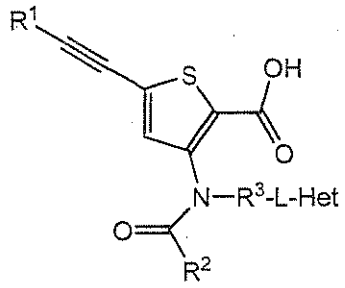
HCV virus (Neumann, et al., *Science* **1998**, *282*, 103-7; Fukimoto, et al., *Hepatology*, **1996**, *24*, 1351-4; Domingo, et al., *Gene*, **1985**, *40*, 1-8; Martell, et al., *J. Virol.* **1992**, *66*, 3225-9.

Currently, there are primarily two antiviral compounds, ribavirin, a nucleoside analog, and interferon-alpha (α) (IFN), that are used for the treatment of chronic HCV infections in humans. Ribavirin alone is not effective in reducing viral RNA levels, has significant toxicity, and is known to induce anemia. The combination of IFN and ribavirin has been reported to be effective in the management of chronic hepatitis C (Scott, L. J., et al. *Drugs* **2002**, *62*, 507-556) but less than half the patients given this treatment show a persistent benefit.

Combined, infections from the *Flaviviridae* virus family cause significant mortality, morbidity and economic losses throughout the world. Alkynyl substituted thiophenes with anti-*Flaviviridae* virus activity have been disclosed by Chan, et al., WO 2008058393; Wunberg, et al., WO 2006072347; and Chan, et al., WO 2002100851; but none of these are currently clinically approved antiviral therapeutics. Therefore, there remains a need to develop effective treatments for *Flaviviridae* virus infections.

SUMMARY OF THE INVENTION

In one aspect, there is provided a compound of Formula I:



Formula (I),

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from the group consisting of optionally substituted C_{1-12} alkyl, and optionally substituted C_{3-12} cycloalkyl,

wherein, each substituted R^1 is substituted with one or more Q^1;

each Q^1 is independently selected from the group consisting of

halogen, optionally substituted C_{1-6} alkyl, 4-12 membered heterocyclyloxy,

and -OH, wherein said heterocyclyl portion of said 4-12 membered heterocyclyloxy comprises one to six heteroatoms selected from O, S, or N;

wherein, each substituted Q^1 independently substituted with one or more halogen;

R^2 is optionally substituted C_{3-12} cycloalkyl;

wherein, each substituted R^2 is substituted with one or more members independently selected from the group consisting of C_{1-6} alkyl

and -OH;

R^3 is selected from the group consisting of optionally substituted C_{1-12} alkylene, C_{3-12} cycloalkylene, substituted C_{3-12} cycloalkylene, optionally substituted C_{6-14} arylene, and optionally substituted 3 -12 membered heterocyclylene, wherein said optionally substituted 3-12 membered heterocyclylene comprises one to six heteroatoms selected from O, S, or N;

wherein each substituted R^3 is substituted with one or more Q^3;

each Q^3, independently, is selected from the group consisting of optionally substituted C_{1-6} alkyl and -OH;

wherein, each substituted Q^3 is independently substituted with 3-10 membered heterocyclyl comprising one to six heteroatoms selected from O, S, or N;

L is selected from the group consisting of –O-, -S-, -S(O)-, and $-S(O)_2-$;

Het is an optionally substituted 3-12 membered heterocyclyl or optionally substituted 5-10 membered heteroaryl, wherein said optionally substituted 3-12 membered heterocyclyl or optionally substituted 5-10 membered heteroaryl comprises one to four heteroatoms selected from O, S, or N;

wherein, each substituted Het is substituted with one or more Q^4;

each Q^4, independently, is selected from the group consisting of halogen, oxo, oxide, $-S(O)_2R^{40}$, $-C(O)NR^{41}R^{42}$, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-6} cycloalkyl, optionally substituted C_{1-6} alkyloxy, optionally substituted 3-10 membered heterocyclyl, -OH, $-NR^{41}R^{42}$, $-C(O)OR^{40}$, and -CN, wherein said optionally substituted 3-10 membered heterocyclyl comprises one to six heteroatoms selected from O, S, or N;

each R^{40}, R^{41}, and R^{42}, independently is selected from the group consisting of H, optionally substituted C_{1-12} alkyl and optionally substituted 3-12 membered heterocyclyl, wherein said optionally substituted 3-12 membered heterocyclyl comprises one to six heteroatoms selected from O, S, or N;

or R^{41} and R^{42} taken together with the atoms to which they are attached form a 3 to 10 membered heterocyclyl, wherein said 3-10 membered heterocyclyl or comprises one to six heteroatoms selected from O, S, or N;

wherein, each substituted Q^4, substituted R^{40}, substituted R^{41}, or substituted R^{42} is independently substituted with one or more Q^5;

each Q^5, individually, is selected from the group consisting of halogen, oxo, optionally substituted 3-10 membered heterocyclyl, and $-NR^{51}R^{52}$, wherein said optionally substituted 3-10 membered heterocyclyl comprises one to six heteroatoms selected from O, S, or N;

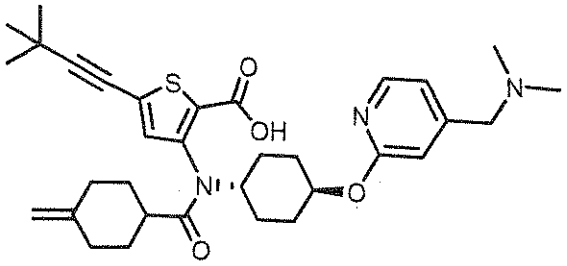
each R^{51}, and R^{52}, independently is C_{1-12} alkyl;

wherein, each substituted Q^5 is independently substituted with one or more Q^6;

each Q^6, independently, is selected from the group consisting of halogen, oxo, 3-10 membered heterocyclyl, -OH, and $-NR^{61}R^{62}$, wherein said 3-10 membered heterocyclyl comprises one to six heteroatoms selected from O, S, or N; and

each R^{61}, and R^{62}, independently, is C_{1-12} alkyl.

