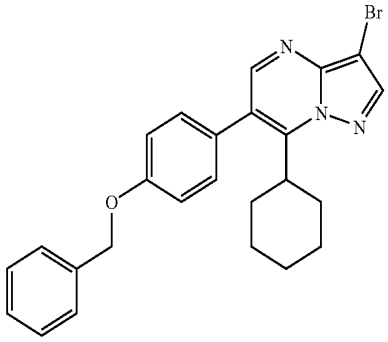
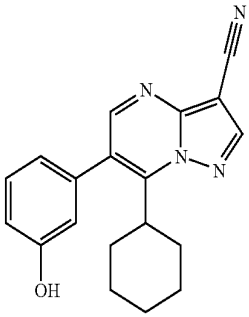
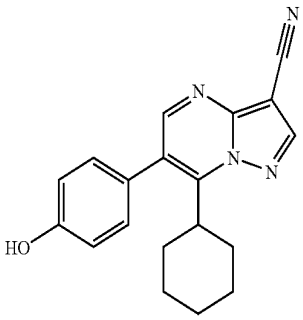
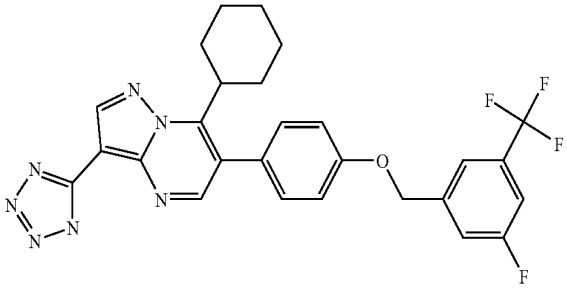
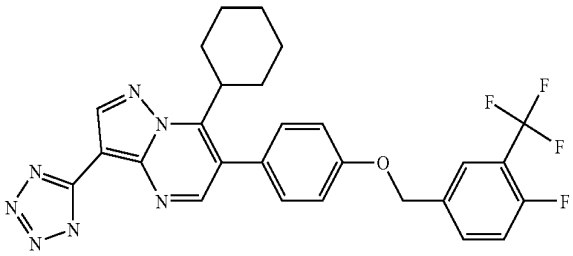
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
334		A	
335		A	
336		A	
337		B	B
338		B	B

TABLE 1-continued

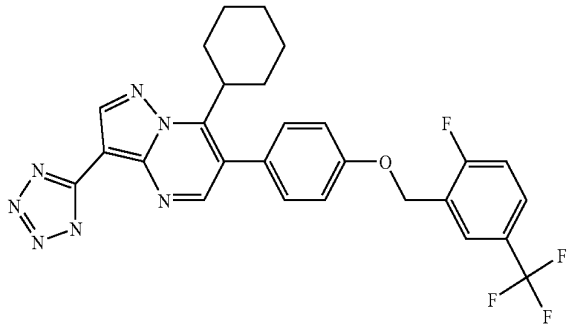
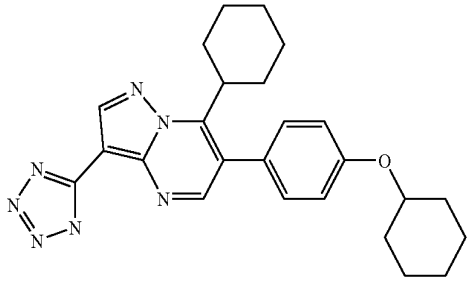
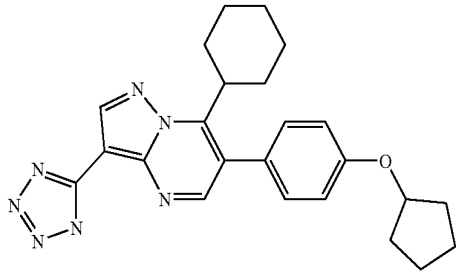
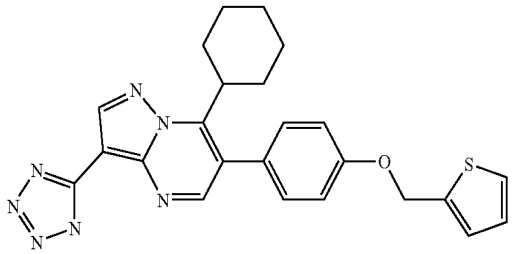
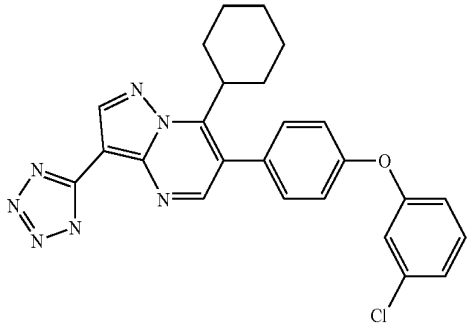
Compound	MOLSTRUCTURE	Δ-55 Activity	Δ-21 Activity
	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM		
339		B	B
340		B	C
341		B	B
342		B	C
343		C	C

TABLE 1-continued

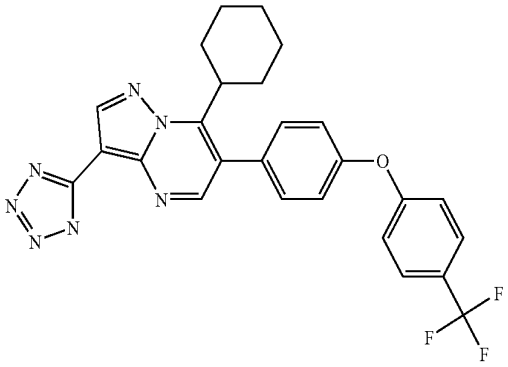
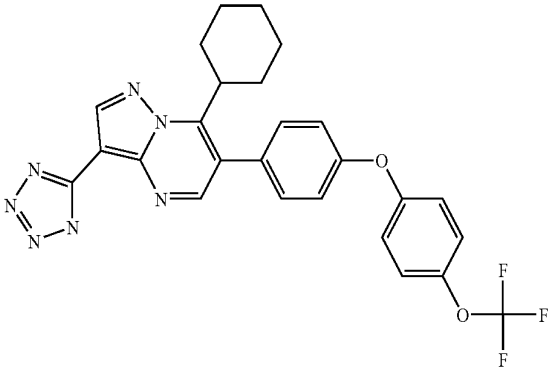
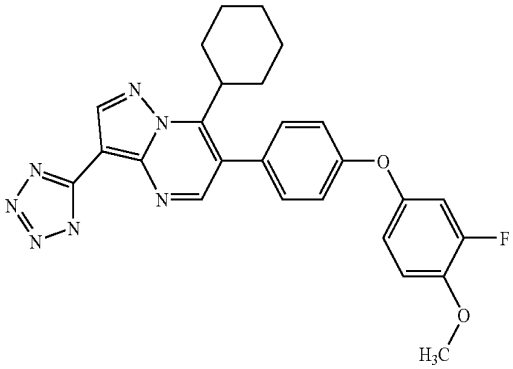
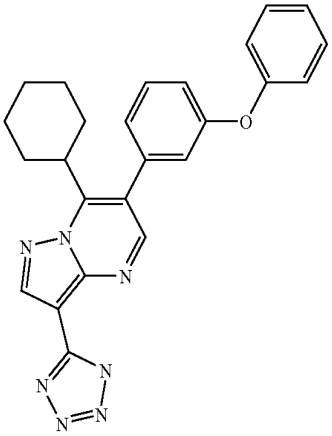
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
344		B	B
345		B	B
346		C	C
347		B	

TABLE 1-continued

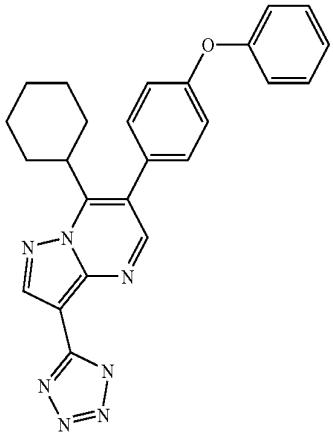
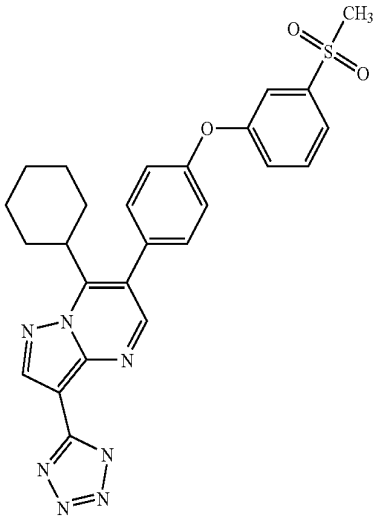
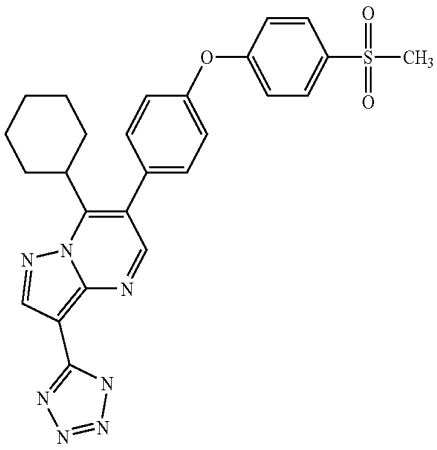
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
348		C	C
349		B	C
350		B	

TABLE 1-continued

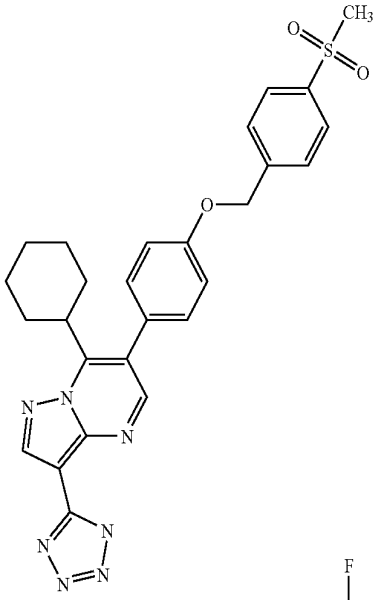
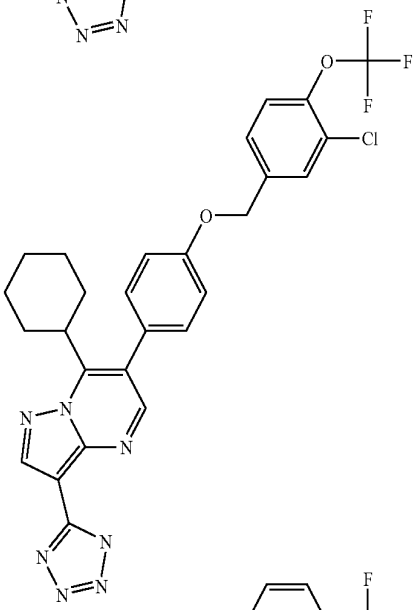
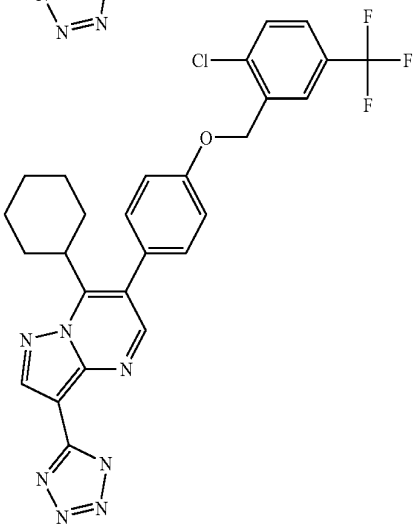
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
351		B	C
352		B	
353		B	

TABLE 1-continued

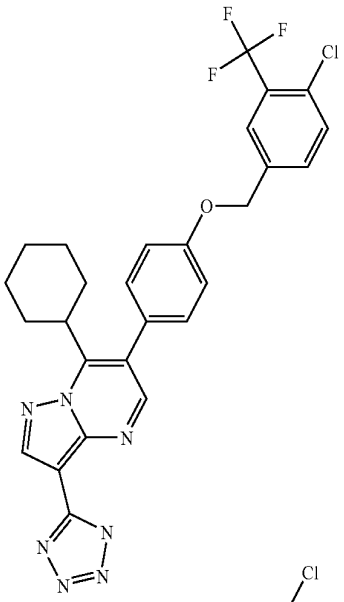
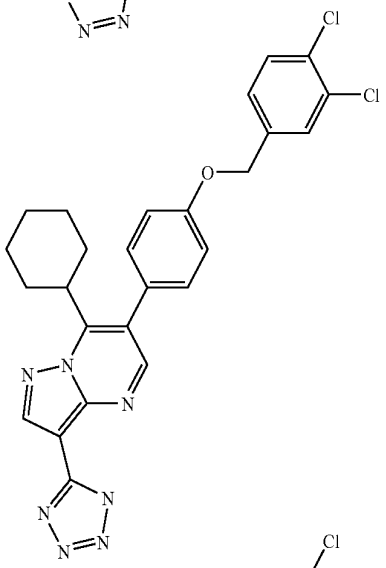
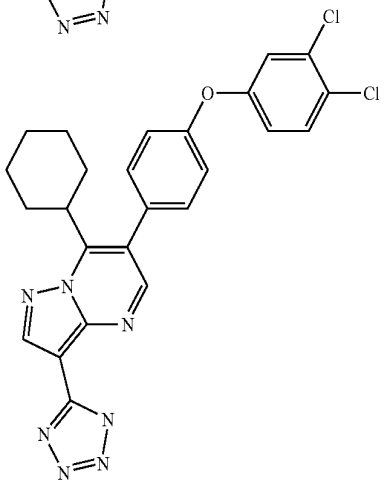
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
354		B	
355		B	
356		B	

TABLE 1-continued

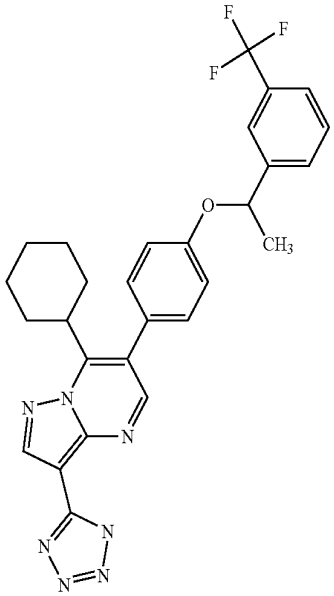
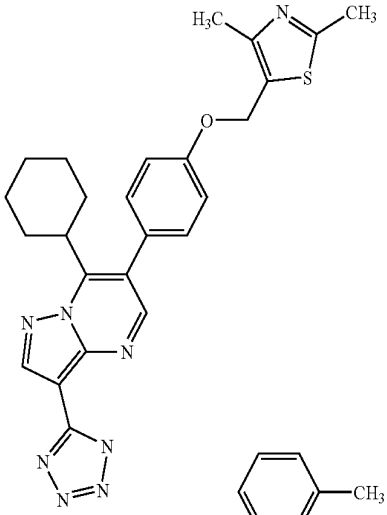
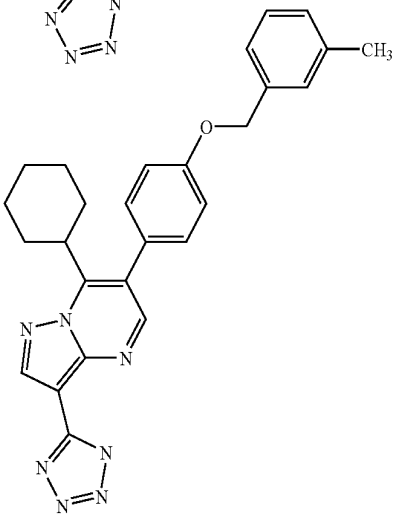
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
357		B	
358		B	C
359		B	

TABLE 1-continued

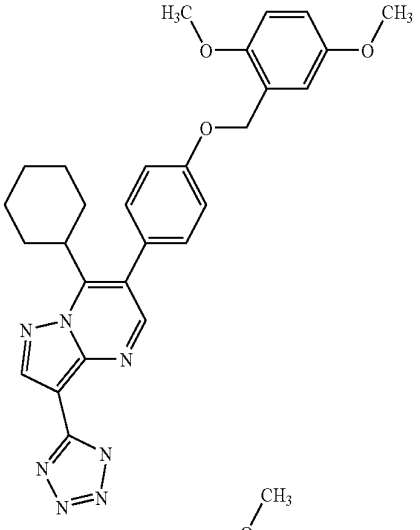
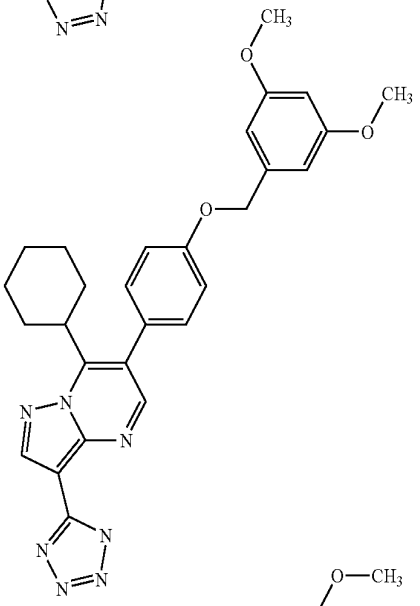
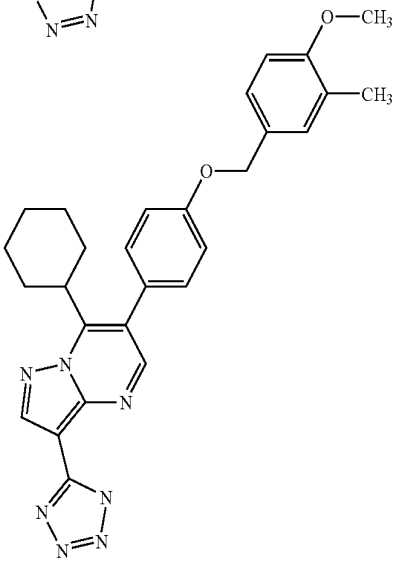
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
360		B	C
361		B	C
362		B	

TABLE 1-continued

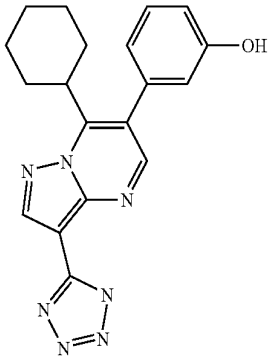
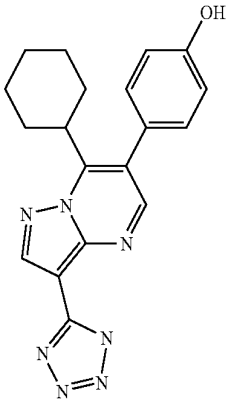
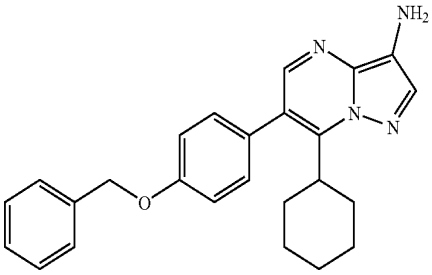
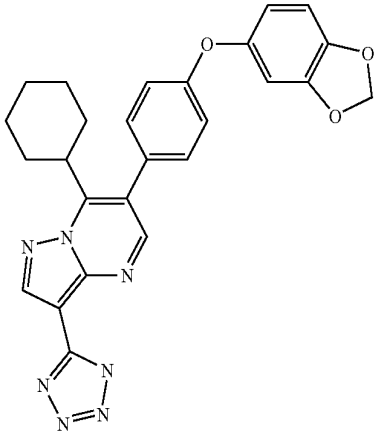
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
363		A	
364		A	
365		A	
366		B	

TABLE 1-continued

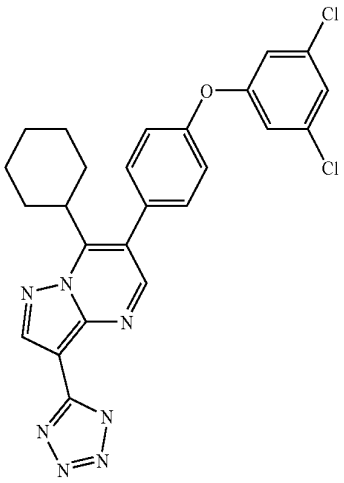
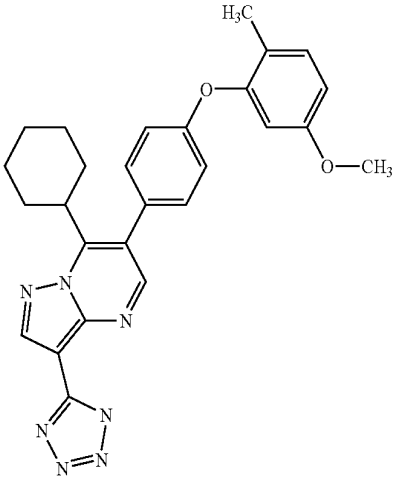
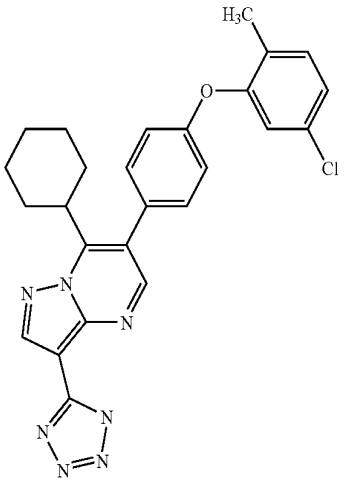
Compound	MOLSTRUCTURE	Δ-55 Activity	Δ-21 Activity
	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM		
367		B	
368		B	
369		B	