In one aspect, there is provided a compound that is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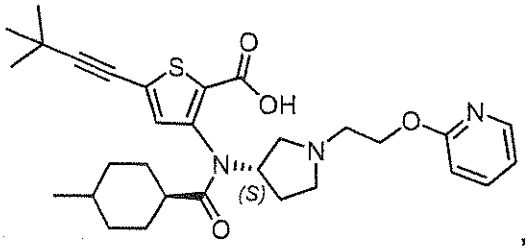
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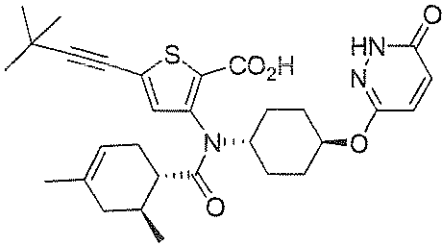
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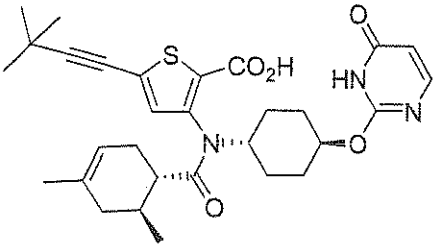
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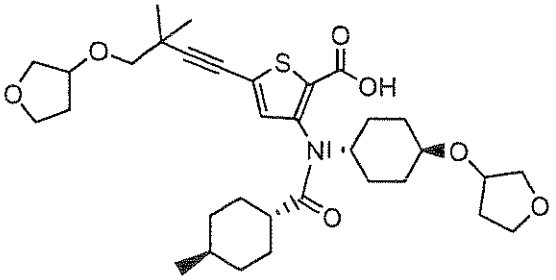
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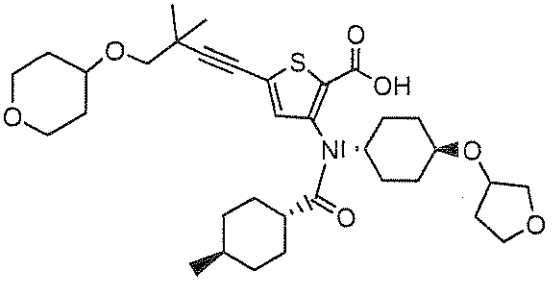
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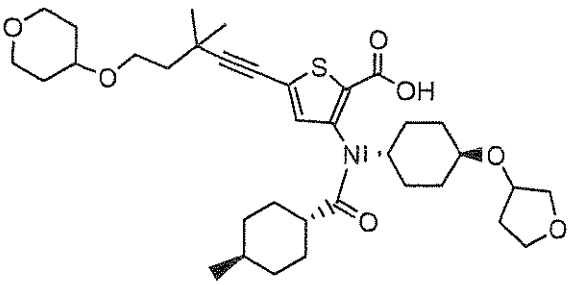

;

or a pharmaceutically acceptable salt thereof.

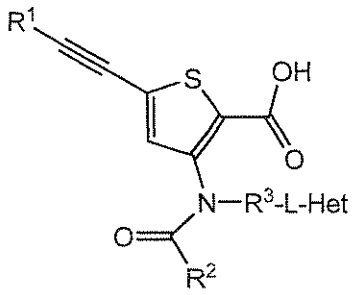
In one aspect, there is provided a pharmaceutical composition comprising a therapeutically effective amount of a compound as defined above and a pharmaceutically acceptable carrier or excipient.

In one aspect, there is provided the use of a compound as defined above or a pharmaceutical composition as defined above in the manufacture of a medicament for treating a *Flaviridae* viral infection in a mammal in need thereof.

In one aspect, there is provided the use of a compound as defined above in the manufacture of a medicament for the treatment of Hepatitis C virus infection.

In one aspect, there is provided a compound as defined above for use in therapy.

Provided are compounds of Formula I:



Formula (I),

or a pharmaceutically acceptable salt or ester thereof, wherein:

R^1 is selected from the group consisting of optionally substituted C_{1-12} alkyl, optionally substituted C_{2-12} alkenyl, optionally substituted C_{2-12} alkynyl, optionally substituted C_{3-12} cycloalkyl, optionally substituted C_{6-14} aryl, optionally substituted 3 - 14 membered heteroaryl, optionally substituted 3 -12 membered heterocyclyl,

each R^{60}, R^{61}, and R^{62}, independently, is selected from the group consisting of H, C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{3-12} cycloalkyl, C_{1-12} haloalkyl, C_{6-14} aryl, 3 - 14 membered heteroaryl, 3-12 membered heterocyclyl, 3-18 membered heteroarylalkyl, and C_{6-18} arylalkyl;

or R^{61} and R^{62} taken together with the atoms to which they are attached form a 3 to 10 membered heterocyclyl;

each R^{63} independently is selected from the group consisting of H, C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{3-12} cycloalkyl, C_{6-14} aryl, 3 - 14 membered heteroaryl, 3-12 membered heterocyclyl, 3-18 membered heteroarylalkyl, C_{6-18} arylalkyl, -CN, -$C(O)R^{64}$, -CHO and -$S(O)_2R^{64}$; and

each R^{64} individually is C_{1-12} alkyl.

Disclosed is~~In another aspect,~~ a method for treating *Flaviviridae* viral infections ~~is provided~~ comprising administering a therapeutically effective amount of a compound of Formula I to a mammal in need thereof. The compound of Formula I is administered to a human subject in need thereof, such as a human being who is infected with viruses of the *Flaviviridae* family. In another embodiment, the compound of Formula I is administered to a human subject in need thereof, such as a human being who is infected with a HCV virus. In one embodiment, the treatment results in the reduction of one or more of the in viral loads or clearance of viral RNA in a patient.

In another embodiment, provided is a method of treating and/or preventing a disease caused by a viral infection wherein the viral infection is caused by a virus selected from the group consisting of dengue virus, yellow fever virus, West Nile virus, Japanese encephalitis virus, tick-borne encephalitis virus, Junjin virus, Murray Valley encephalitis virus, St Louis encephalitis virus, Omsk hemorrhagic fever virus, bovine viral disarrhea virus, Zika virus and Hepatitis C virus; by administering to a subject in need thereof a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt or ester thereof.

Disclosed~~In another aspect, provided~~ is the use of a compound of Formula I for the manufacture of a medicament for the treatment of *Flaviviridae* viral infections. Also disclosed~~In another aspect, provided~~ is a compound of Formula I for use in treating a *Flaviviridae* viral infection. In one embodiment, the *Flaviviridae* viral infection is acute or chronic HCV infection. In one embodiment of each aspect of use and compound, the

treatment results in the reduction of one or more of the viral loads or clearance of RNA in the patient.

Disclosed~~In another aspect, provided~~ is a method for treating or preventing HCV comprising administering an effective amount of a compound of Formula I to a patient in need thereof. Also disclosed is~~In another aspect, provided~~ is the use of a compound of the present disclosure~~invention~~ for the manufacture of a medicament for the treatment or prevention of HCV.

Disclosed~~In another aspect, provided~~ is a pharmaceutical composition comprising a compound of Formula I or a pharmaceutically acceptable salt or ester thereof and one or more pharmaceutically acceptable carriers or excipients. The pharmaceutical composition of Formula I may further comprise one or more additional therapeutic agents. The one or more additional therapeutic agent may be, without limitation, selected from: interferons, ribavirin or its analogs, HCV NS3 protease inhibitors, NS5a inhibitors, alpha-glucosidase 1 inhibitors, hepatoprotectants, mevalonate decarboxylase antagonists, antagonists of the renin-angiotensin system, other anti-fibrotic agents, endothelin antagonists, nucleoside or nucleotide inhibitors of HCV NS5B polymerase, non-nucleoside inhibitors of HCV NS5B polymerase, HCV NS5A inhibitors, TLR-7 agonists, cyclophillin inhibitors, HCV IRES inhibitors, pharmacokinetic enhancers and other drugs for treating HCV; or mixtures thereof.

Also disclosed~~In another aspect, provided~~ is a method for the treatment or prevention of the symptoms or effects of an HCV infection in an infected animal which comprises administering to, i.e. treating, said animal with a pharmaceutical combination composition or formulation comprising an effective amount of a Formula I compound, and a second compound having anti-HCV properties.

In another embodiment, provided are compounds of Formula I and pharmaceutically acceptable salts and esters thereof and all racemates, enantiomers, diastereomers, tautomers, polymorphs, pseudopolymorphs and amorphous forms thereof.

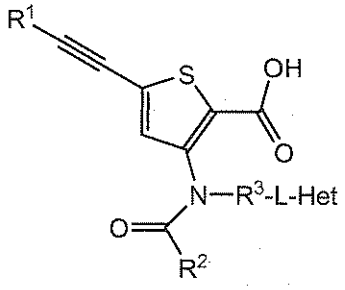
In another embodiment~~aspect~~, provided are processes and novel intermediates disclosed herein which are useful for preparing Formula I compounds.

In other embodiments~~aspects~~, novel methods for synthesis, analysis, separation, isolation, purification, characterization, and testing of the compounds of Formula I are provided.

The present disclosure~~invention~~ includes combinations of aspects and embodiments, as well as preferences, as herein described throughout the present specification.

WHAT IS CLAIMED IS:

1. A compound of Formula I:



Formula (I),

or a pharmaceutically acceptable salt ~~or ester~~ thereof, wherein:

$\mathbf{R^1}$ is selected from the group consisting of optionally substituted C_{1-12} alkyl, ~~optionally substituted C_{2-12} alkenyl, optionally substituted C_{2-12} alkynyl,~~ and optionally substituted C_{3-12} cycloalkyl~~, optionally substituted C_{6-14} aryl, optionally substituted 3 - 14 membered heteroaryl, optionally substituted 3 -12 membered heterocyclyl, optionally substituted 3-18 membered heteroarylalkyl, optionally substituted 3-18 membered heterocyclylalkyl and optionally substituted C_{6-18} arylalkyl~~,

wherein, each substituted R^1 is substituted with one or more Q^1;

each Q^1 is independently selected from the group consisting of halogen, ~~oxo, oxide, $-NO_2$, $-N(=O)$, $-SR^{10}$, $-S(O)R^{10}$, $-S(O)_2R^{10}$, $-S(O)_2NR^{10}R^{11}$, $-NR^{10}C(O)R^{11}$, $-NR^{10}C(O)NR^{11}R^{12}$, $-NR^{10}S(O)R^{11}$, $-NR^{10}S(O)_2R^{11}$, $-OP(O)R^{11}R^{12}$, $-P(O)R^{11}R^{12}$, $-P(O)OR^{11}R^{12}$, $-P(O)(OR^{11})OR^{12}$, $-C(O)NR^{11}R^{12}$,~~ optionally substituted C_{1-6} alkyl, ~~optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted C_{3-6} cycloalkyl, optionally substituted C_{6-12} arylalkyl, optionally substituted C_{6-12} aryl, optionally substituted 3 - 14 membered heteroaryl, optionally substituted C_{1-6} alkyloxy, optionally substituted C_{2-6} alkenyloxy, optionally substituted C_{2-6} alkynyloxy, optionally substituted C_{3-6} cycloalkyloxy, optionally substituted C_{6-12} aryloxy, optionally substituted 3 - 14 membered heteroaryloxy, optionally substituted~~ 4-12 membered heterocyclyloxy, ~~optionally substituted $-C(O)C_{1-6}$ alkyl, optionally substituted $-C(O)C_{2-6}$ alkenyl, optionally substituted $-C(O)C_{2-6}$ alkynyl, optionally substituted $-C(O)C_{3-6}$ cycloalkyl, optionally substituted $-C(O)C_{6-12}$ aryl, optionally substituted $-C(O)$-3 - 14 membered heteroaryl, optionally substituted $-C(O)C_{6-12}$~~

~~arylalkyl, optionally substituted 3-10 membered heterocyclyl,~~and ~~-OH, -NR^{11}R^{12}, -C(O)OR^{10}, -CN, -N$_3$, -C(=NR^{13})NR^{11}R^{12}, -C(=NR^{13})OR^{10}, -NR^{10}C(=NR^{13})NR^{11}R^{12}, -NR^{11}C(O)OR^{10}, and -OC(O)NR^{11}R^{12}~~, wherein said heterocyclyl portion of said 4-12 membered heterocyclyloxy comprises one to six heteroatoms selected from O, S, or N;

~~each R^{10}, R^{11}, and R^{12}, independently, is selected from the group consisting of H, optionally substituted C$_{1-12}$ alkyl, optionally substituted C$_{2-12}$ alkenyl, optionally substituted C$_{2-12}$ alkynyl, optionally substituted C$_{3-12}$ cycloalkyl, optionally substituted C$_{6-14}$ aryl, optionally substituted 3 - 14 membered heteroaryl, optionally substituted 3-12 membered heterocyclyl, optionally substituted 3-18 membered heteroarylalkyl, and optionally substituted C$_{6-18}$ arylalkyl;~~

~~or R^{11} and R^{12} taken together with the atoms to which they are attached form a 3 to 10 membered heterocyclyl;~~

~~each R^{13}, independently, is selected from the group consisting of H, optionally substituted C$_{1-12}$ alkyl, optionally substituted C$_{2-12}$ alkenyl, optionally substituted C$_{2-12}$ alkynyl, optionally substituted C$_{3-12}$ cycloalkyl, optionally substituted C$_{6-14}$ aryl, optionally substituted 3 - 14 membered heteroaryl, optionally substituted 3-12 membered heterocyclyl, optionally substituted 3-18 membered heteroarylalkyl, optionally substituted C$_{6-18}$ arylalkyl, -CN, -C(O)R^{14}, -CHO and -S(O)$_2$R^{14};~~

~~each R^{14}, independently, is optionally substituted C$_{1-12}$ alkyl;~~

wherein, each substituted Q^1, ~~substituted R^{10}, substituted R^{11}, substituted R^{12}, substituted R^{13}, or substituted R^{14} is~~ independently substituted with one or more ~~Q^6~~halogen;

R^2 is ~~selected from the group consisting of optionally substituted C$_{1-12}$ alkyl, optionally substituted C$_{2-12}$ alkenyl, optionally substituted C$_{2-12}$ alkynyl,~~ optionally substituted C$_{3-12}$ cycloalkyl, ~~optionally substituted C$_{6-14}$ aryl, optionally substituted 3 - 14 membered heteroaryl, optionally substituted 3 -12 membered heterocyclyl, optionally substituted 3-18 membered heteroarylalkyl, and optionally substituted C$_{6-18}$ arylalkyl~~;

wherein, each substituted R^2 is substituted with one or more ~~Q^2~~;

~~each Q^2,~~ members independently, ~~is~~ selected from the group consisting of

~~halogen, oxo, oxide, -NO$_2$, -N(=O), -SR^{20}, -S(O)R^{20}, -S(O)$_2$R^{20}, -S(O)$_2$ NR^{20}R^{21}, -NR^{20}C(O)R^{21}, -NR^{20}C(O)NR^{21}R^{22}, -NR^{20}S(O)R^{21}, -NR^{20}S(O)$_2$R^{21}, -OP(O)R^{21}R^{22}, -P(O)R^{21}R^{22}, -P(O)OR^{21}R^{22}, -P(O)(OR^{21})OR^{22}, -C(O)NR^{21}R^{22}, optionally substituted~~ C$_{1-6}$ alkyl, ~~optionally substituted C$_{2-6}$ alkenyl, optionally substituted C$_{2-6}$ alkynyl, optionally substituted C$_{3-6}$ cycloalkyl, optionally substituted C$_{6-12}$ arylalkyl, optionally substituted C$_{6-12}$ aryl, optionally substituted 3 - 14 membered heteroaryl, optionally~~