TABLE 1-continued

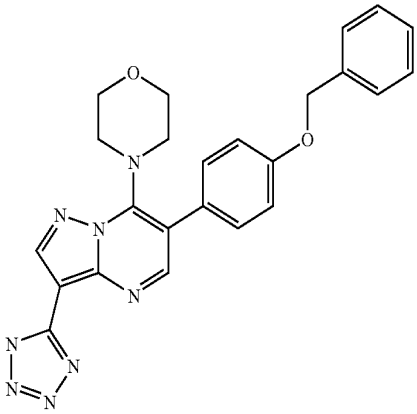
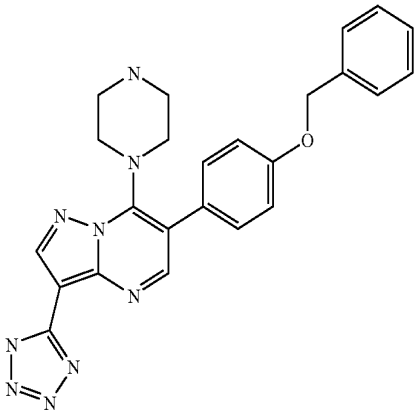
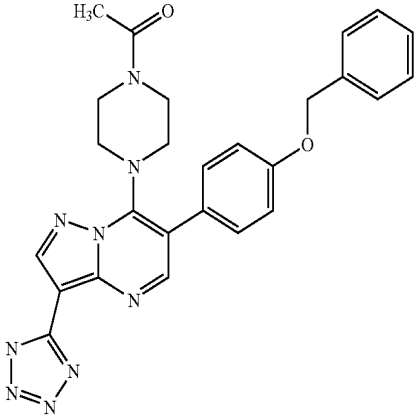
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM	
		Δ-55 Activity	Δ-21 Activity
370		A	A
371		A	A
372		A	A

TABLE 1-continued

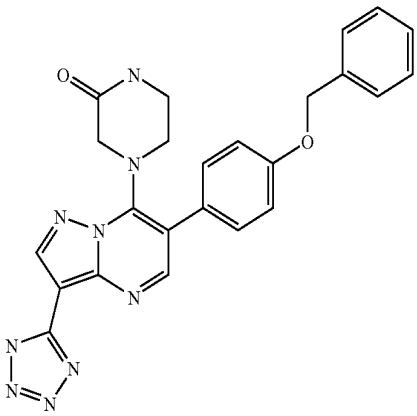
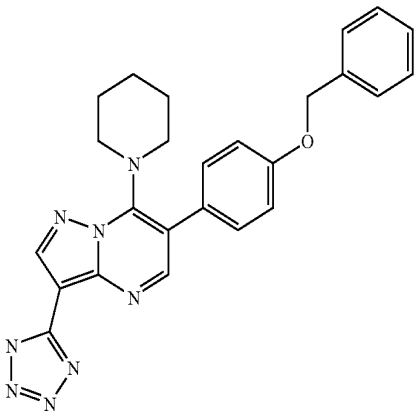
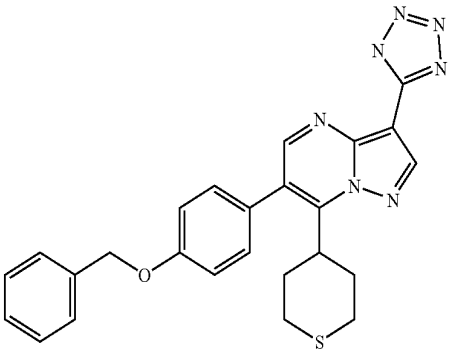
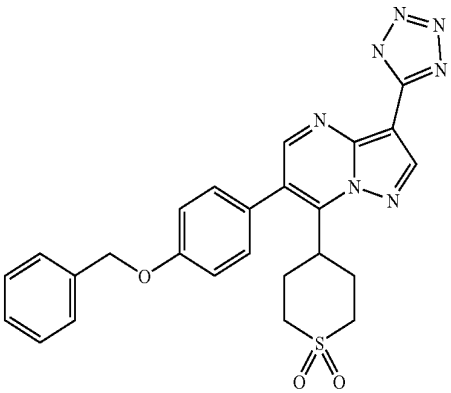
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
373		A	A
374		B	B
375		B	B
376		A	

TABLE 1-continued

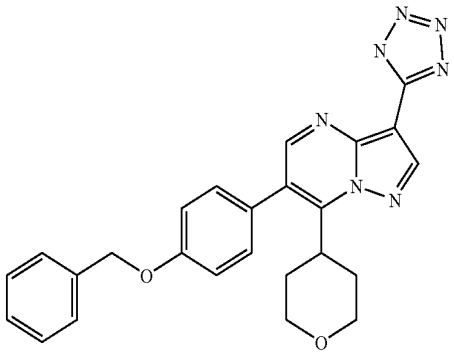
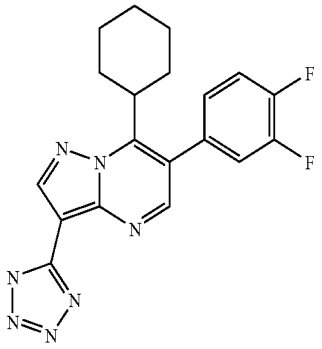
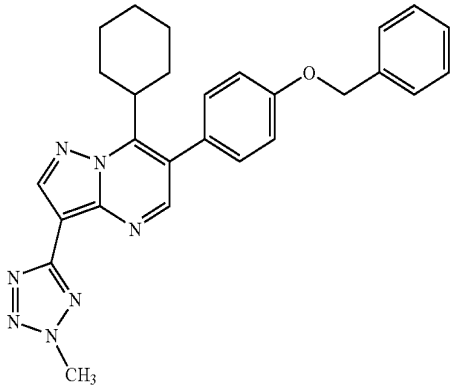
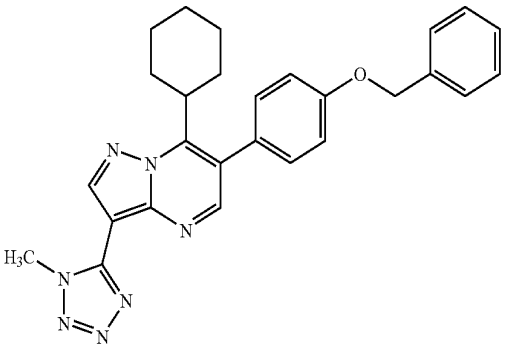
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
377		A	
378		B	C
379		A	
380		A	

TABLE 1-continued

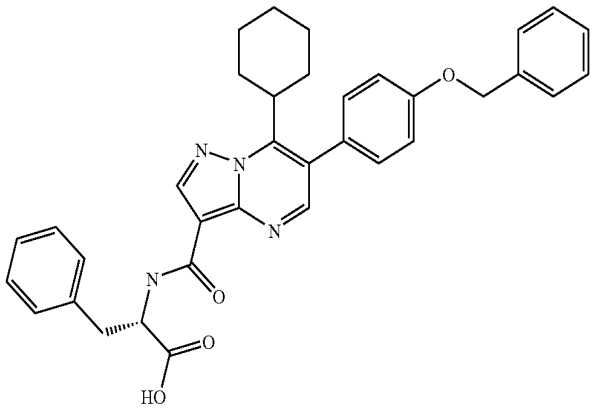
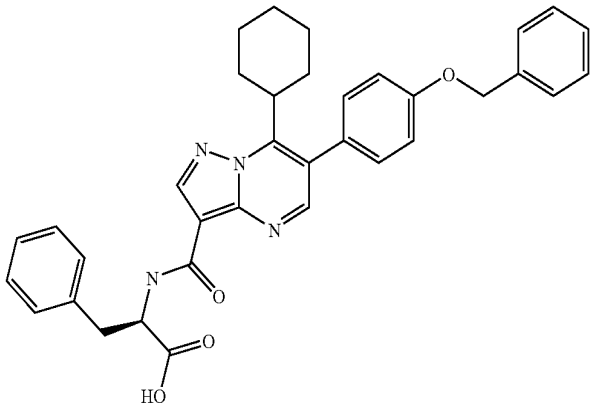
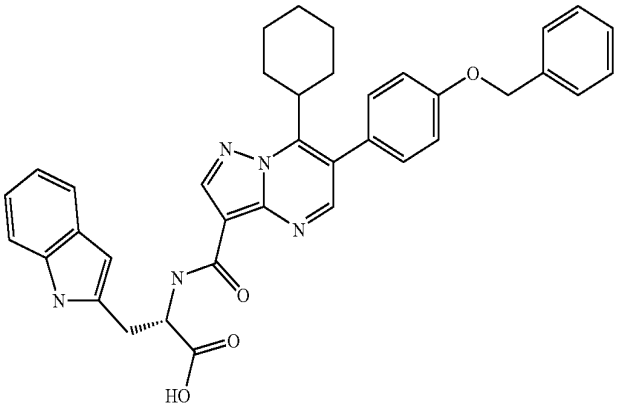
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
381		B	C
382		B	
383		C	C

TABLE 1-continued

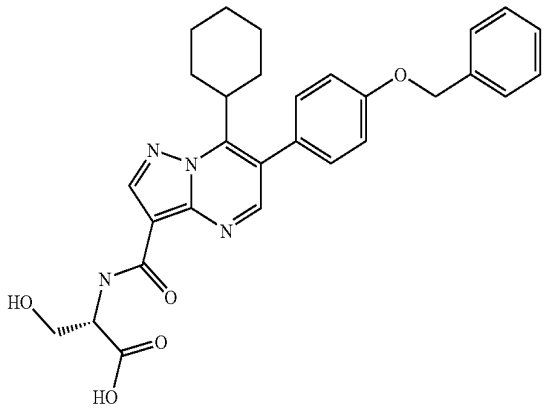
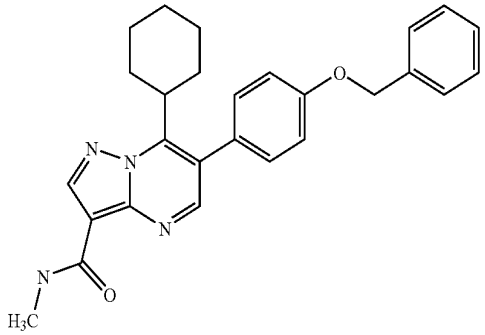
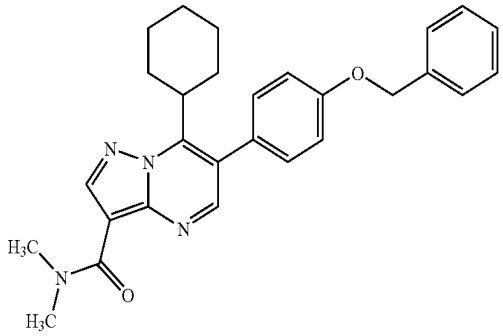
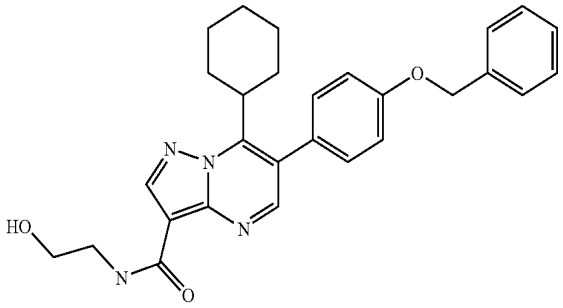
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
384		B	
385		A	
386		A	
387		B	

TABLE 1-continued

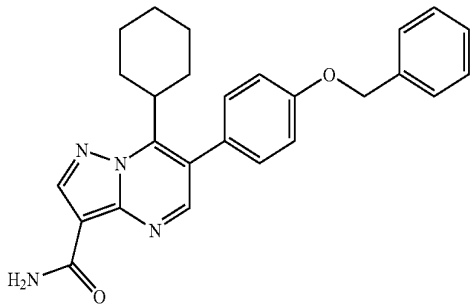
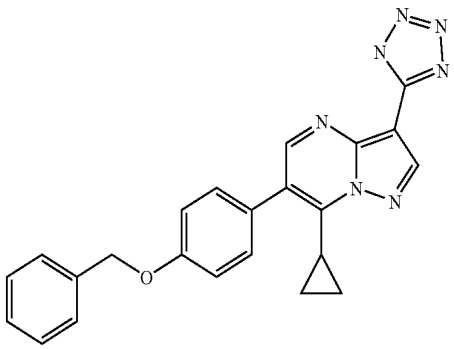
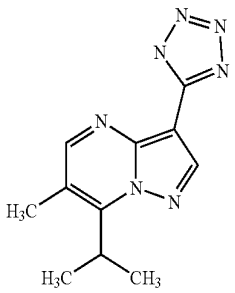
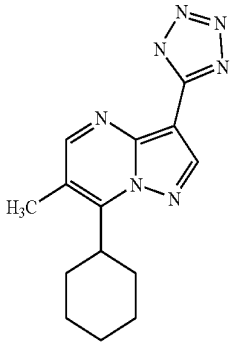
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
388		B	
389		A	
390		A	
391		A	A

TABLE 1-continued

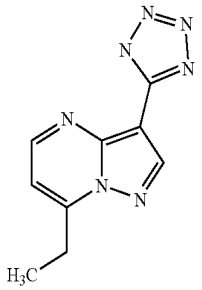
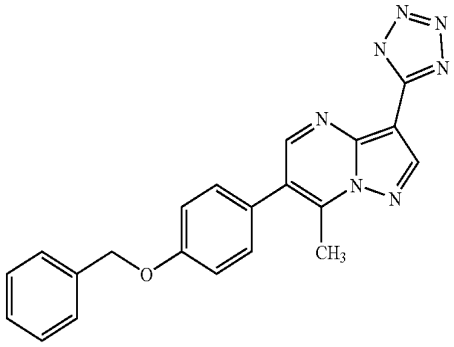
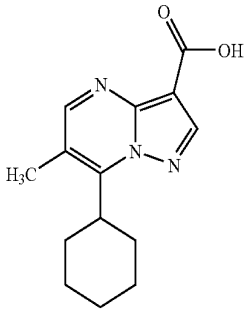
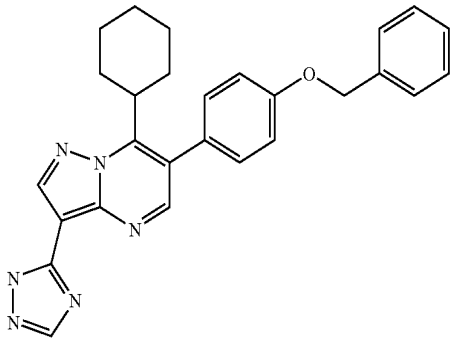
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
392		A	A
393		A	A
394		A	A
395		A	B

TABLE 1-continued

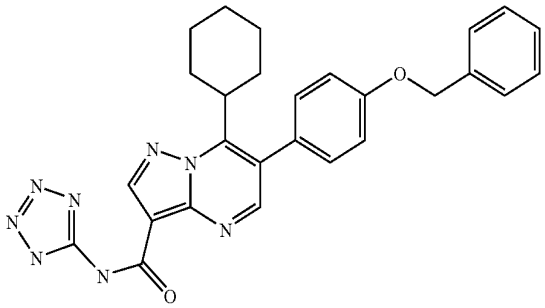
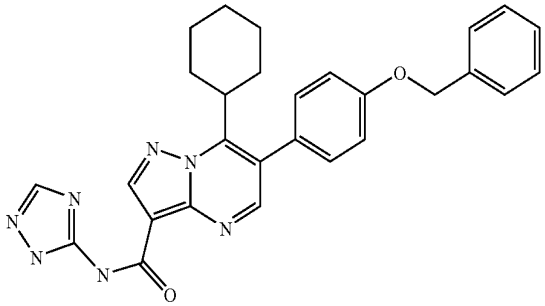
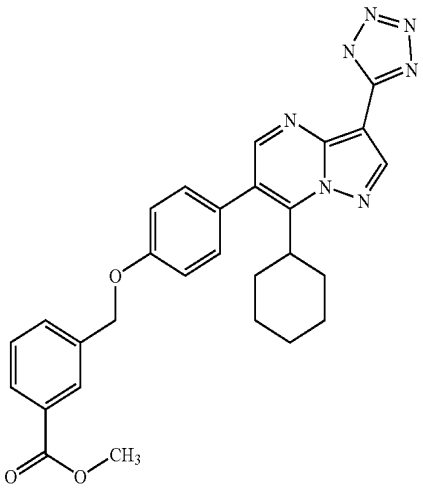
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM	
		Δ-55 Activity	Δ-21 Activity
396		B	C
397		A	B
398		C	C

TABLE 1-continued

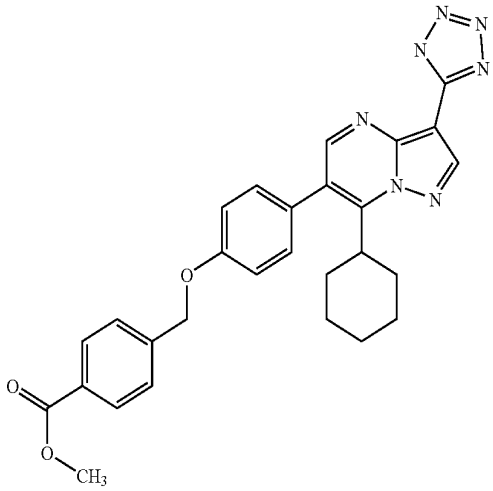
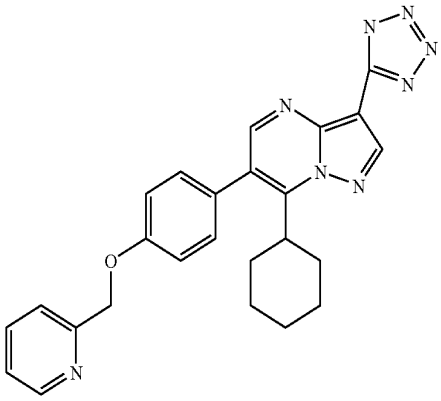
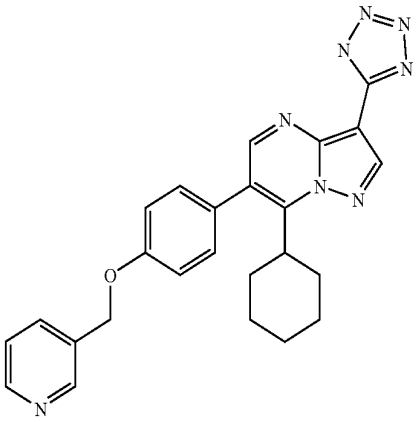
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
399		C	C
400		B	C
401		B	C

TABLE 1-continued

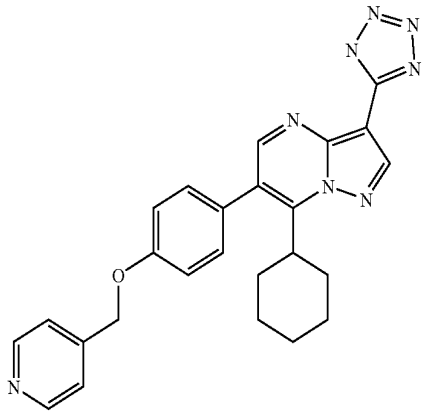
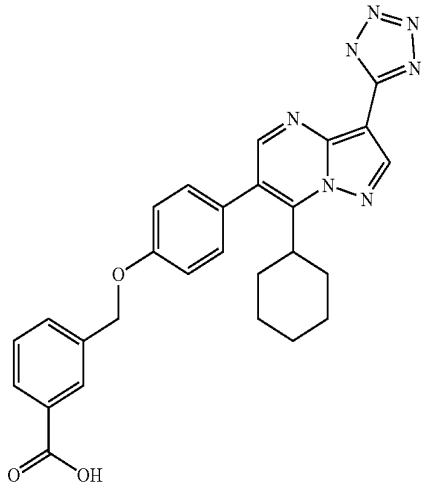
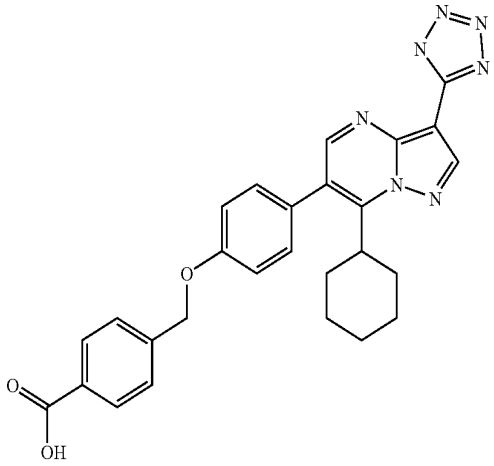
Compound	MOLSTRUCTURE	Δ-55 Activity	Δ-21 Activity
	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM		
402		C	C
403		B	C
404		C	C