~~substituted C_{1-6} alkyloxy, optionally substituted C_{2-6} alkenyloxy, optionally substituted C_{2-6} alkynyloxy, optionally substituted C_{3-6} cycloalkyloxy, optionally substituted C_{6-12} aryloxy, optionally substituted 3 - 14 membered heteroaryloxy, optionally substituted 4-12 membered heterocyclyloxy, optionally substituted $-C(O)C_{1-6}$ alkyl, optionally substituted $-C(O)C_{2-6}$ alkenyl, optionally substituted $-C(O)C_{2-6}$ alkynyl, optionally substituted $-C(O)C_{3-6}$ cycloalkyl, optionally substituted $-C(O)C_{6-12}$ aryl, optionally substituted -C(O)-3 -14 membered heteroaryl, optionally substituted $-C(O)C_{6-12}$ arylalkyl, optionally substituted 3-10 membered heterocyclyl,~~ and ~~-OH, $-NR^{21}R^{22}$, $-C(O)OR^{20}$, -CN, $-N_3$, $-C(=NR^{23})NR^{21}R^{22}$, $-C(=NR^{23})OR^{20}$, $-NR^{20}C(=NR^{23})NR^{21}R^{22}$, $-NR^{21}C(O)OR^{20}$, and $-OC(O)NR^{21}R^{22}$;~~

~~each R^{20}, R^{21}, and R^{22}, independently, is selected from the group consisting of H, optionally substituted C_{1-12} alkyl, optionally substituted C_{2-12} alkenyl, optionally substituted C_{2-12} alkynyl, optionally substituted C_{3-12} cycloalkyl, optionally substituted C_{6-14} aryl, optionally substituted 3 - 14 membered heteroaryl, optionally substituted 3-12 membered heterocyclyl, optionally substituted 3-18 membered heteroarylalkyl, and optionally substituted C_{6-18} arylalkyl;~~

~~or R^{21} and R^{22} taken together with the atoms to which they are attached form a 3 to 10 membered heterocyclyl;~~

~~each R^{23}, independently, is selected from the group consisting of H, optionally substituted C_{1-12} alkyl, optionally substituted C_{2-12} alkenyl, optionally substituted C_{2-12} alkynyl, optionally substituted C_{3-12} cycloalkyl, optionally substituted C_{6-14} aryl, optionally substituted 3 - 14 membered heteroaryl, optionally substituted 3-12 membered heterocyclyl, optionally substituted 3-18 membered heteroarylalkyl, optionally substituted C_{6-18} arylalkyl, -CN, $-C(O)R^{24}$, -CHO and $-S(O)_2R^{24}$;~~

~~each R^{24} individually is optionally substituted C_{1-12} alkyl;~~

~~wherein, each substituted Q^2, substituted R^{20}, substituted R^{21}, substituted R^{22}, substituted R^{23}, or substituted R^{24} is independently substituted with one or more Q^6;~~

$\mathbf{R^3}$ is selected from the group consisting of optionally substituted C_{1-12} alkylene, ~~C_{2-12} alkenylene, substituted C_{2-12} alkenylene, C_{2-12} alkynylene, substituted C_{2-12} alkynylene,~~ C_{3-12} cycloalkylene, substituted C_{3-12} cycloalkylene, optionally substituted C_{6-14} arylene, ~~optionally substituted 3 - 14 membered heteroarylene,~~ and optionally substituted 3 -12 membered heterocyclylene~~, optionally substituted 3-18 membered heteroarylalkylene, and optionally substituted C_{6-18} arylalkylene~~, wherein said optionally substituted 3-12 membered heterocyclylene comprises one to six heteroatoms selected from O, S, or N;

wherein each substituted R^3 is substituted with one or more Q^3;

each Q^3, independently, is selected from the group consisting of

~~halogen, oxo, oxide, $-NO_2$, $-N(=O)$, $-SR^{30}$, $-S(O)R^{30}$, $-S(O)_2R^{30}$, $-S(O)_2NR^{30}R^{31}$, $-NR^{30}C(O)R^{31}$, $-NR^{30}C(O)NR^{31}R^{32}$, $-NR^{30}S(O)R^{31}$, $-NR^{30}S(O)_2R^{31}$, $-OP(O)R^{31}R^{32}$, $-P(O)R^{31}R^{32}$, $-P(O)OR^{31}R^{32}$, $-P(O)(OR^{31})OR^{32}$, $-C(O)NR^{31}R^{32}$,~~ optionally substituted C_{1-6} alkyl~~, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted C_{3-6} cycloalkyl, optionally substituted C_{6-12} arylalkyl, optionally substituted C_{6-12} aryl, optionally substituted 3 – 14 membered heteroaryl, optionally substituted C_{1-6} alkyloxy, optionally substituted C_{2-6} alkenyloxy, optionally substituted C_{2-6} alkynyloxy, optionally substituted C_{3-6} cycloalkyloxy, optionally substituted C_{6-12} aryloxy, optionally substituted 3 – 14 membered heteroaryloxy, optionally substituted 4-12 membered heterocyclyloxy, optionally substituted $-C(O)C_{1-6}$ alkyl, optionally substituted $-C(O)C_{2-6}$ alkenyl, optionally substituted $-C(O)C_{2-6}$ alkynyl, optionally substituted $-C(O)C_{3-6}$ cycloalkyl, optionally substituted $-C(O)C_{6-12}$ aryl, optionally substituted –C(O)– 3 –14 membered heteroaryl, optionally substituted $-C(O)C_{6-12}$ arylalkyl, optionally substituted 3-10 membered heterocyclyl,~~ and ~~-OH, $-NR^{31}R^{32}$, $-C(O)OR^{30}$, $-CN$, $-N_3$, $-C(=NR^{33})NR^{31}R^{32}$, $-C(=NR^{33})OR^{30}$, $-NR^{30}C(=NR^{33})NR^{31}R^{32}$, $-NR^{31}C(O)OR^{30}$, and $-OC(O)NR^{31}R^{32}$~~;

~~each R^{30}, R^{31}, and R^{32}, independently is selected from the group consisting of H, optionally substituted C_{1-12} alkyl, optionally substituted C_{2-12} alkenyl, optionally substituted C_{2-12} alkynyl, optionally substituted C_{3-12} cycloalkyl, optionally substituted C_{6-14} aryl, optionally substituted 3 – 14 membered heteroaryl, optionally substituted 3-12 membered heterocyclyl, optionally substituted 3-18 membered heteroarylalkyl, and optionally substituted C_{6-18} arylalkyl;~~

~~or R^{31} and R^{32} taken together with the atoms to which they are attached form a 3 to 10 membered heterocyclyl;~~

~~each R^{33} independently is selected from the group consisting of H, optionally substituted C_{1-12} alkyl, optionally substituted C_{2-12} alkenyl, optionally substituted C_{2-12} alkynyl, optionally substituted C_{3-12} cycloalkyl, optionally substituted C_{6-14} aryl, optionally substituted 3 – 14 membered heteroaryl, optionally substituted 3-12 membered heterocyclyl, optionally substituted 3-18 membered heteroarylalkyl, optionally substituted C_{6-18} arylalkyl, –CN, $-C(O)R^{34}$, –CHO and $-S(O)_2R^{34}$~~;

~~each R^{34} individually is optionally substituted C_{1-12} alkyl;~~

wherein, each substituted Q^3~~, substituted R^{30}, substituted R^{31}, substituted R^{32}, substituted R^{33}, or substituted R^{34}~~ is independently substituted with ~~one or more~~ Q^6 3-10 membered heterocyclyl comprising one to six heteroatoms selected from O, S, or N;

L is selected from the group consisting of –O-, -S-, -S(O)-, and -$S(O)_2$-;

Het is an optionally substituted 3-12 membered heterocyclyl or optionally substituted ~~3-14~~5-10 membered heteroaryl, wherein said optionally substituted 3-12 membered heterocyclyl or optionally substituted 5-10 membered heteroaryl comprises one to four heteroatoms selected from O, S, or N;

wherein, each substituted Het is substituted with one or more Q^4;

each Q^4, independently, is selected from the group consisting of halogen, oxo, oxide, ~~$-NO_2$, $-N(=O)_2$, $-SR^{40}$, $-S(O)R^{40}$,~~ $-S(O)_2R^{40}$, ~~$-S(O)_2NR^{40}R^{41}$, $-NR^{40}C(O)R^{41}$, $-NR^{40}C(O)NR^{41}R^{42}$, $-NR^{40}S(O)R^{41}$, $-NR^{40}S(O)_2R^{41}$, $-OP(O)R^{41}R^{42}$, $-P(O)R^{41}R^{42}$, $-P(O)OR^{41}R^{42}$, $-P(O)(OR^{41})OR^{42}$,~~ $-C(O)NR^{41}R^{42}$, optionally substituted C_{1-6} alkyl, ~~optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl,~~ optionally substituted C_{3-6} cycloalkyl, ~~optionally substituted C_{6-12} arylalkyl, optionally substituted C_{6-12} aryl, optionally substituted 3 - 14 membered heteroaryl,~~ optionally substituted C_{1-6} alkyloxy, ~~optionally substituted C_{2-6} alkenyloxy, optionally substituted C_{2-6} alkynyloxy, optionally substituted C_{3-6} cycloalkyloxy, optionally substituted C_{6-12} aryloxy, optionally substituted 3 - 14 membered heteroaryloxy, optionally substituted 4-12 membered heterocyclyloxy, optionally substituted $-C(O)C_{1-6}$ alkyl, optionally substituted $-C(O)C_{2-6}$ alkenyl, optionally substituted $-C(O)C_{2-6}$ alkynyl, optionally substituted $-C(O)C_{3-6}$ cycloalkyl, optionally substituted $-C(O)C_{6-12}$ aryl, optionally substituted -C(O)- 3 -14 membered heteroaryl, optionally substituted $-C(O)C_{6-12}$ arylalkyl,~~ optionally substituted 3-10 membered heterocyclyl, -OH, $-NR^{41}R^{42}$, $-C(O)OR^{40}$, and ~~-CN, $-N_3$, $-C(=NR^{43})NR^{41}R^{42}$, $-C(=NR^{43})OR^{40}$, $-NR^{40}C(=NR^{43})N R^{41}R^{42}$, $-NR^{41}C(O)OR^{40}$, and $-OC(O)NR^{41}R^{42}$,~~ wherein said optionally substituted 3-10 membered heterocyclyl comprises one to six heteroatoms selected from O, S, or N;

each R^{40}, R^{41}, and R^{42}, independently is selected from the group consisting of H, optionally substituted C_{1-12} alkyl, ~~optionally substituted C_{2-12} alkenyl, optionally substituted C_{2-12} alkynyl, optionally substituted C_{3-12} cycloalkyl, optionally substituted~~