TABLE 1-continued

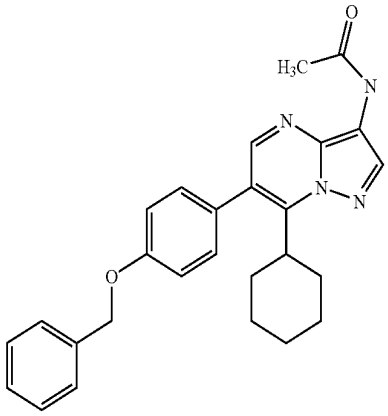
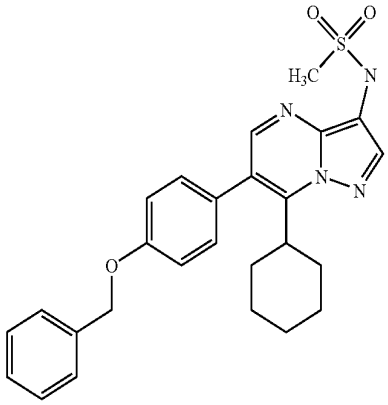
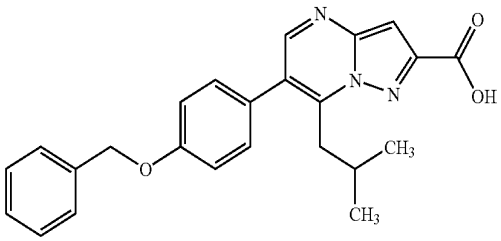
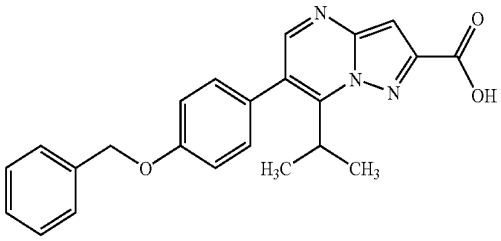
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
405		A	A
406		A	A
407		A	A
408		A	A

TABLE 1-continued

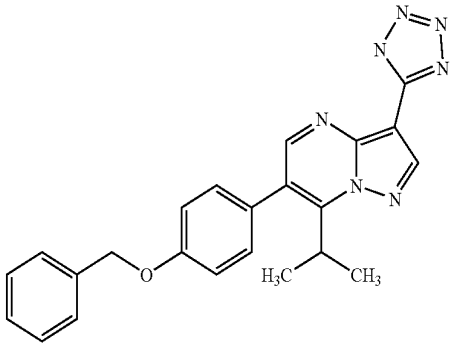
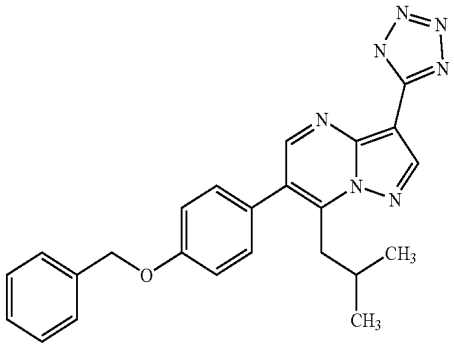
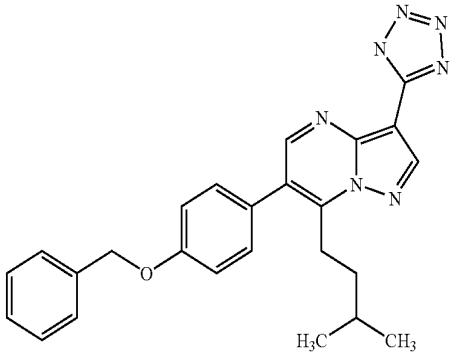
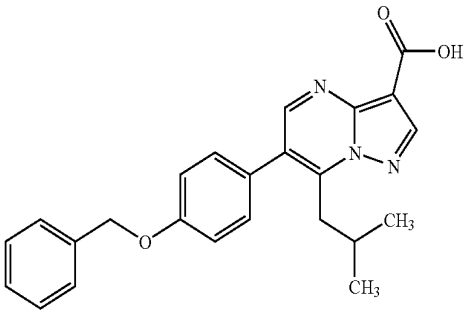
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM	
		Δ-55 Activity	Δ-21 Activity
409		A	B
410		B	B
411		A	B
412		A	A

TABLE 1-continued

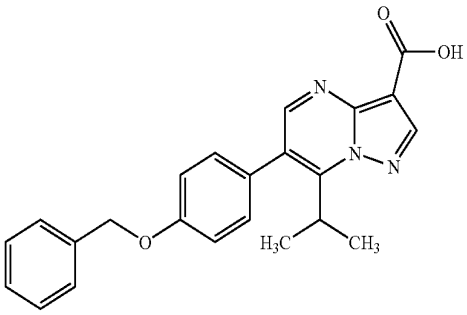
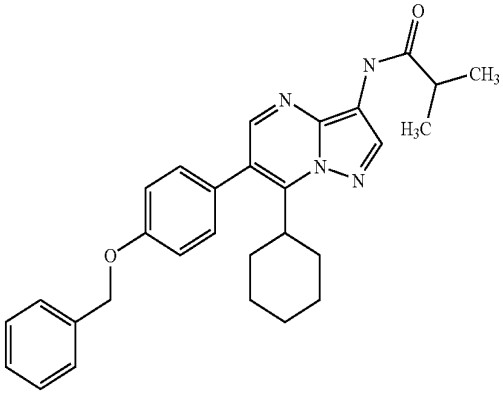
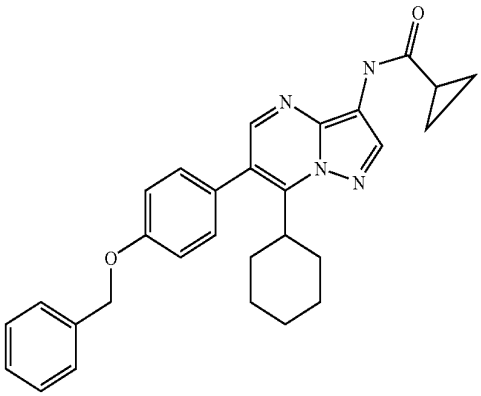
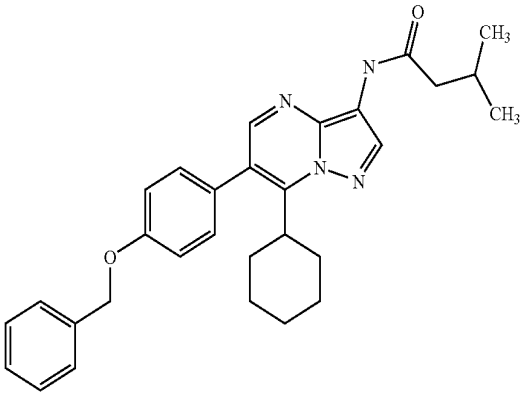
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
413		A	A
414		A	A
415		A	A
416		A	A

TABLE 1-continued

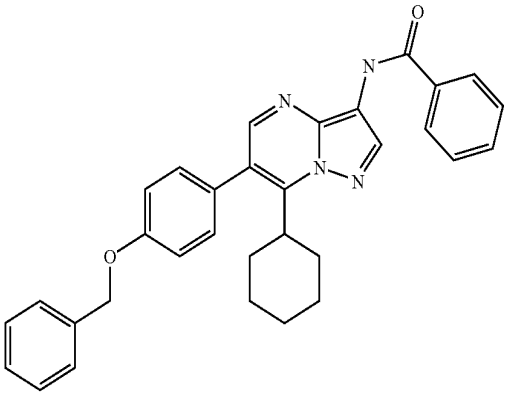
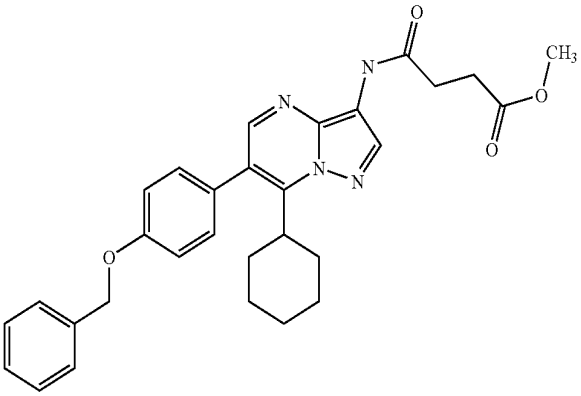
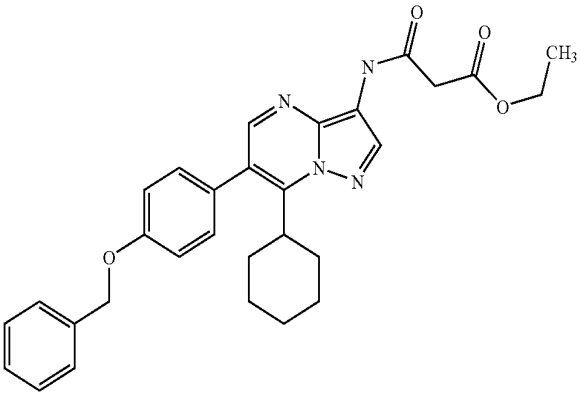
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
417		A	
418		A	
419		A	

TABLE 1-continued

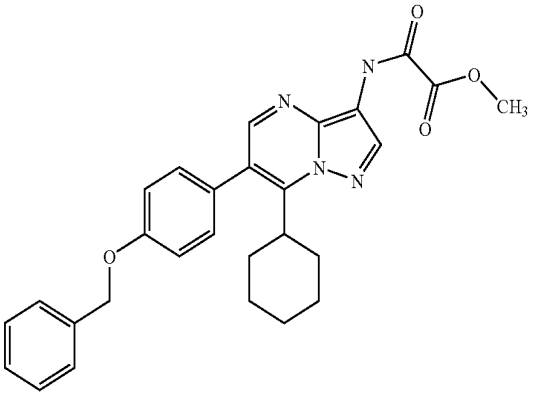
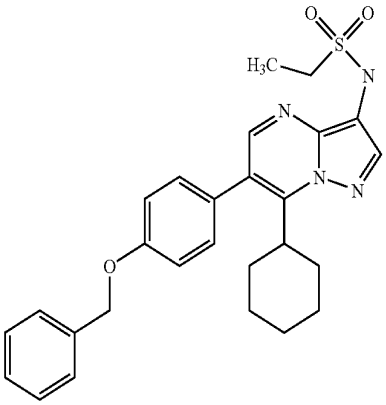
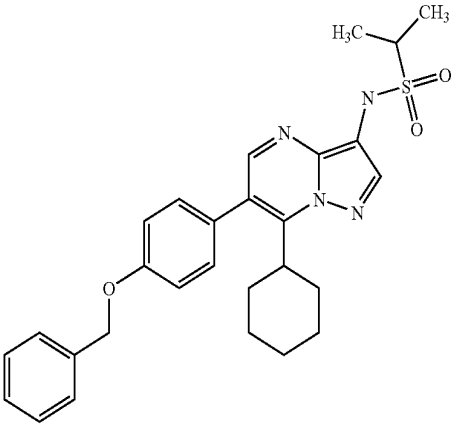
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
420		A	
421		A	
422		A	

TABLE 1-continued

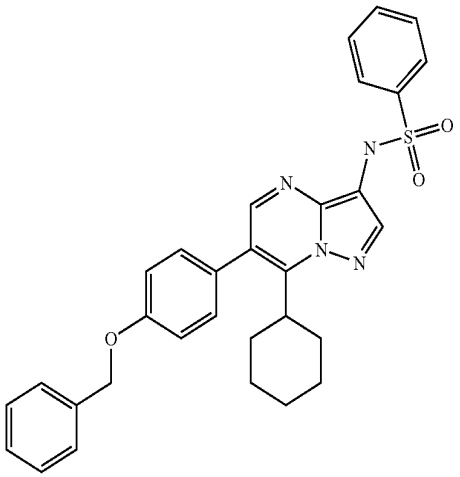
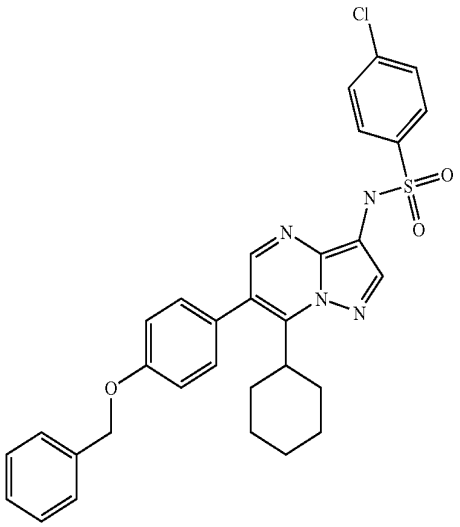
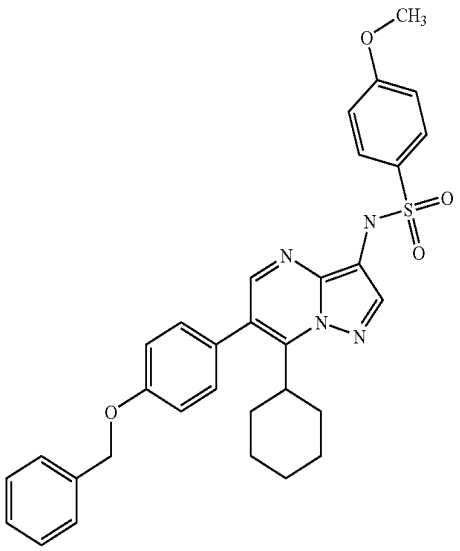
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
423		A	
424		A	
425		A	

TABLE 1-continued

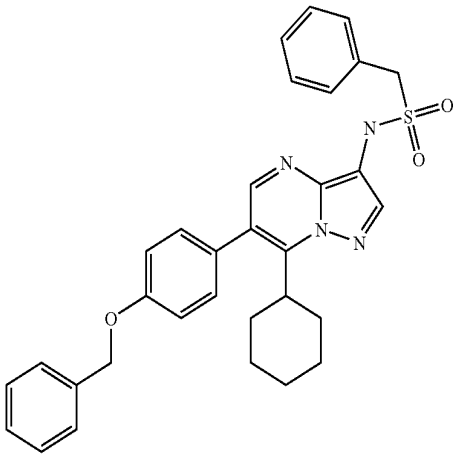
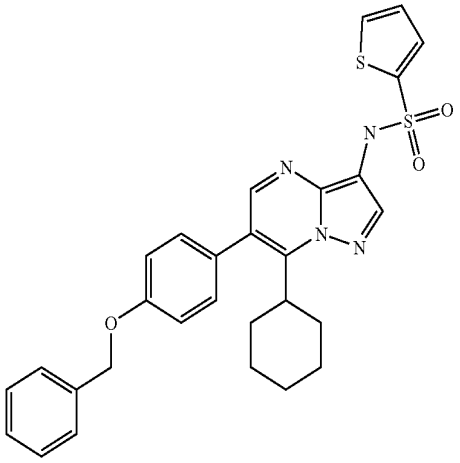
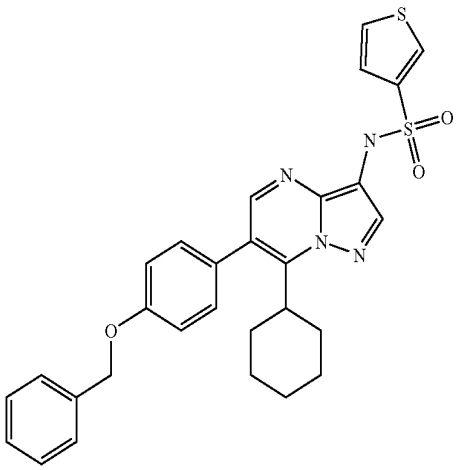
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
426		A	
427		A	
428		A	

TABLE 1-continued

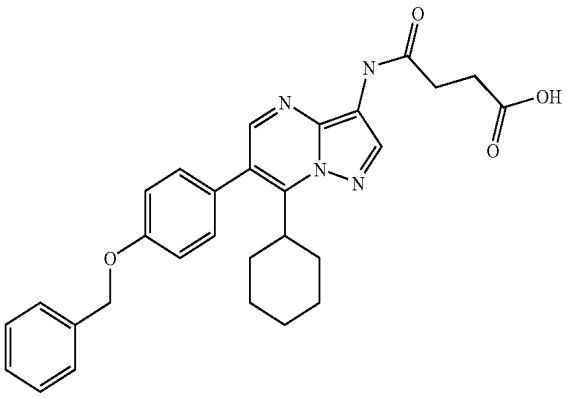
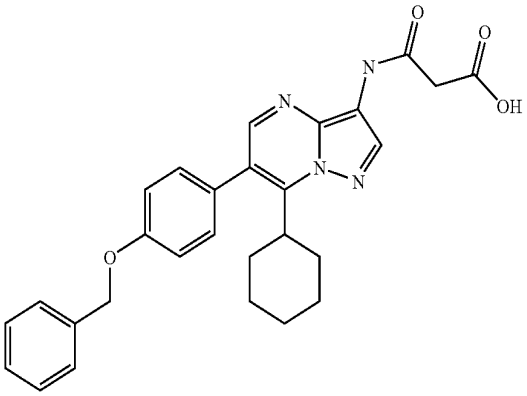
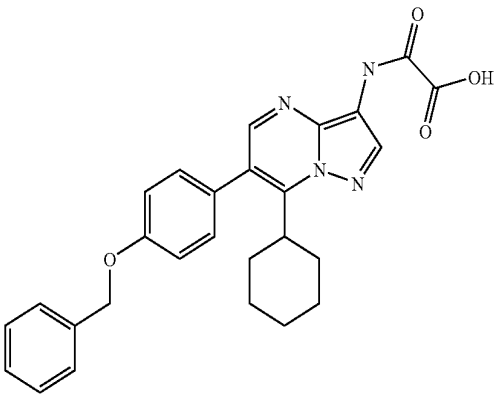
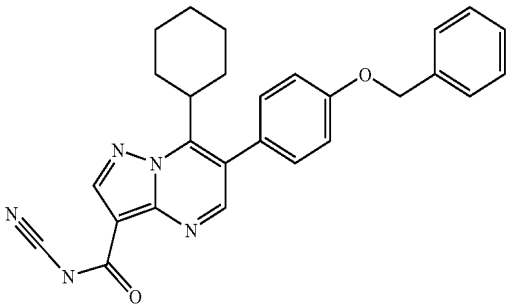
Compound	MOLSTRUCTURE	Δ-55 Activity	Δ-21 Activity
	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM		
429		B	B
430		B	B
431		B	B
432		B	C

TABLE 1-continued

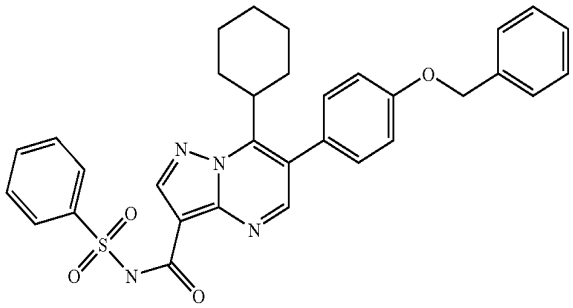
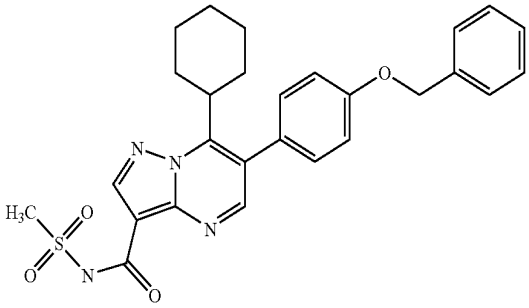
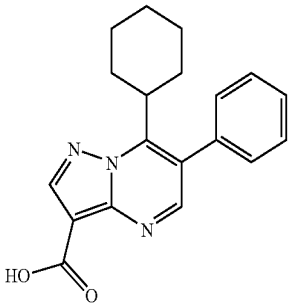
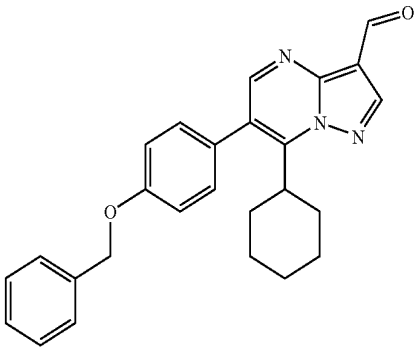
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
433		B	C
434		B	B
435		B	C
436		A	A