~~C_{6-14} aryl, optionally substituted 3 - 14 membered heteroaryl,~~ and optionally substituted 3-12 membered heterocyclyl, ~~optionally substituted 3-18 membered heteroarylalkyl, and optionally substituted C_{6-18} arylalkyl,~~ wherein said optionally substituted 3-12 membered heterocyclyl comprises one to six heteroatoms selected from O, S, or N;

or R^{41} and R^{42} taken together with the atoms to which they are attached form a 3 to 10 membered heterocyclyl, wherein said 3-10 membered heterocyclyl or comprises one to six heteroatoms selected from O, S, or N;

~~each R^{43}, independently, is selected from the group consisting of H, optionally substituted C_{1-12} alkyl, optionally substituted C_{2-12} alkenyl, optionally substituted C_{2-12} alkynyl, optionally substituted C_{3-12} cycloalkyl, optionally substituted C_{6-14} aryl, optionally substituted 3 - 14 membered heteroaryl, optionally substituted 3-12~~

membered heterocyclyl, optionally substituted 3-18 membered heteroarylalkyl, optionally substituted C_{6-18} arylalkyl, -CN, $-C(O)R^{44}$, -CHO and $-S(O)_2R^{44}$;

each R^{44} individually is optionally substituted C_{1-12} alkyl;

wherein, each substituted Q^4, substituted R^{40}, substituted R^{41}, or substituted R^{42}, substituted R^{43}, or substituted R^{44} is independently substituted with one or more Q^5;

each Q^5, individually, is selected from the group consisting of halogen, oxo, oxide, $-NO_2$, -N(=O), $-SR^{50}$, $-S(O)R^{50}$, $-S(O)_2R^{50}$, $-S(O)_2-NR^{50}R^{51}$, $-NR^{50}C(O)R^{51}$, $-NR^{50}C(O)NR^{51}R^{52}$, $-NR^{50}S(O)R^{51}$, $-NR^{50}S(O)_2R^{51}$, $-OP(O)R^{51}R^{52}$, $-P(O)R^{51}R^{52}$, $-P(O)OR^{51}R^{52}$, $-P(O)(OR^{51})OR^{52}$, $-C(O)NR^{51}R^{52}$, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted C_{3-6} cycloalkyl, optionally substituted C_{6-12} arylalkyl, optionally substituted C_{6-12} aryl, optionally substituted 3 - 14 membered heteroaryl, optionally substituted C_{1-6} alkyloxy, optionally substituted C_{2-6} alkenyloxy, optionally substituted C_{2-6} alkynyloxy, optionally substituted C_{3-6} cycloalkyloxy, optionally substituted C_{6-12} aryloxy, optionally substituted 3 - 14 membered heteroaryloxy, optionally substituted 4-12 membered heterocyclyloxy, optionally substituted $-C(O)C_{1-6}$ alkyl, optionally substituted $-C(O)C_{2-6}$ alkenyl, optionally substituted $-C(O)C_{2-6}$ alkynyl, optionally substituted $-C(O)C_{3-6}$ cycloalkyl, optionally substituted $-C(O)C_{6-12}$ aryl, optionally substituted -C(O)- 3 -14 membered heteroaryl, optionally substituted $-C(O)C_{6-12}$ arylalkyl, optionally substituted 3-10 membered heterocyclyl, -OH, and $-NR^{51}R^{52}$, $-C(O)OR^{50}$, -CN, $-N_3$, $-C(=NR^{53})NR^{51}R^{52}$, $-C(=NR^{53})OR^{50}$, $-NR^{50}C(=NR^{53})N R^{51}R^{52}$, $-NR^{51}C(O)OR^{50}$, and $-OC(O)NR^{51}R^{52}$, wherein said optionally substituted 3-10 membered heterocyclyl comprises one to six heteroatoms selected from O, S, or N;

each R^{50}, R^{51}, and R^{52}, independently is selected from the group consisting of H, optionally substituted C_{1-12} alkyl, optionally substituted C_{2-12} alkenyl, optionally substituted C_{2-12} alkynyl, optionally substituted C_{3-12} cycloalkyl, optionally substituted C_{6-14} aryl, optionally substituted 3 - 14 membered heteroaryl, optionally substituted 3-12 membered heterocyclyl, optionally substituted 3-18 membered heteroarylalkyl, and optionally substituted C_{6-18} arylalkyl;

or R^{51} and R^{52} taken together with the atoms to which they are attached form a 3 to 10 membered heterocyclyl;

each R^{53}, independently, is selected from the group consisting of H, optionally substituted C_{1-12} alkyl, optionally substituted C_{2-12} alkenyl, optionally substituted C_{2-12} alkynyl, optionally substituted C_{3-12} cycloalkyl, optionally substituted C_{6-14} aryl, optionally substituted 3 - 14 membered heteroaryl, optionally substituted 3-12

membered heterocyclyl, optionally substituted 3-18 membered heteroarylalkyl, optionally substituted C_{6-18} arylalkyl, -CN, $-C(O)R^{64}$, -CHO and $-S(O)_2R^{64}$;