TABLE 1-continued

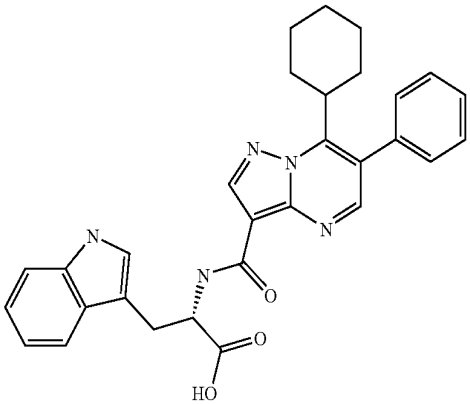
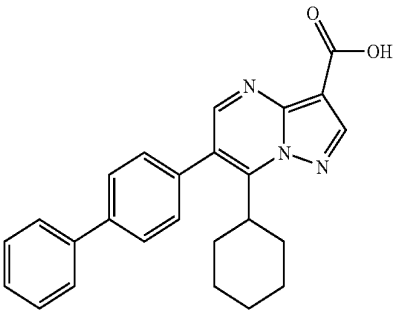
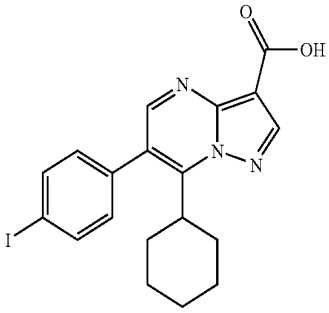
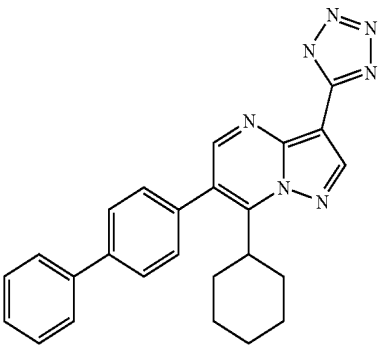
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
437		C	C
438		B	B
439		B	B
440		B	B

TABLE 1-continued

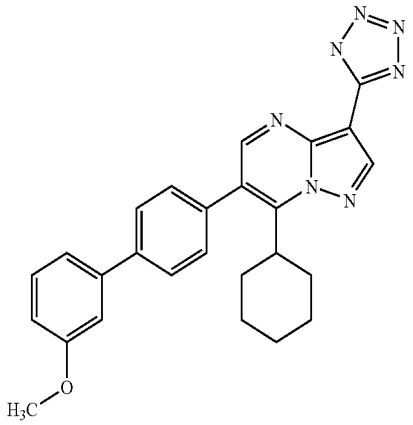
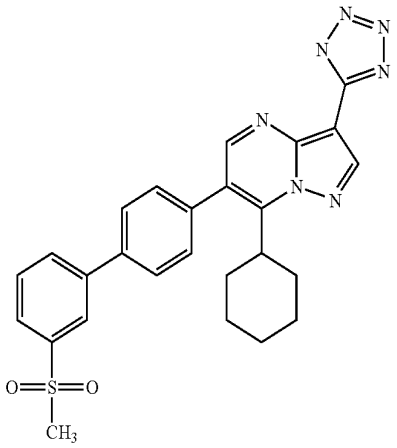
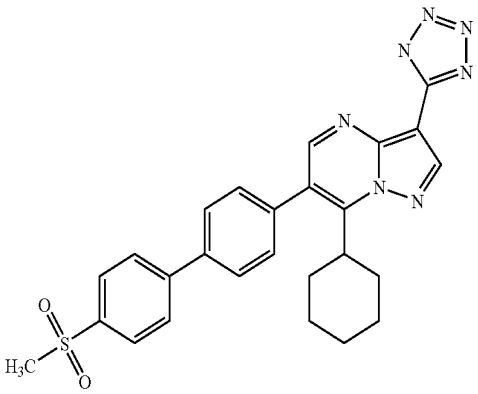
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
441		B	B
442		B	C
443		B	C

TABLE 1-continued

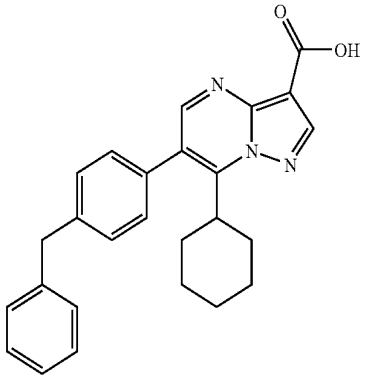
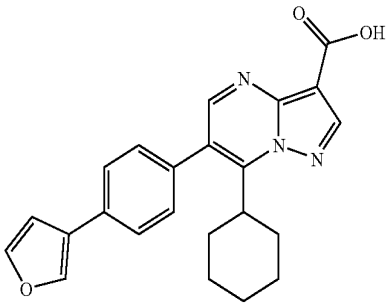
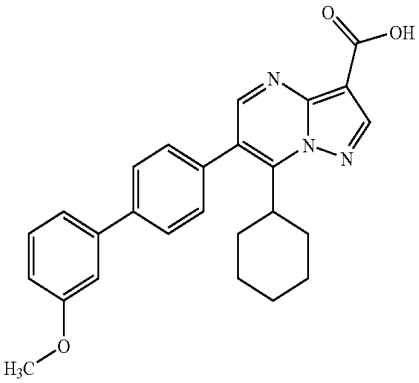
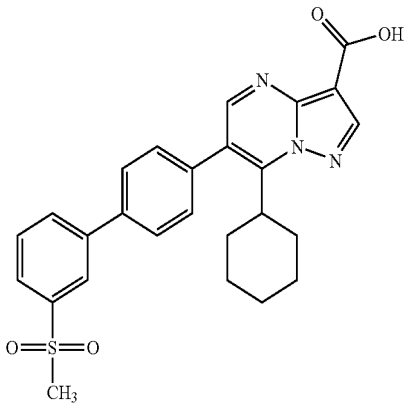
Compound	MOLSTRUCTURE	Δ-55 Activity	Δ-21 Activity
	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM		
444		B	B
445		B	B
446		B	B
447		B	B

TABLE 1-continued

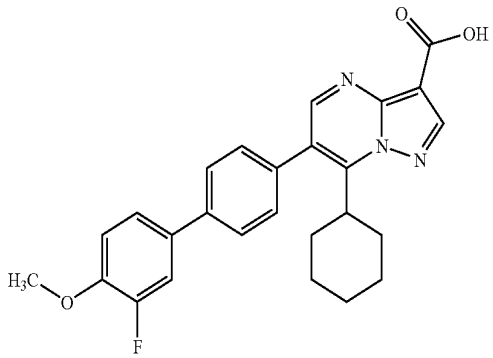
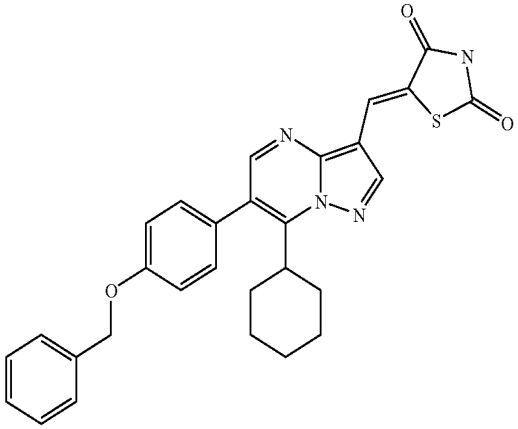
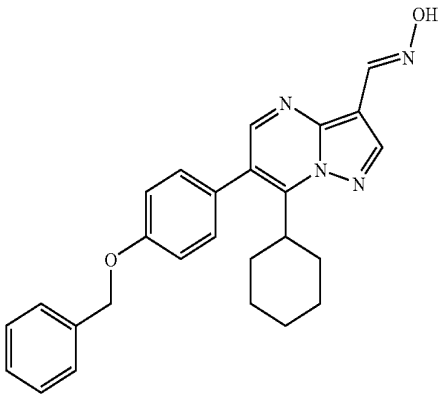
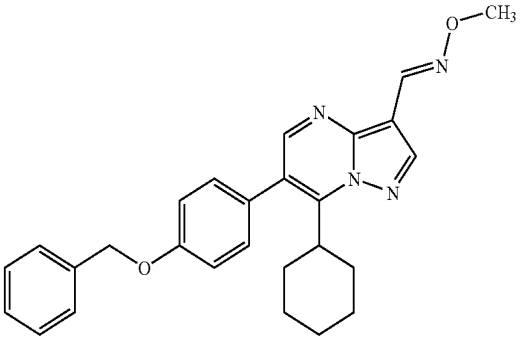
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
448		B	B
449		A	
450		A	
451		A	

TABLE 1-continued

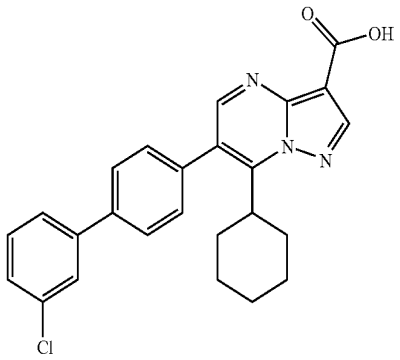
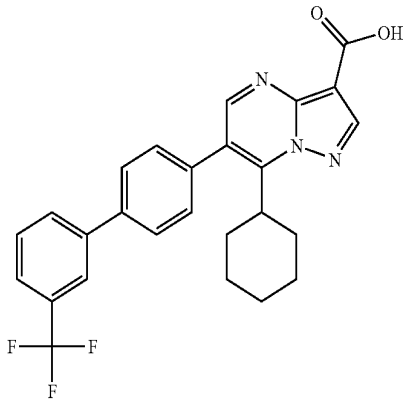
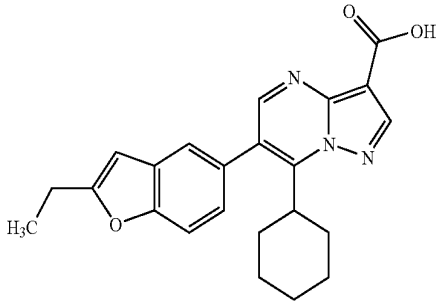
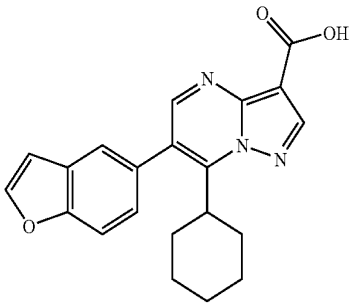
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM	
		Δ-55 Activity	Δ-21 Activity
452		B	B
453		A	B
454			B
455			B

TABLE 1-continued

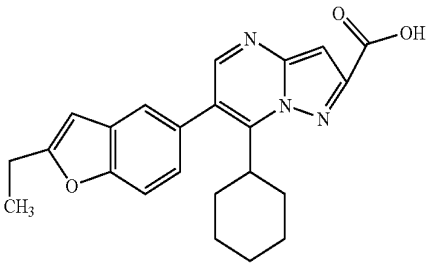
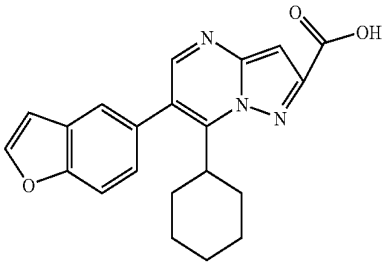
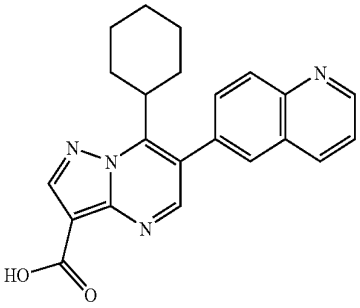
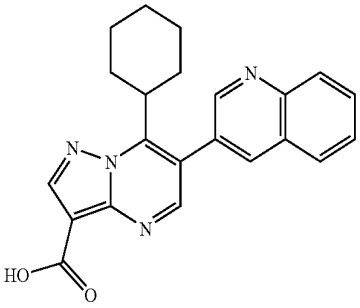
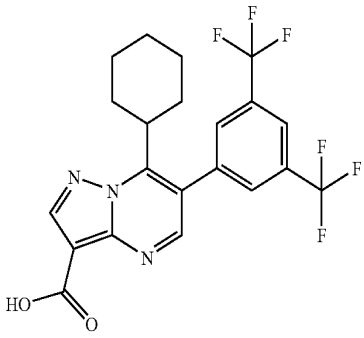
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
456			B
457			A
458		A	A
459		A	
460		A	

TABLE 1-continued

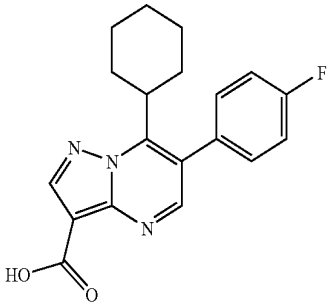
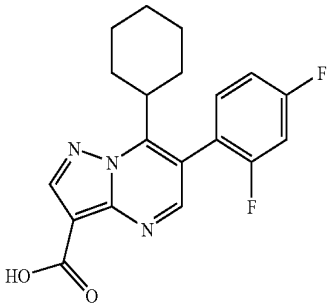
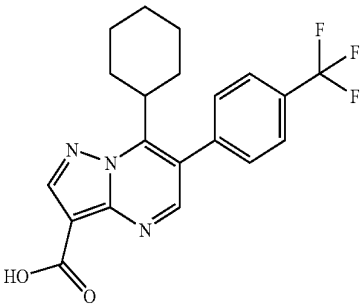
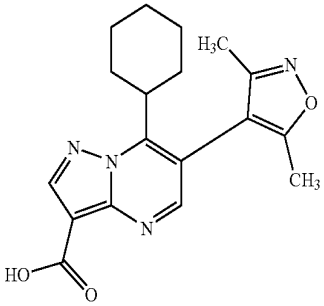
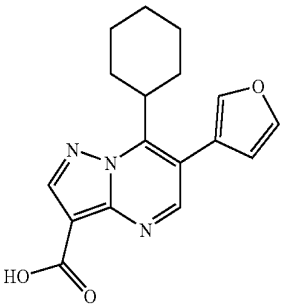
Compound	MOLSTRUCTURE	Δ-55 Activity	Δ-21 Activity
	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM		
461		B	C
462		B	B
463		A	A
464		A	
465		B	B

TABLE 1-continued

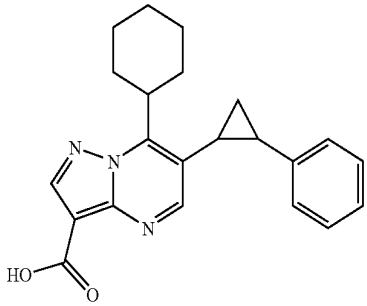
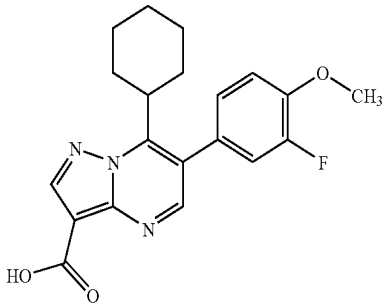
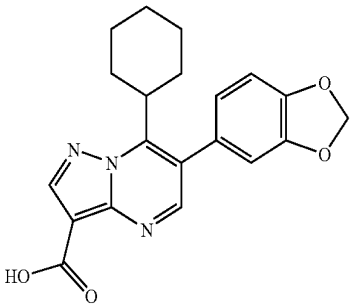
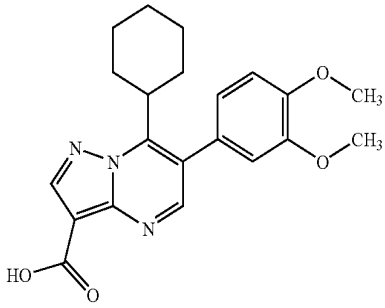
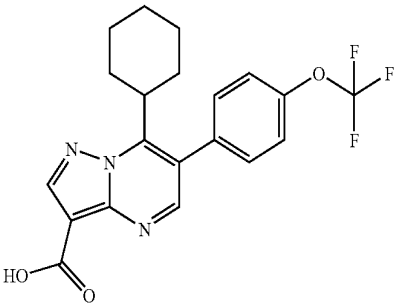
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
466		A	A
467		B	B
468		B	B
469		A	
470		A	B

TABLE 1-continued

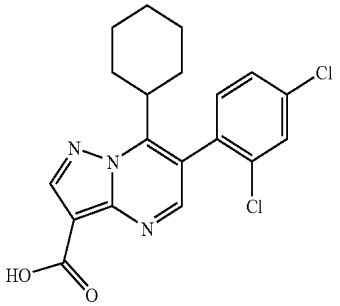
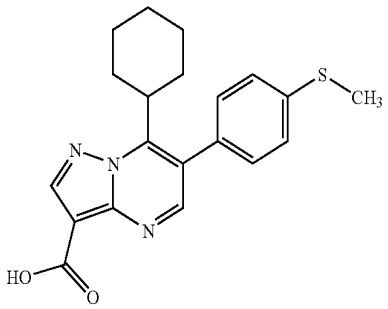
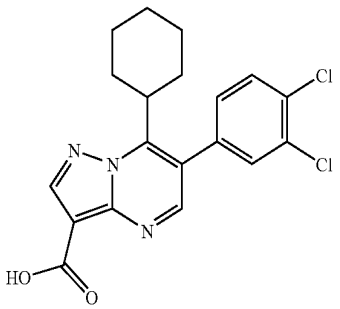
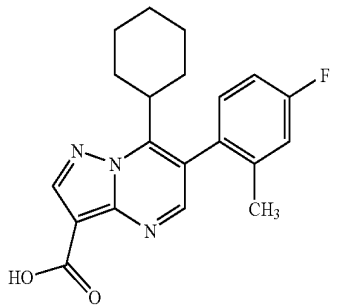
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
471		B	B
472		B	B
473		B	B
474		A	A

TABLE 1-continued

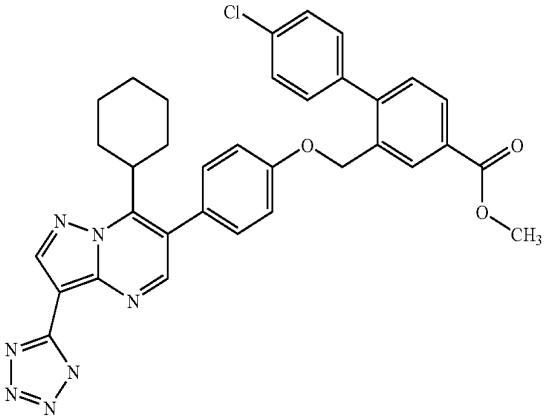
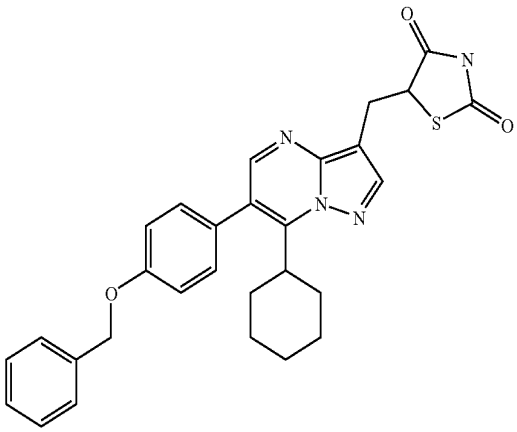
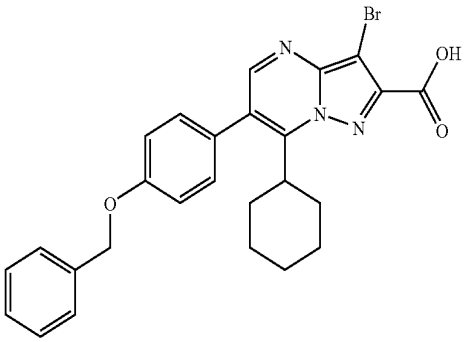
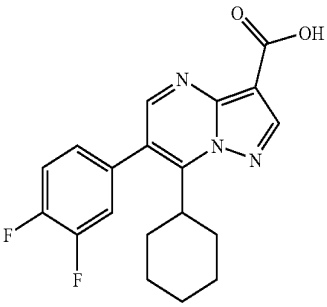
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
475		C	C
476		A	A
477		B	B
478		B	B

TABLE 1-continued

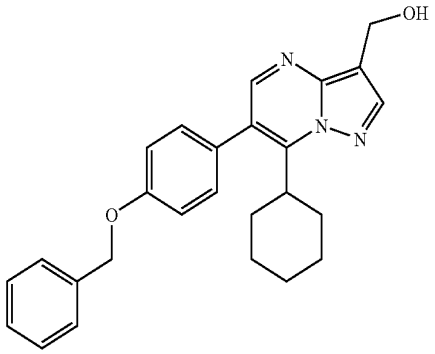
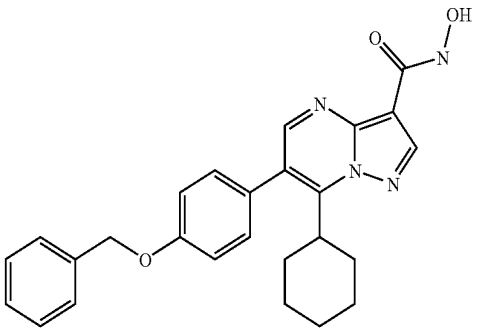
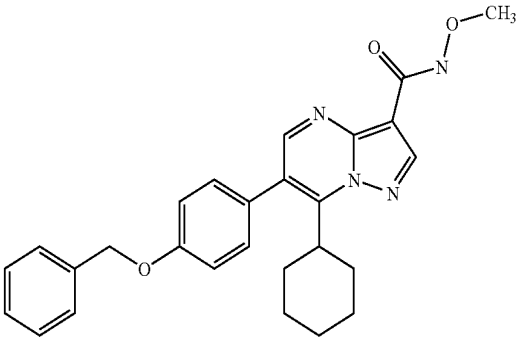
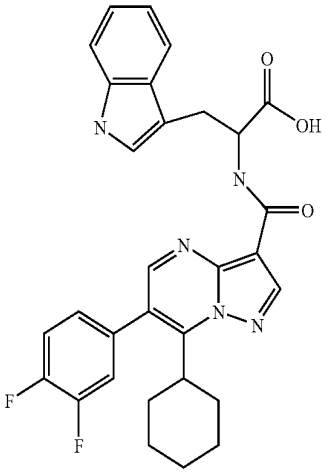
Compound	MOLSTRUCTURE	Δ-55 Activity	Δ-21 Activity
	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM		
479		A	A
480		A	B
481		A	A
482		C	C

TABLE 1-continued

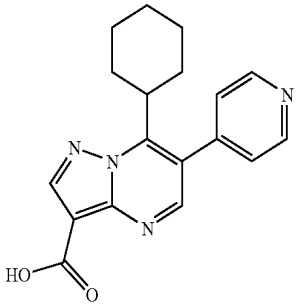
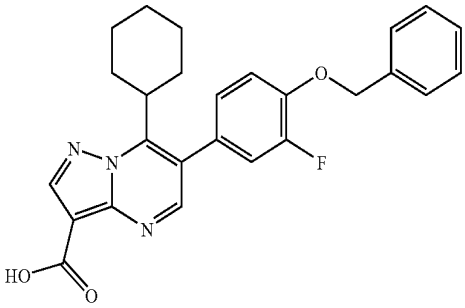
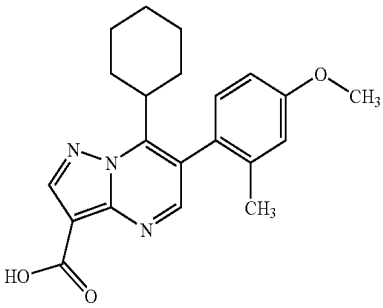
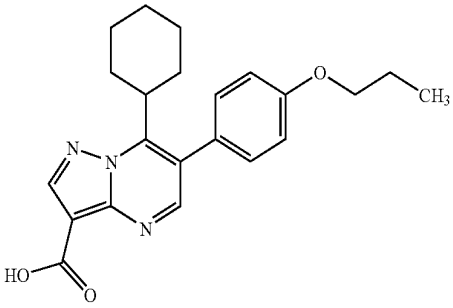
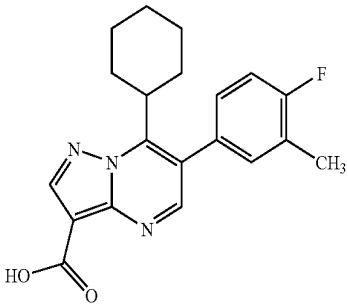
Compound	MOLSTRUCTURE	Δ-55 Activity	Δ-21 Activity
	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM		
483		A	B
484		B	C
485		B	B
486		B	B
487		B	B

TABLE 1-continued

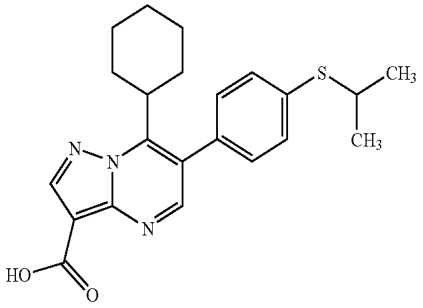
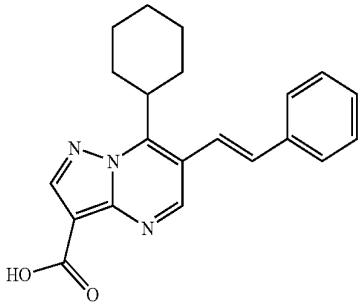
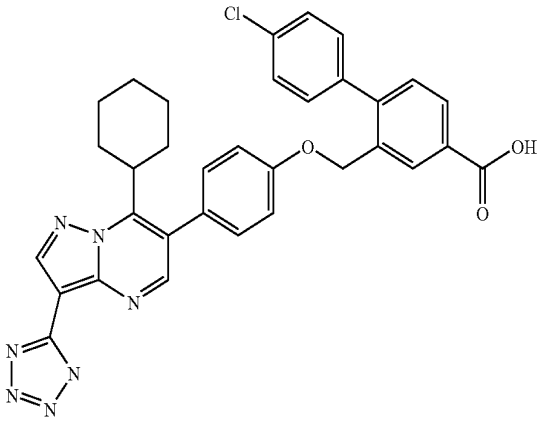
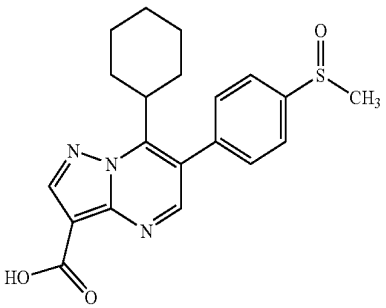
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
488		B	B
489		B	B
490		C	C
491		A	A

TABLE 1-continued

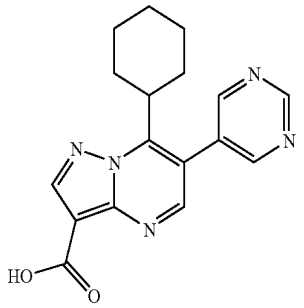
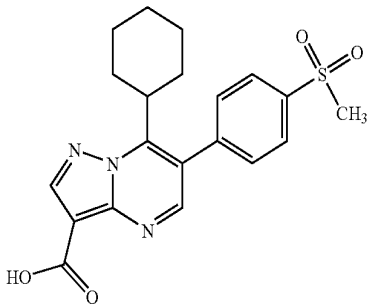
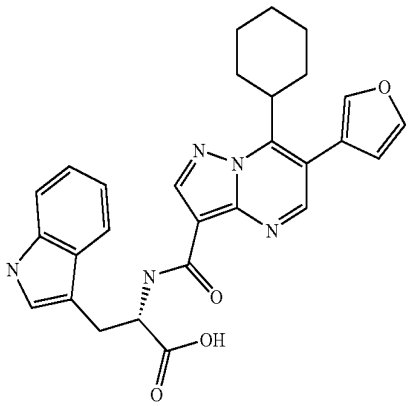
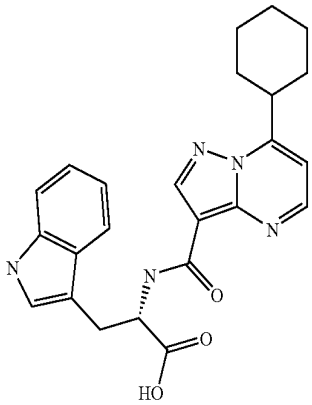
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
492		A	A
493		A	B
494		C	C
495		A	B

TABLE 1-continued

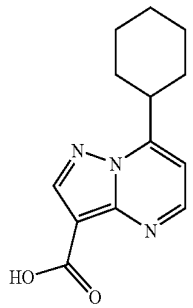
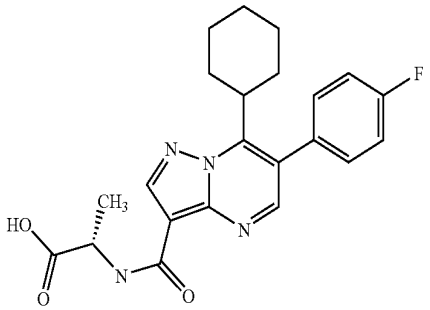
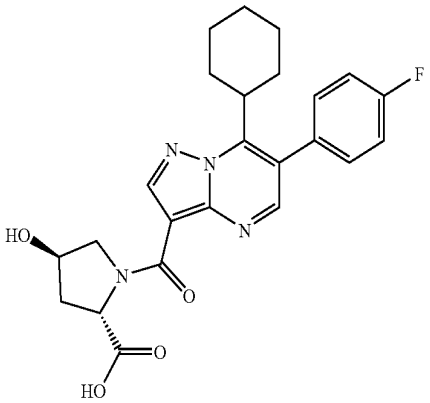
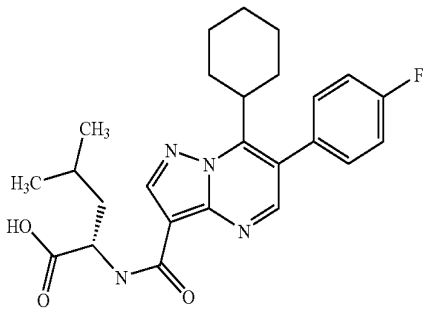
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
496		A	A
497		B	C
498		A	A
499		B	C

TABLE 1-continued

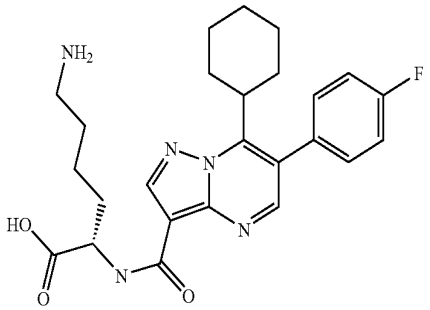
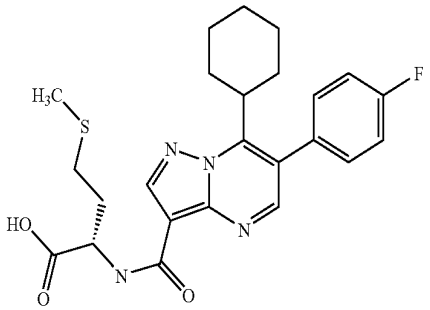
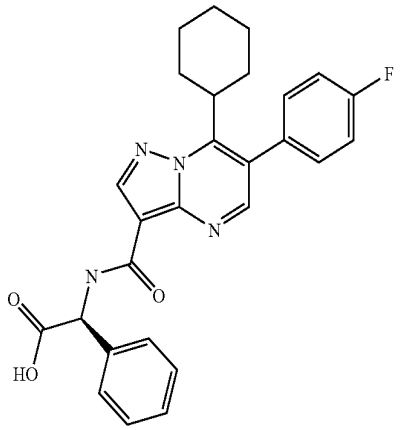
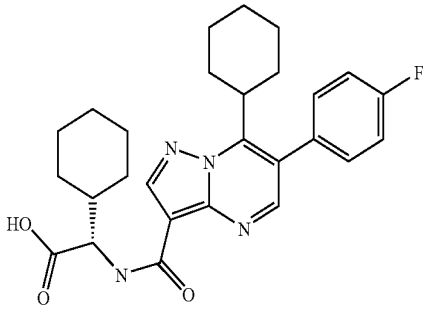
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM	
		Δ-55 Activity	Δ-21 Activity
500		B	C
501		B	C
502		C	C
503		B	C

TABLE 1-continued

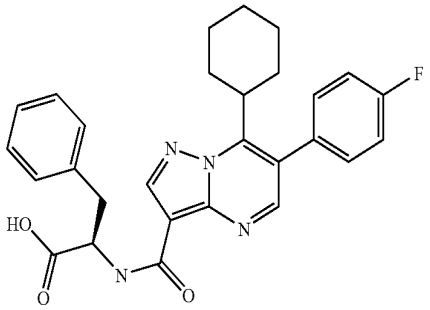
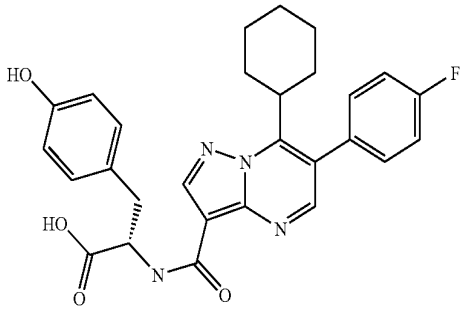
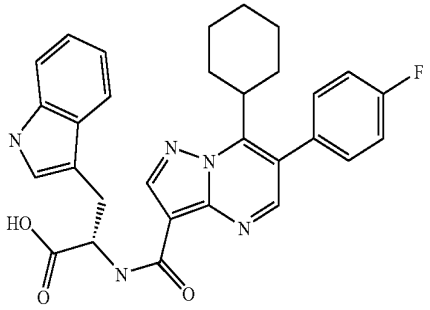
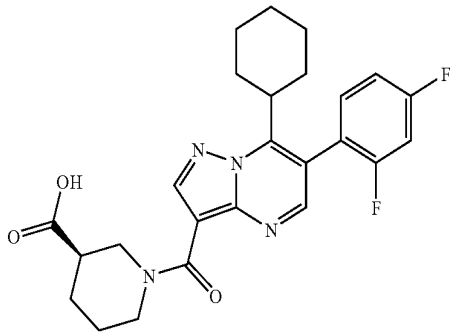
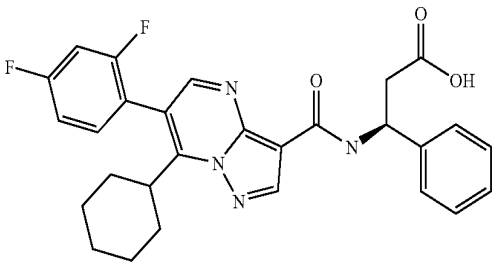
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
504		B	B
505		C	C
506		C	C
507		A	A
508		B	B

TABLE 1-continued

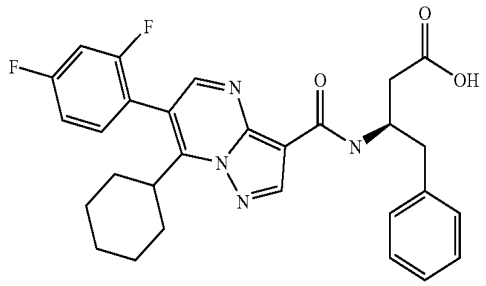
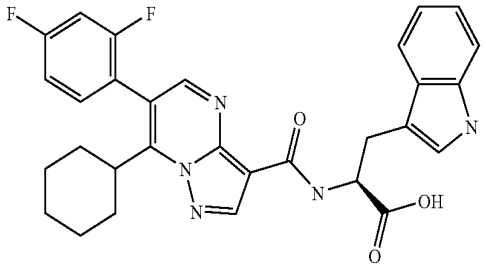
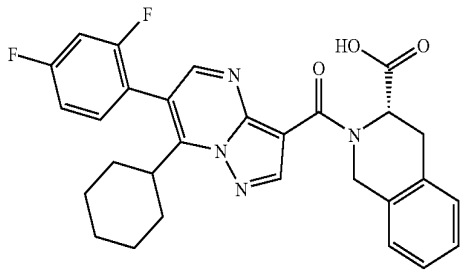
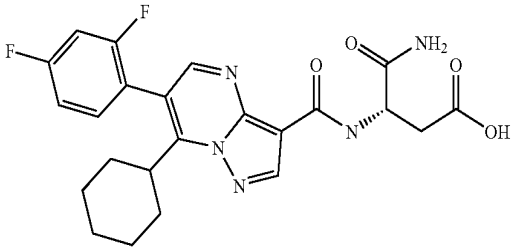
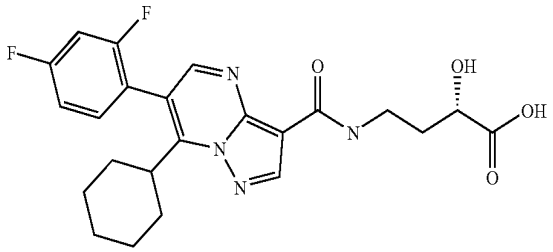
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM	
		Δ-55 Activity	Δ-21 Activity
509		A	B
510		C	C
511		A	B
512		B	C
513		A	C

TABLE 1-continued

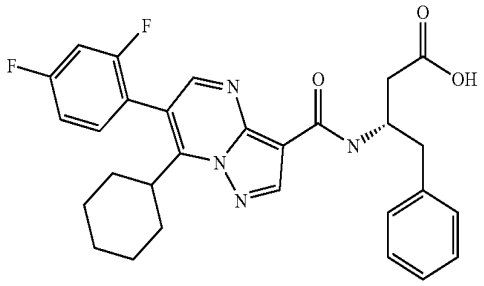
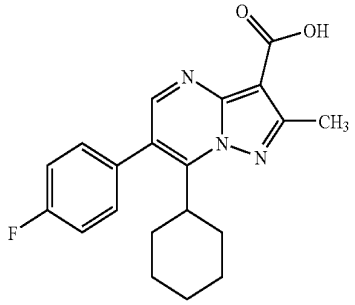
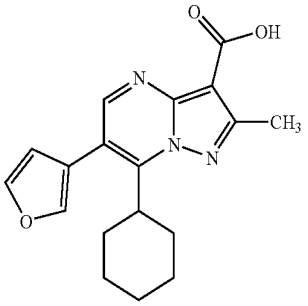
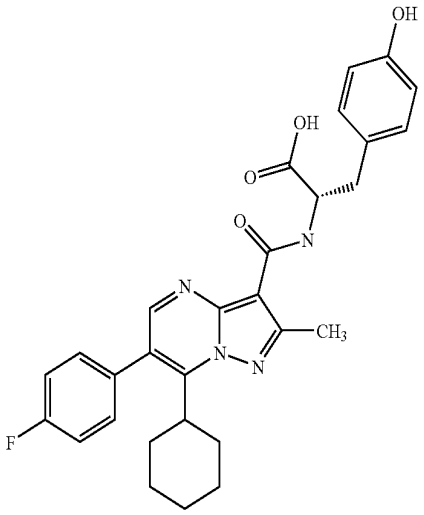
Compound	MOLSTRUCTURE	Δ-55 Activity	Δ-21 Activity
	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM		
514		B	C
515			A
516			A
517			C

TABLE 1-continued

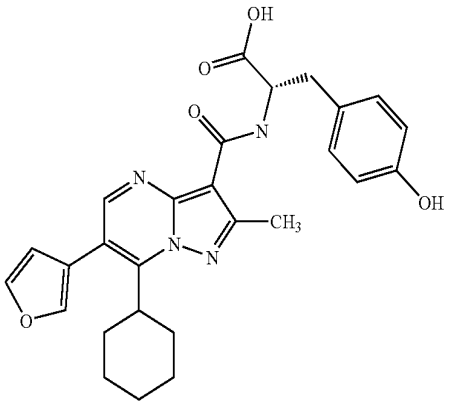
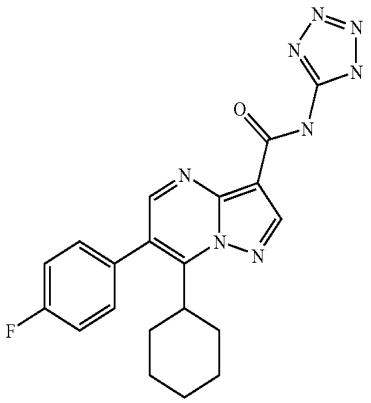
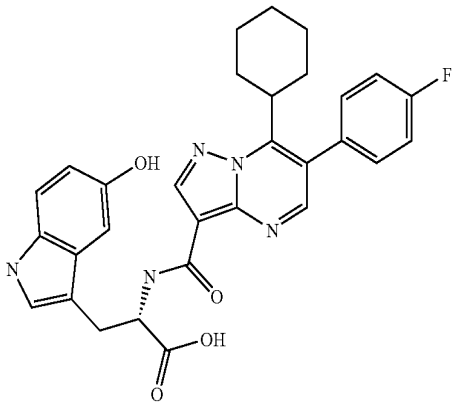
Compound	MOLSTRUCTURE	Δ-55 Activity	Δ-21 Activity
	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM		
518			C
519			B
520		C	C

TABLE 1-continued

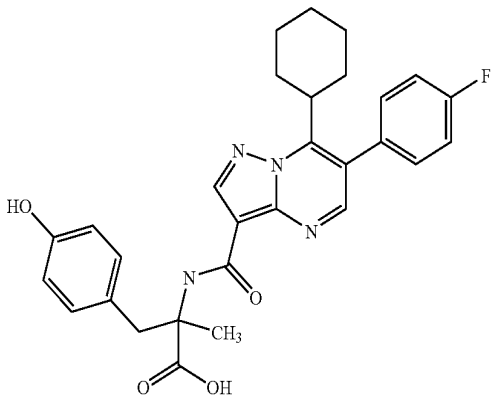
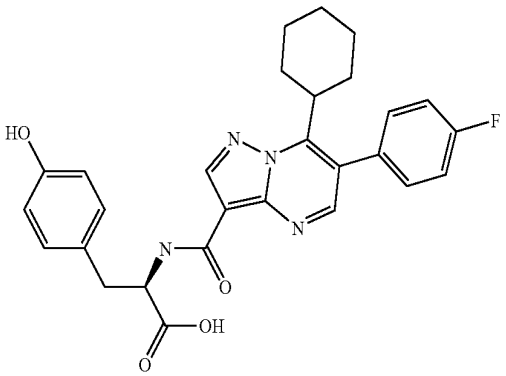
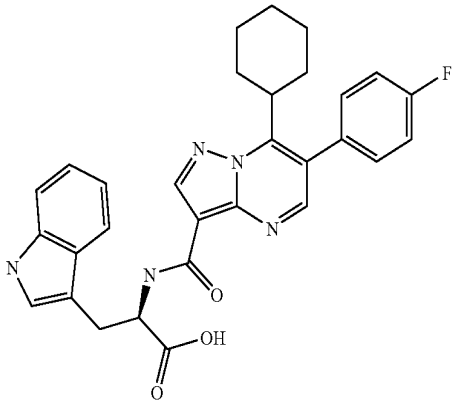
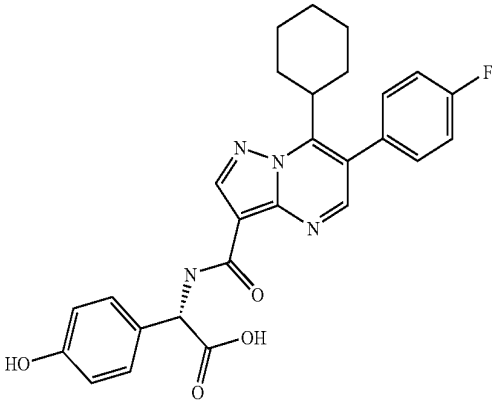
Compound	MOLSTRUCTURE	Δ-55 Activity	Δ-21 Activity
	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM		
521			C
522			C
523			C
524			C

TABLE 1-continued

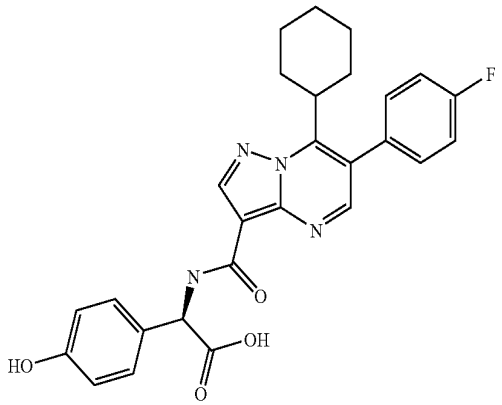
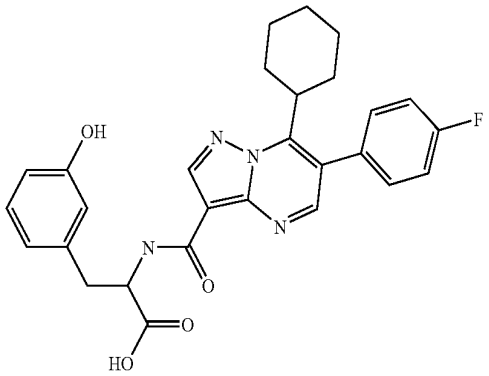
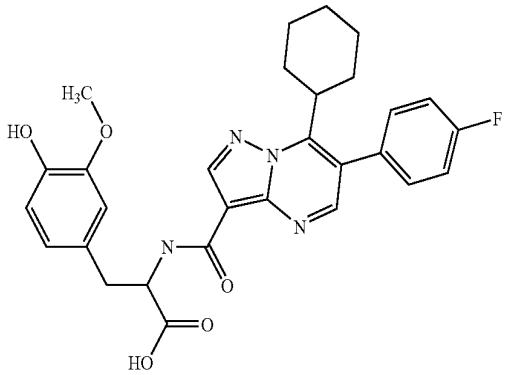
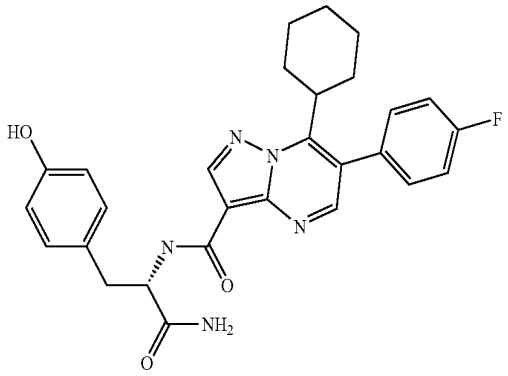
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
525			C
526			C
527			C
528			C

TABLE 1-continued

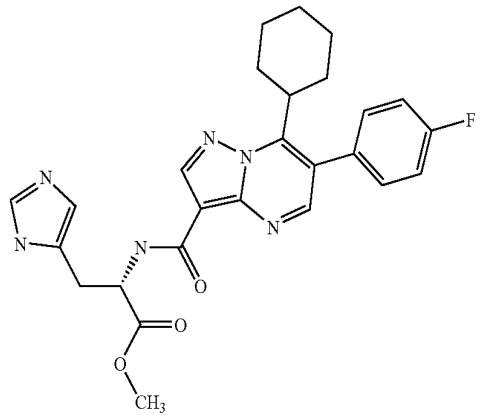
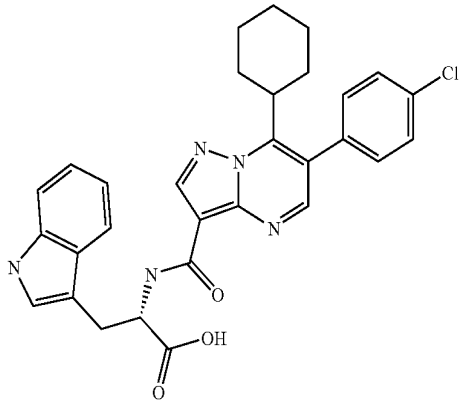
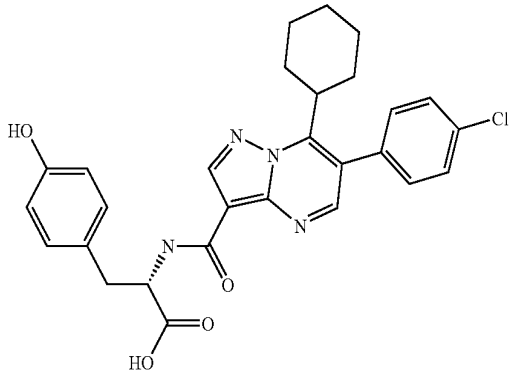
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
529			C
530			C
531			C

TABLE 1-continued

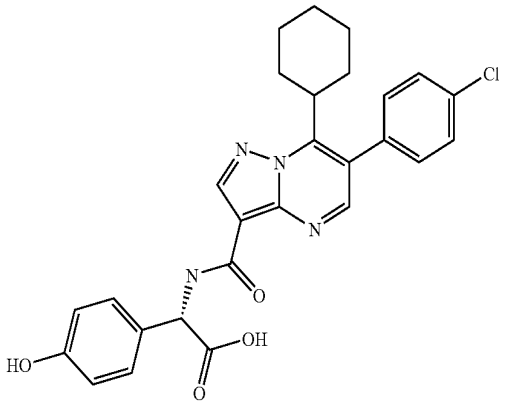
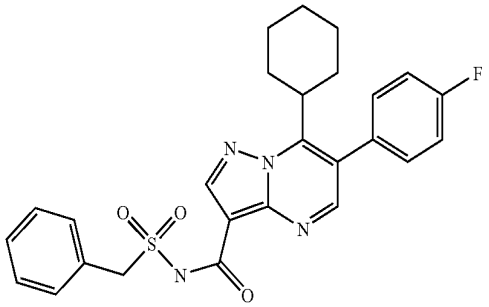
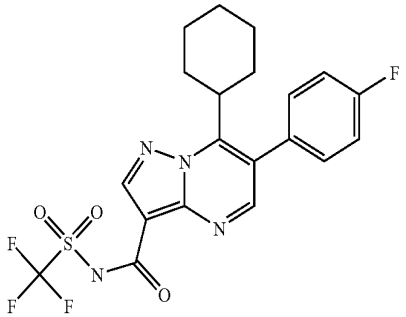
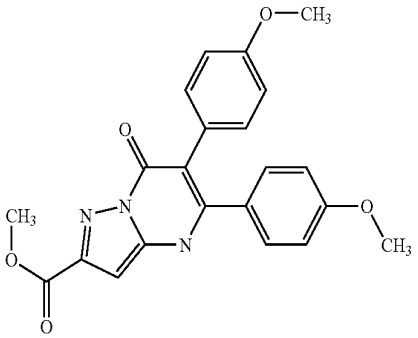
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
532			C
533		B	C
534			B
535		A	

TABLE 1-continued

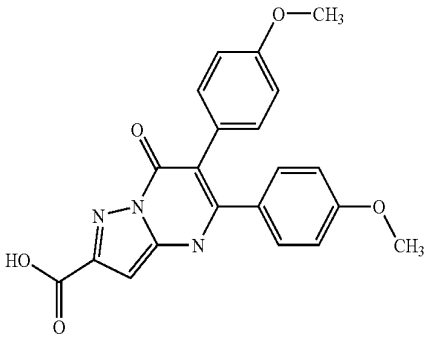
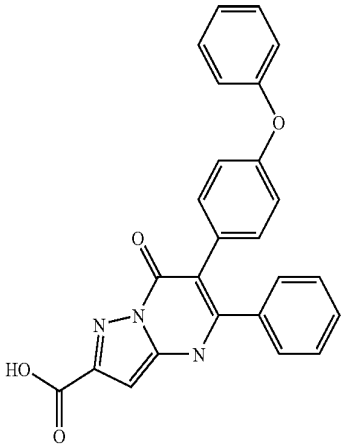
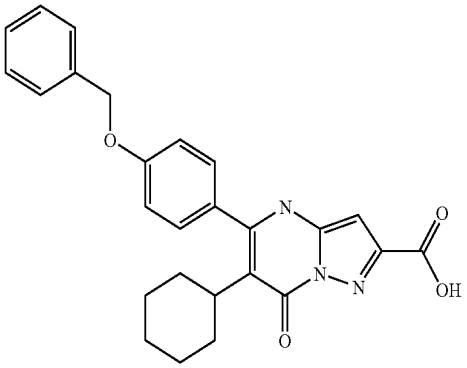
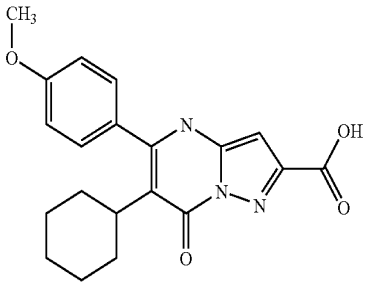
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
536		A	
537		A	
538		B	
539		B	

TABLE 1-continued

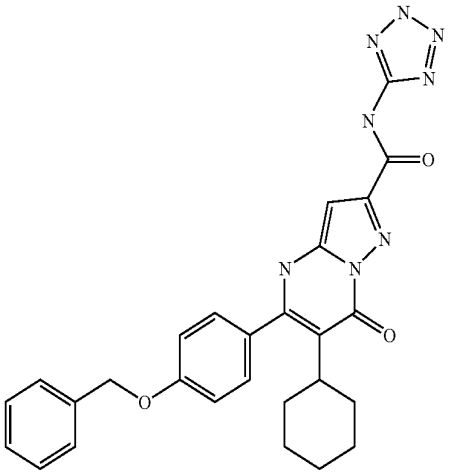
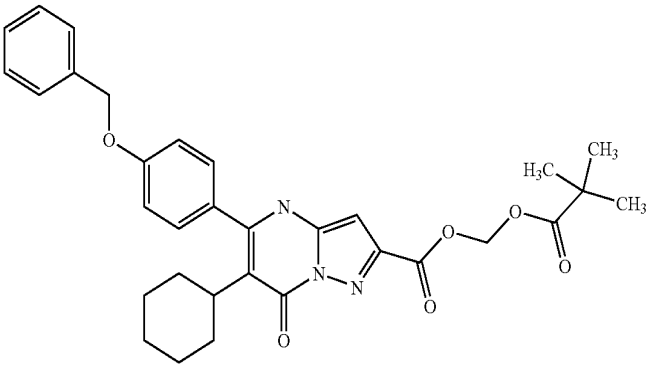
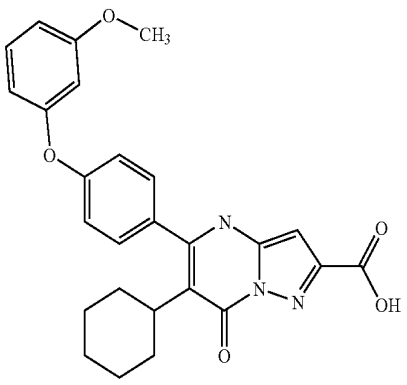
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
540		B	C
541		A	
542		C	

TABLE 1-continued

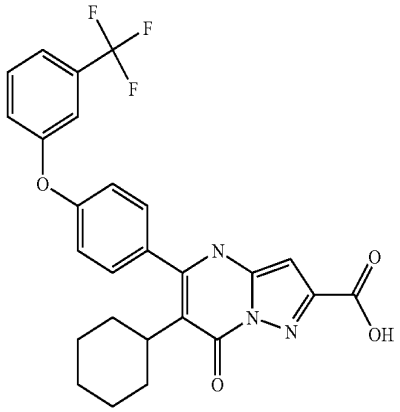
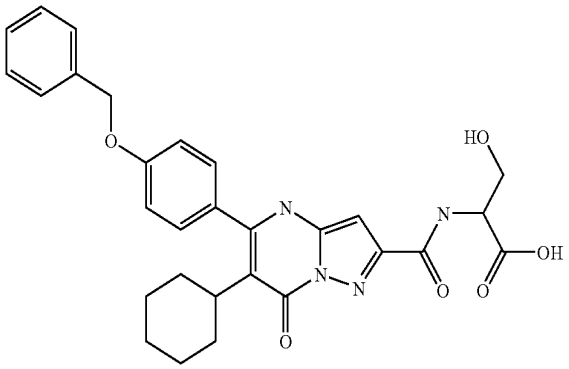
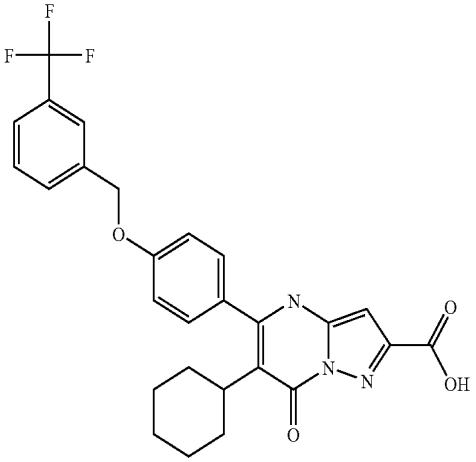
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
543		C	
544		B	
545		B	C

TABLE 1-continued

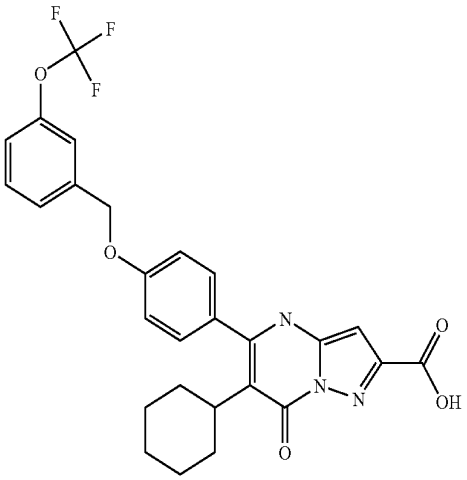
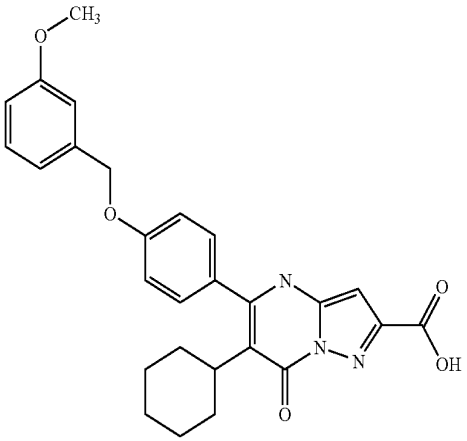
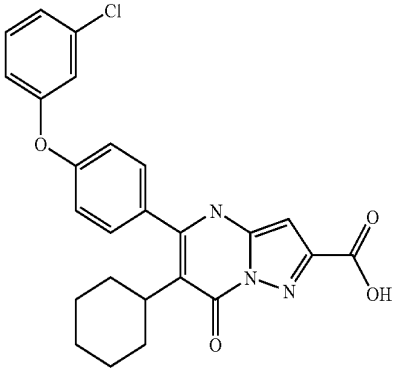
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
546		B	
547		B	
548		B	

TABLE 1-continued

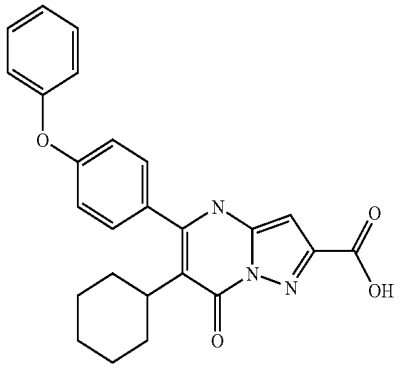
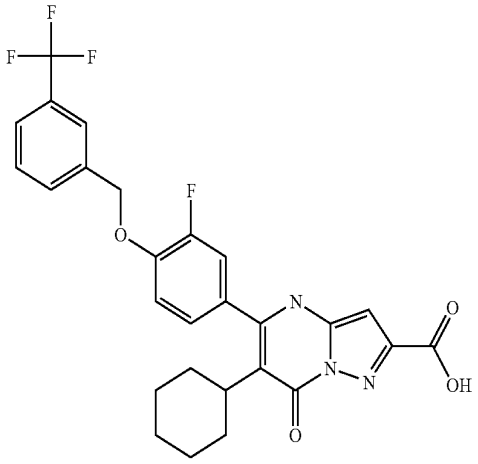
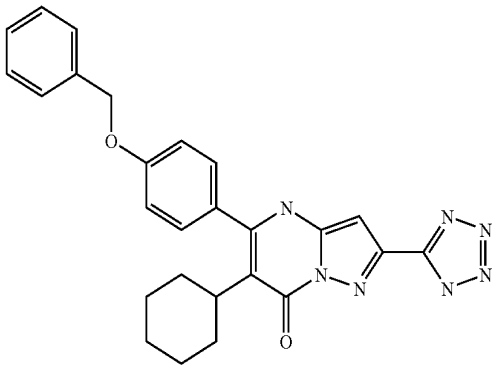
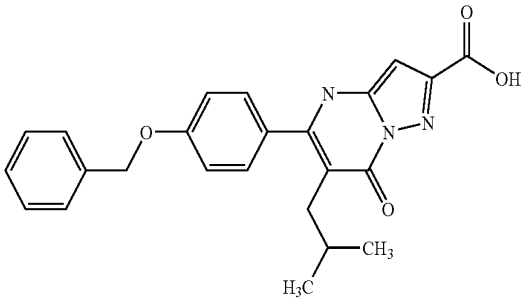
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
549		B	
550		B	B
551		C	C
552		A	B

TABLE 1-continued

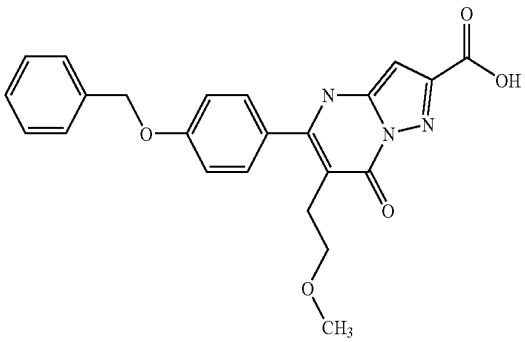
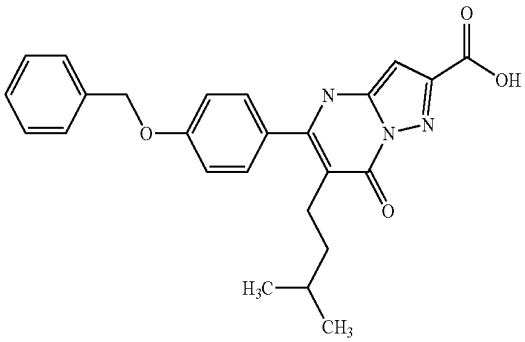
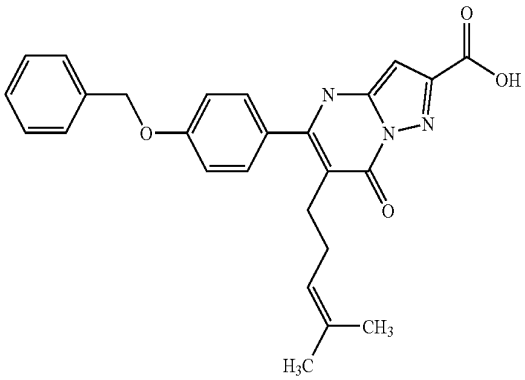
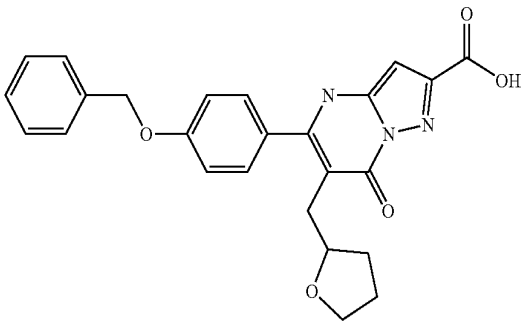
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM	
		Δ-55 Activity	Δ-21 Activity
553		A	B
554		B	B
555		B	C
556		A	B

TABLE 1-continued

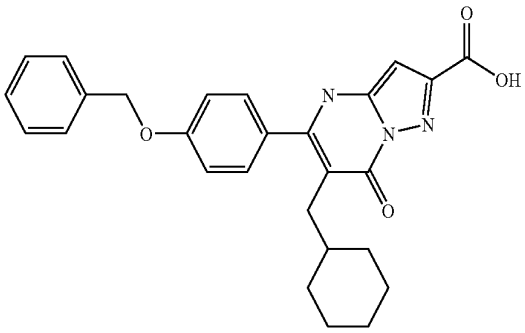
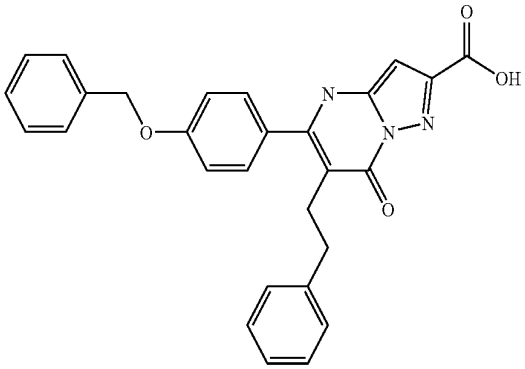
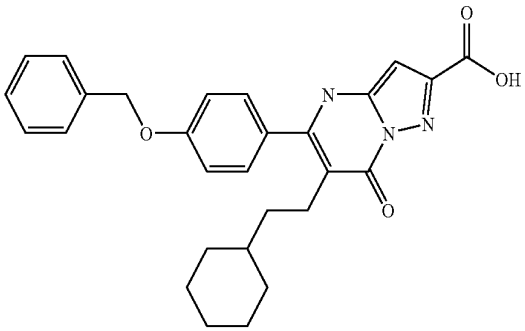
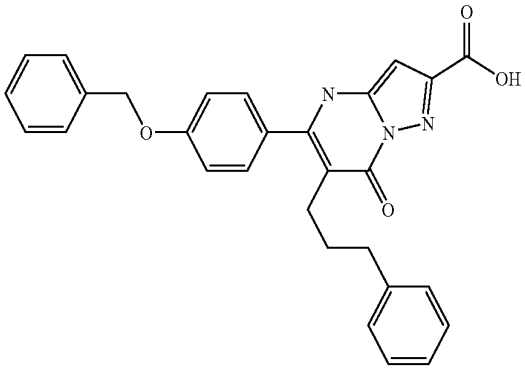
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
557		B	C
558		B	B
559		C	C
560		B	B

TABLE 1-continued

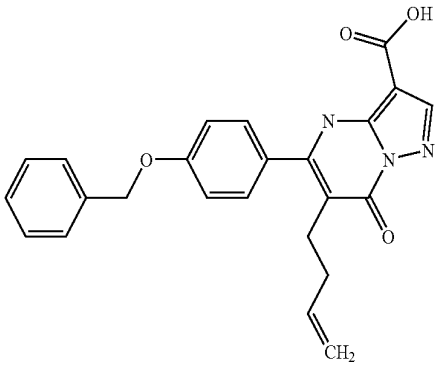
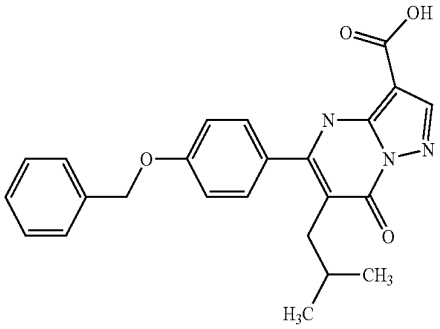
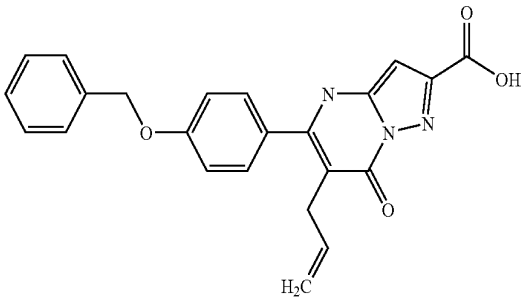
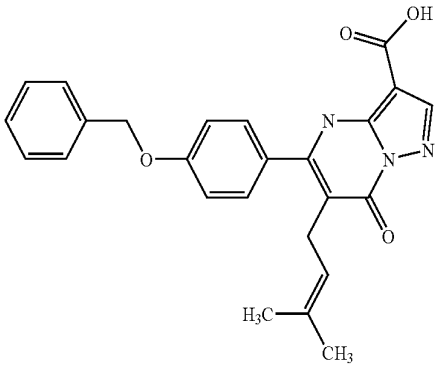
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM	
		Δ-55 Activity	Δ-21 Activity
561		A	A
562		A	B
563		A	A
564		A	B

TABLE 1-continued

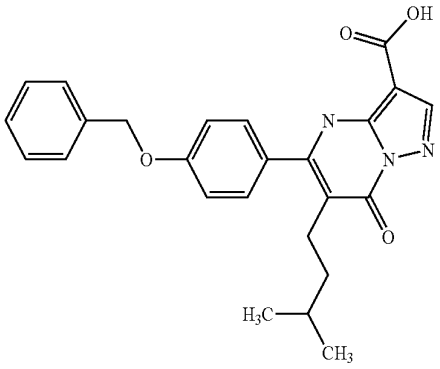
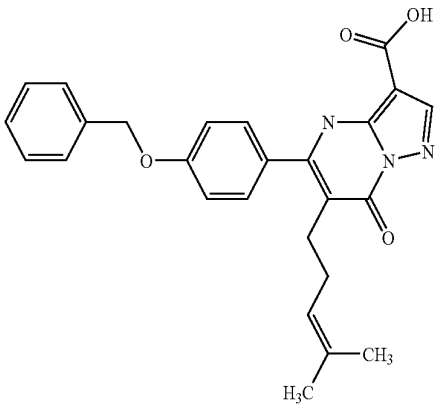
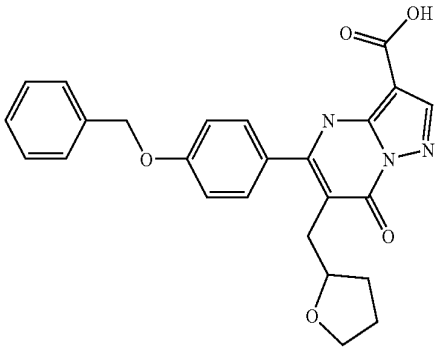
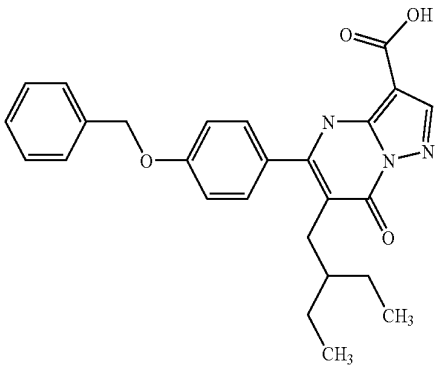
Compound	MOLSTRUCTURE	Δ-55 Activity	Δ-21 Activity
	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM		
565		B	B
566		B	B
567		A	A
568		A	B

TABLE 1-continued

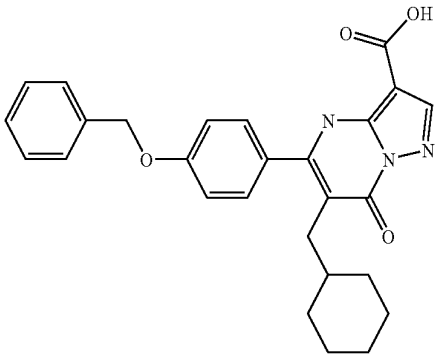
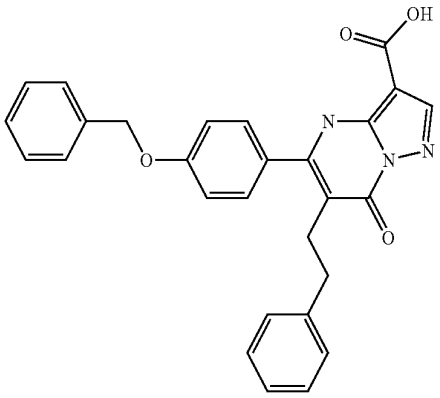
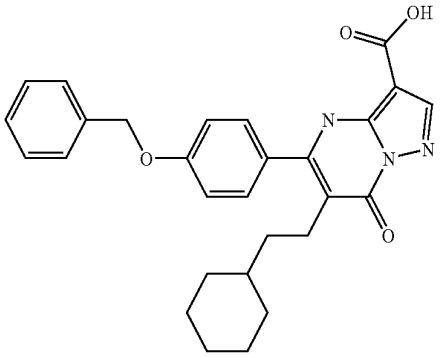
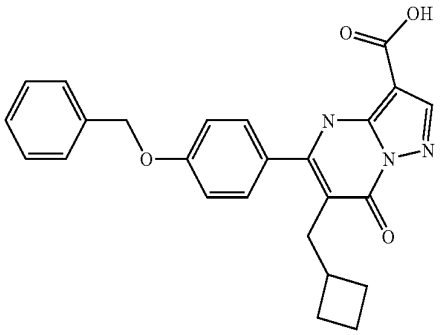
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
569		B	B
570		A	B
571		A	B
572		B	B

TABLE 1-continued

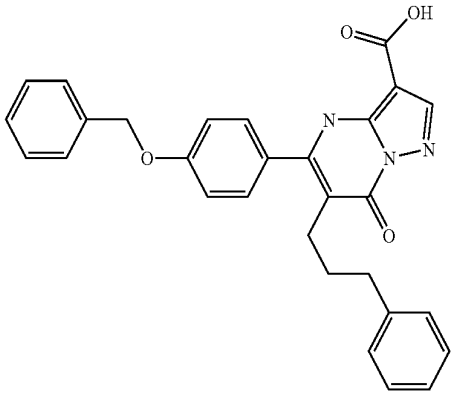
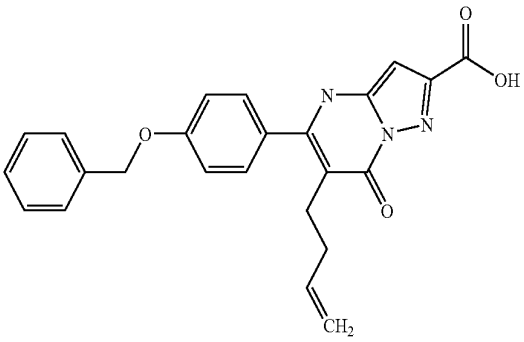
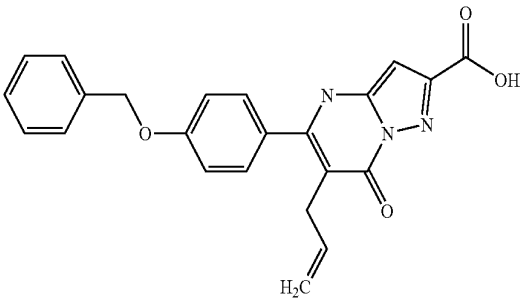
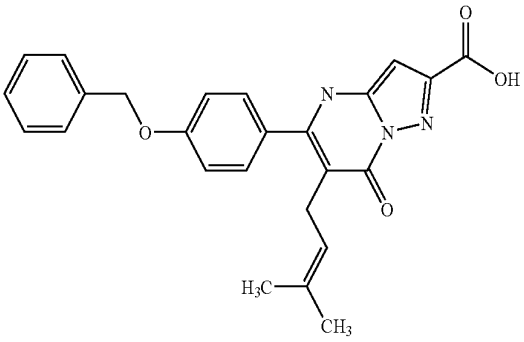
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM	
		Δ-55 Activity	Δ-21 Activity
573		B	B
574		A	B
575		A	A
576		B	B

TABLE 1-continued

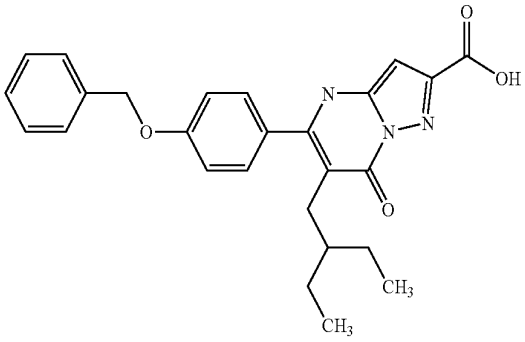
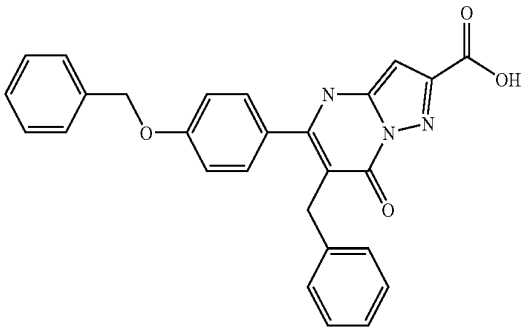
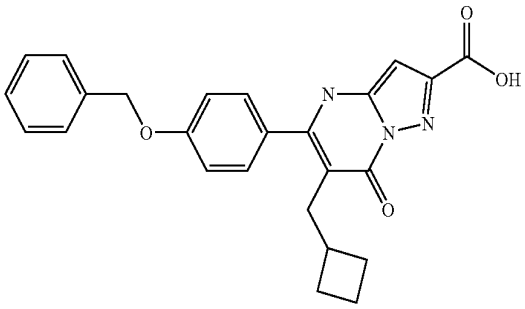
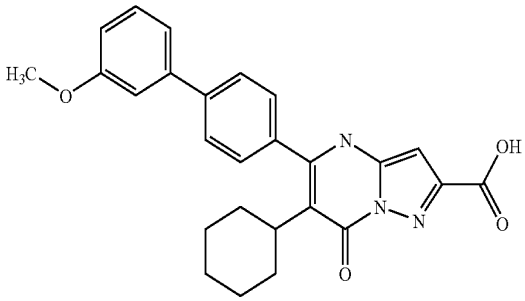
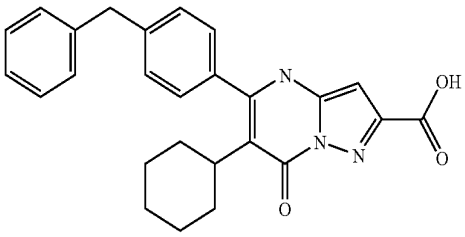
Compound	MOLSTRUCTURE	Δ-55 Activity	Δ-21 Activity
	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM		
577		B	B
578		B	B
579		B	B
580		B	B
581		B	B

TABLE 1-continued

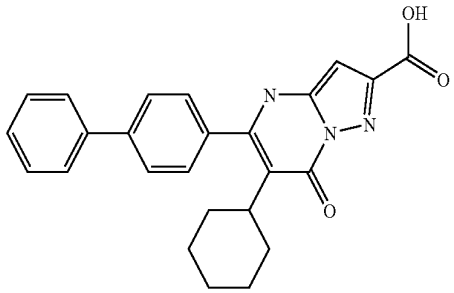
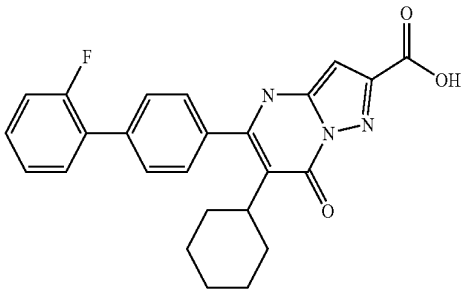
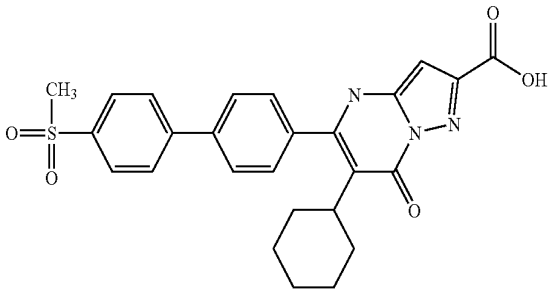
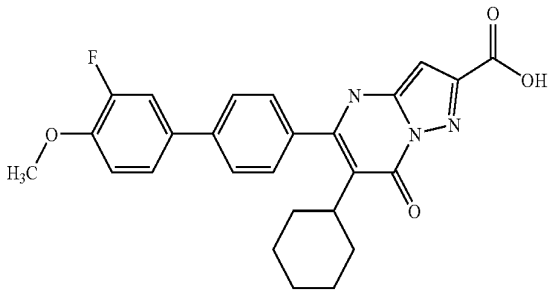
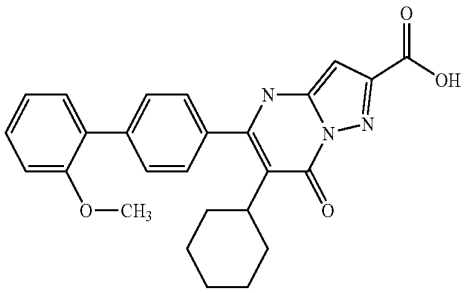
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
582		B	B
583		B	B
584		B	B
585		B	B
586		B	

TABLE 1-continued

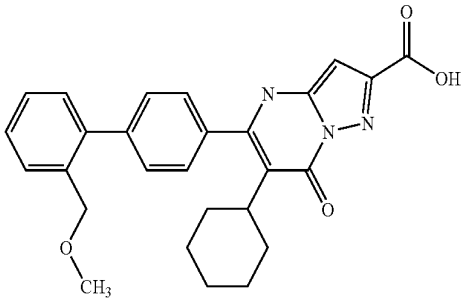
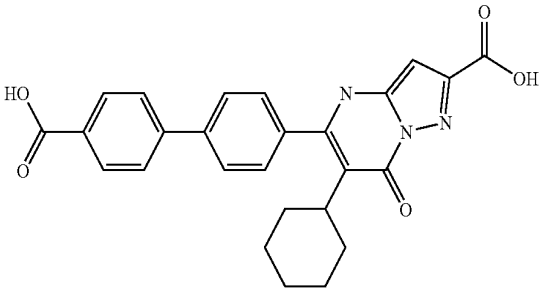
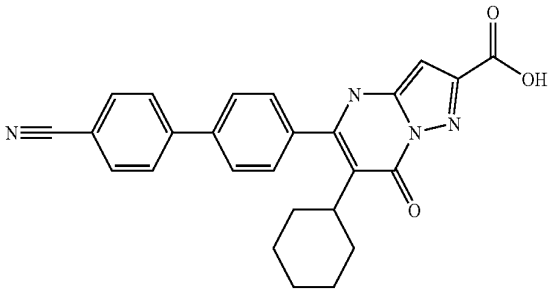
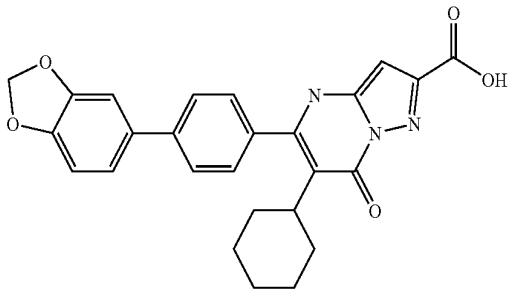
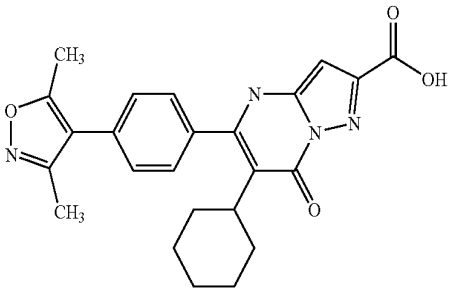
Compound	MOLSTRUCTURE	Δ-55 Activity	Δ-21 Activity
	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM		
587		B	B
588		B	B
589		B	B
590		B	B
591		B	B

TABLE 1-continued

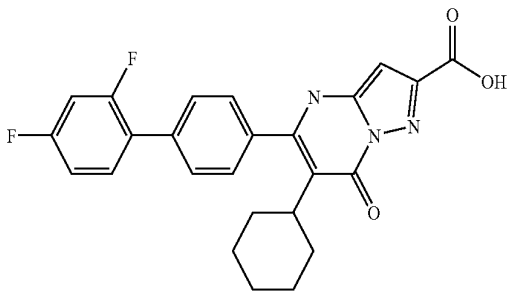
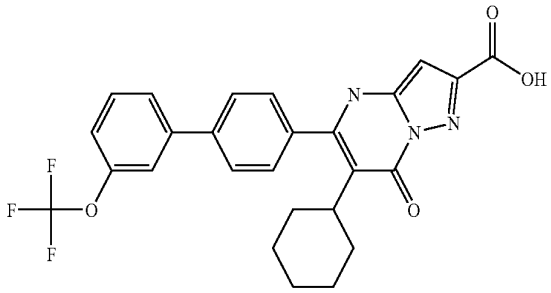
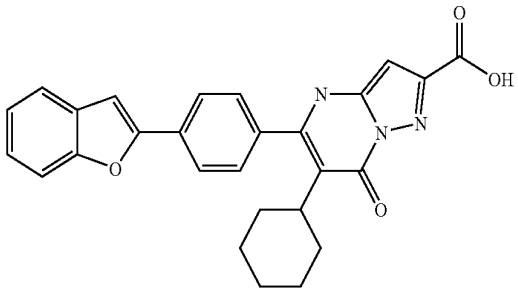
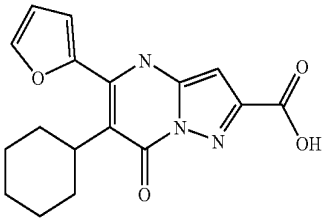
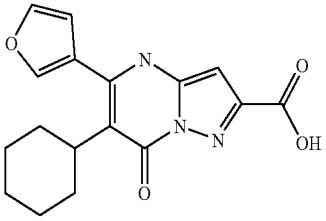
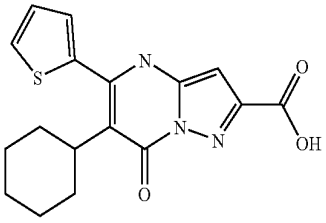
Compound	MOLSTRUCTURE	Δ-55 Activity	Δ-21 Activity
	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM		
592		B	B
593		B	B
594		B	B
595		B	C
596		B	C
597		B	B

TABLE 1-continued

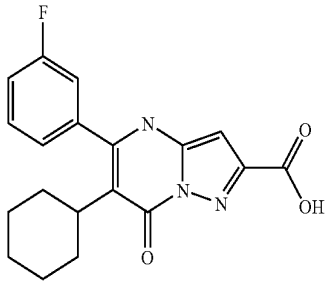
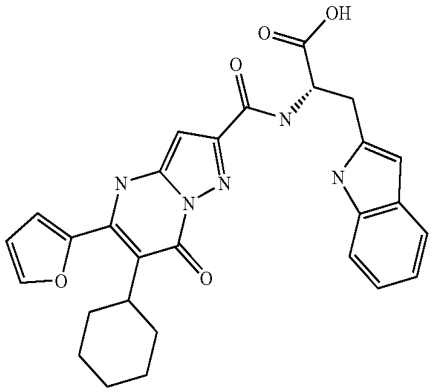
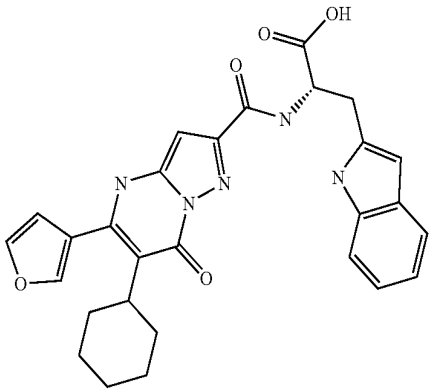
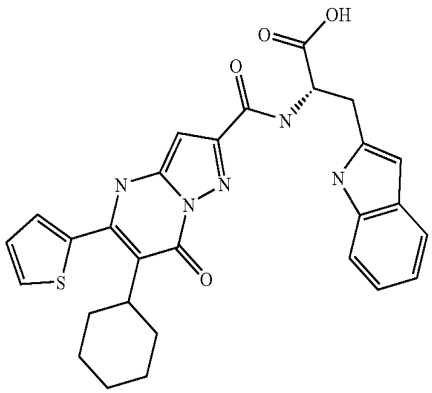
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
598		B	C
599		B	C
600		C	C
601		B	C

TABLE 1-continued

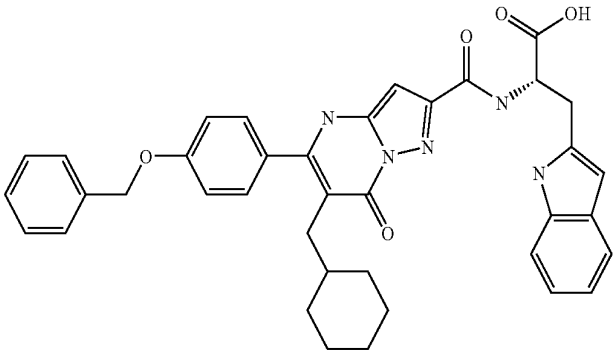
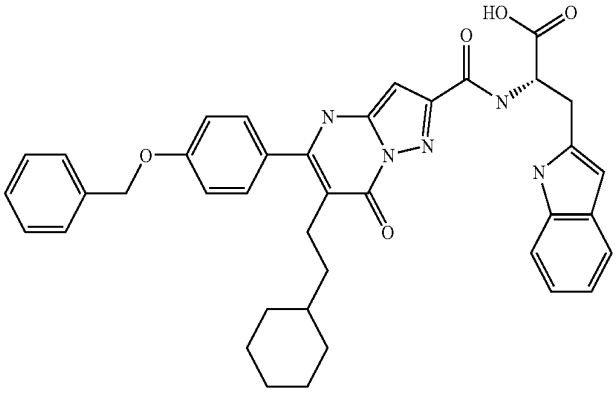
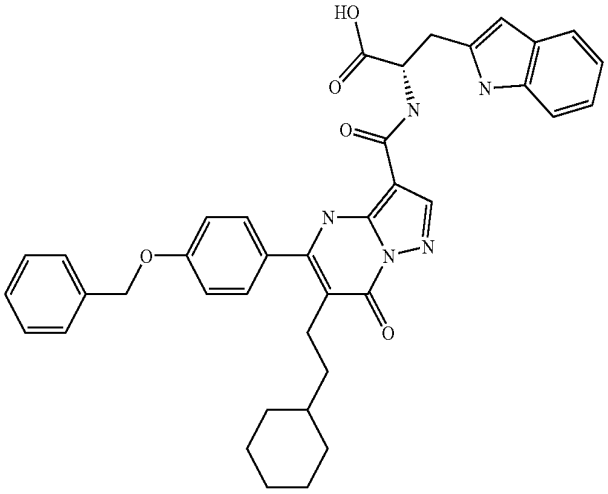
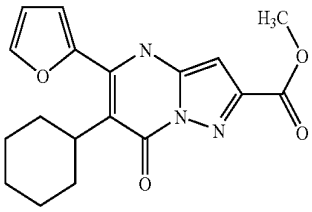
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
602		B	C
603		B	C
604		A	B
605			B

TABLE 1-continued

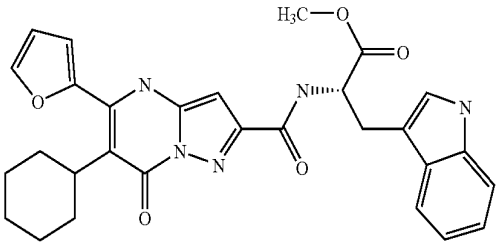
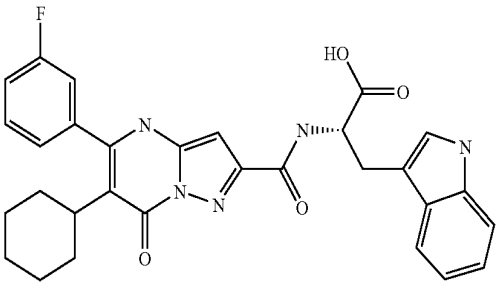
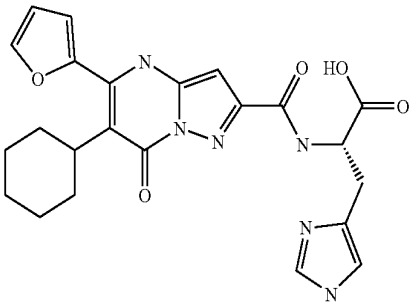
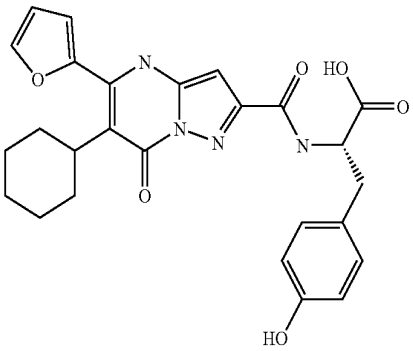
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
606			C
607			C
608			C
609			C

TABLE 1-continued

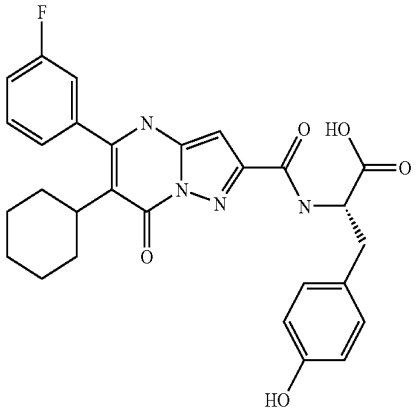
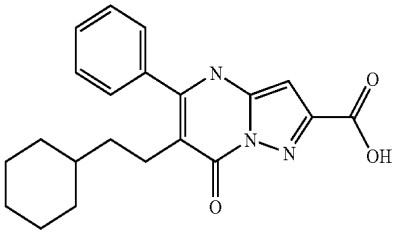
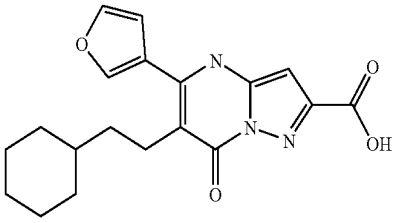
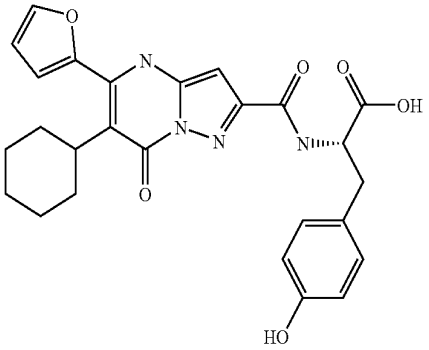
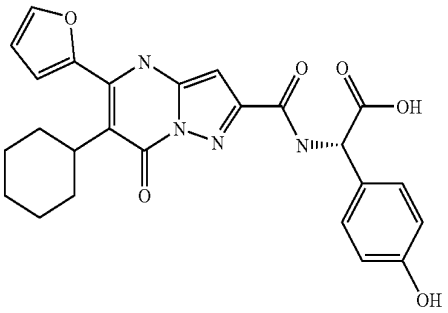
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
610			C
611			C
612			C
613			C
614			C

TABLE 1-continued

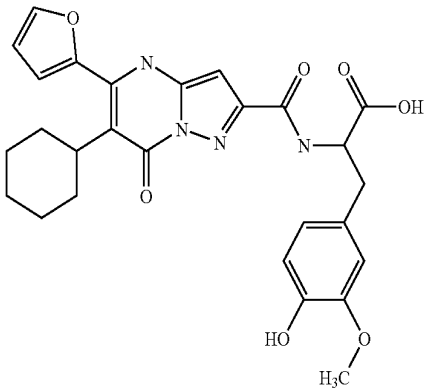
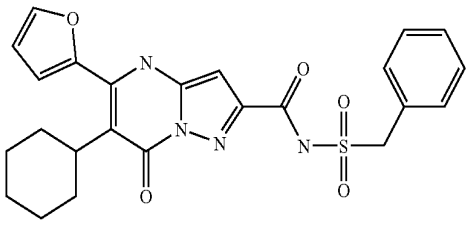
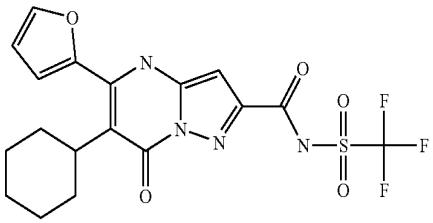
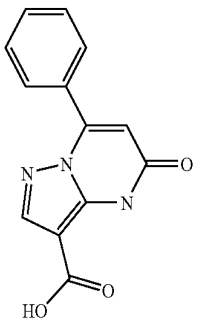
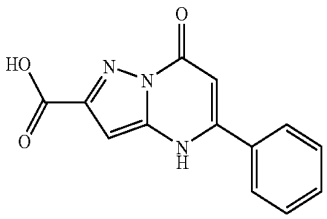
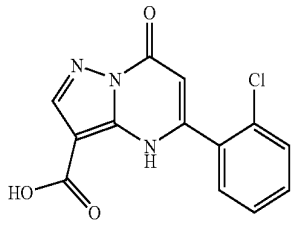
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM	
		Δ-55 Activity	Δ-21 Activity
615			C
616			C
617			B
618		A	
619		A	

TABLE 1-continued

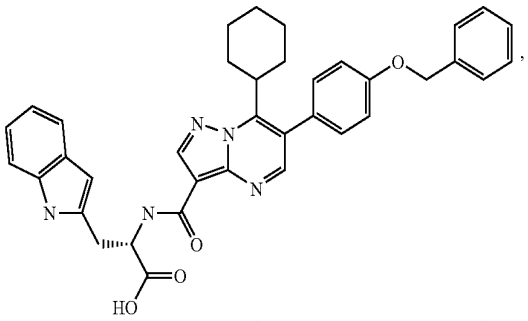
Compound	MOLSTRUCTURE	Inhibition of HCV RdRp[1] A = >10 μM, B = 1–10 μM, C = <1 μM Δ-55 Activity	Δ-21 Activity
620		A	

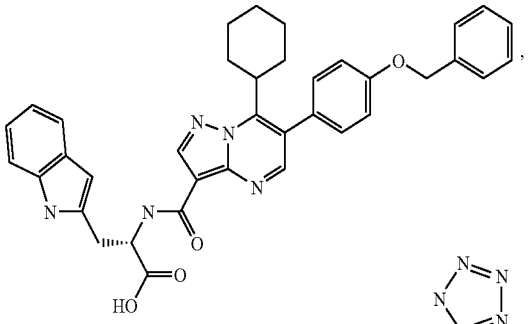
[1]All nitrogen atoms have three valences; where a bond is not explicitly identified, a hydrogen bond is assumed.

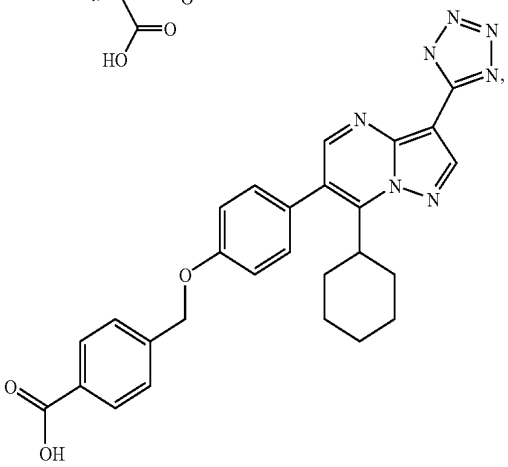
While the foregoing invention has been described in some detail for purposes of clarity and understanding, these particular embodiments are to be considered as illustrative and not restrictive. It will be appreciated by one skilled in the art from a reading of this disclosure that various changes in form and detail can be made without departing from the true scope of the invention and appended claims.

What is claimed is:

1. A compound selected from the group consisting of:







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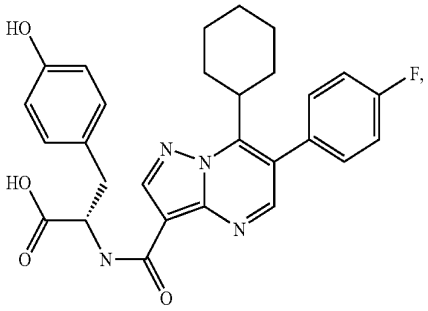

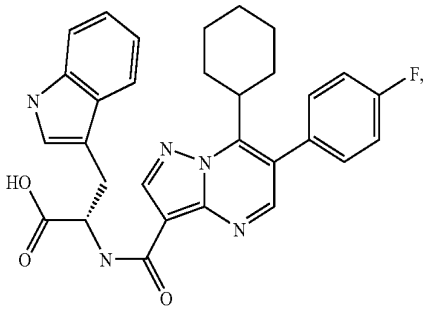

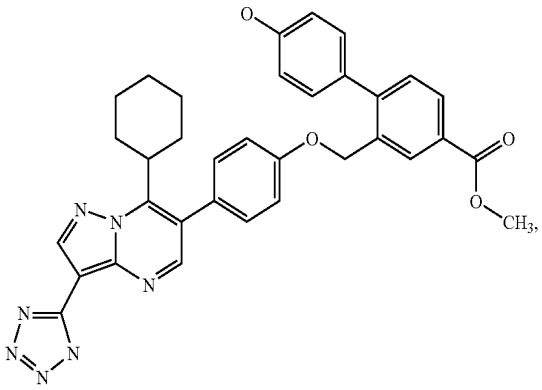

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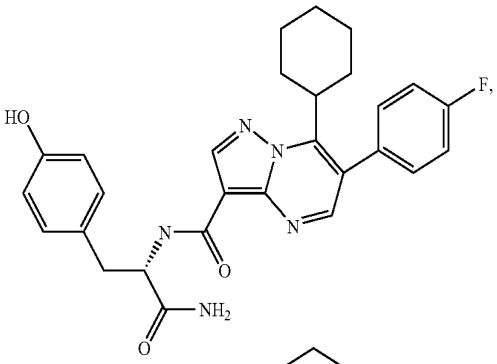

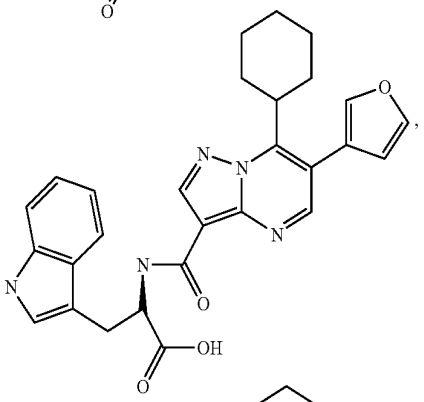

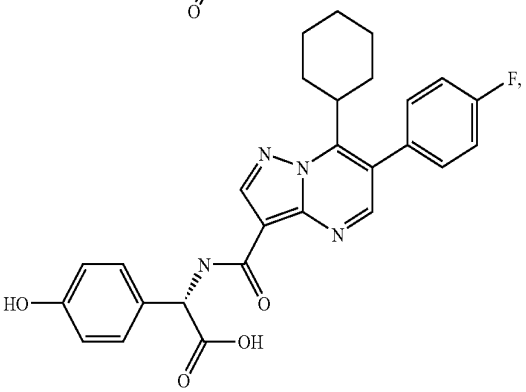

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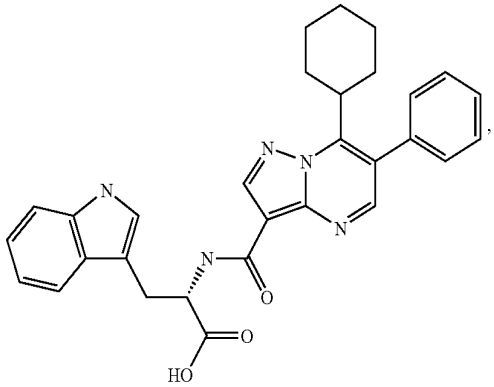

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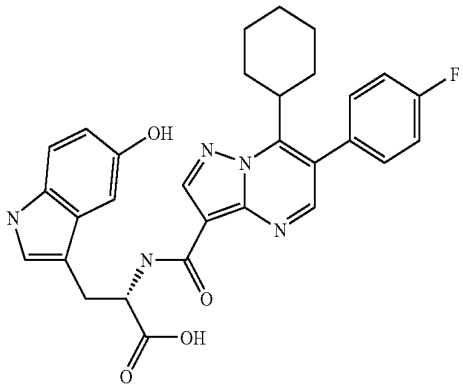

or a pharmaceutically acceptable salt thereof.

2. A pharmaceutical composition comprising at least one compound of claim **1**, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, excipient or diluent.

* * * * *