each R^{64}, independently, is optionally substituted C_{1-12} alkyl;

wherein, each substituted Q^5, substituted R^{60}, substituted R^{61}, substituted R^{62}, substituted R^{63}, or substituted R^{64} is independently substituted with one or more Q^6;

each Q^6, independently, is selected from the group consisting of halogen, oxo, oxide, $-NO_2$, -N(=O), $-SR^{60}$, $-S(O)R^{60}$, $-S(O)_2R^{60}$, $-S(O)_2NR^{60}R^{61}$, $-NR^{60}C(O)R^{61}$, $-NR^{60}C(O)NR^{61}R^{62}$, $-NR^{60}S(O)R^{61}$, $-NR^{60}S(O)_2R^{61}$, $-OP(O)R^{61}R^{62}$, $-P(O)R^{61}R^{62}$, $-P(O)OR^{61}R^{62}$, $-P(O)(OR^{61})OR^{62}$, $-C(O)NR^{61}R^{62}$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{6-12} arylalkyl, C_{6-12} aryl, 3 - 14 membered heteroaryl, C_{1-6} alkyloxy, C_{2-6} alkenyloxy, C_{2-6} alkynyloxy, C_{3-6} cycloalkyloxy, C_{6-12} aryloxy, 3 - 14 membered heteroaryloxy, 4-12 membered heterocyclyloxy, $-C(O)C_{1-6}$ alkyl, $-C(O)C_{2-6}$ alkenyl, $-C(O)C_{2-6}$ alkynyl, $-C(O)C_{3-6}$ cycloalkyl, $-C(O)C_{1-6}$ haloalkyl, $-C(O)C_{6-12}$ aryl, -C(O)- 3-14 membered heteroaryl, $-C(O)C_{6-12}$ arylalkyl, 3-10 membered heterocyclyl, -OH, and $-NR^{61}R^{62}$, $-C(O)OR^{60}$, -CN, $-N_3$, $-C(=NR^{63})NR^{61}R^{62}$, $-C(=NR^{63})OR^{60}$, $-NR^{60}C(=NR^{63})NR^{61}R^{62}$, $-NR^{61}C(O)OR^{60}$, and $-OC(O)NR^{61}R^{62}$, wherein said 3-10 membered heterocyclyl comprises one to six heteroatoms selected from O, S, or N; and

each R^{60}, R^{61}, and R^{62}, independently, is selected from the group consisting of H, C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{3-12} cycloalkyl, C_{1-12} haloalkyl, C_{6-14} aryl, 3 - 14 membered heteroaryl, 3-12 membered heterocyclyl, 3-18 membered heteroarylalkyl, and C_{6-18} arylalkyl;

or R^{61} and R^{62} taken together with the atoms to which they are attached form a 3 to 10 membered heterocyclyl;

each R^{63} independently is selected from the group consisting of H, C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{3-12} cycloalkyl, C_{6-14} aryl, 3 - 14 membered heteroaryl, 3-12 membered heterocyclyl, 3-18 membered heteroarylalkyl, C_{6-18} arylalkyl, -CN, $-C(O)R^{64}$, -CHO and $-S(O)_2R^{64}$; and

each R^{64} individually is C_{1-12} alkyl.

2. The compound of claim 1, wherein R^1 is optionally substituted C_{1-12} alkyl or optionally substituted C_{3-12} cycloalkyl.

32. The compound of claim 1 or 2, wherein R^1 is optionally substituted C_3-C_7 secondary or tertiary alkyl or optionally substituted C_3-C_5 cycloalkyl.

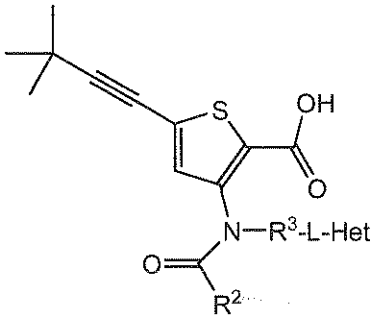
43. The compound of ~~any one of claims 1-3~~claim 1 or 2, wherein R^2 is optionally substituted methylcyclohexyl or optionally substituted methylcyclohexenyl.

~~5. The compound of any one of claims 1-4, wherein R^3 is optionally substituted C_{1-12}-alkylene, C_{3-12}-cycloalkylene, substituted C_{3-12}-cycloalkylene, optionally substituted C_{6-14}-arylene or optionally substituted 3-12 membered heterocyclylene.~~

~~6. The compound of any one of claims 1-5, wherein Het is an optionally substituted 3-12 membered heterocyclyl or optionally substituted 3-14 membered heteroaryl wherein said optionally substituted 3-12 membered heterocyclyl or optionally substituted 3-14 membered heteroaryl comprises one to four heteroatoms selected from O, S, or N.~~

~~7~~4. The compound of any one of claims 1-~~6~~3, wherein Het is optionally substituted pyridinyl, optionally substituted pyridazinyl, optionally substituted tetrahydro-2H-pyranyl, optionally substituted piperidinyl, optionally substituted pyrrolidinyl, optionally substituted tetrahydrothiophenyl, optionally substituted pyrazinyl, optionally substituted 1H-tetrazolyl, optionally substituted azetidinyl, optionally substituted tetrahydrofuranyl, optionally substituted tetrahydro-2*H*-furo[2,3-b]furanyl, optionally substituted thiazoyl, optionally substituted 1*H*-imidazolyl, optionally substituted 4*H*-1,2,4-triazolyl, optionally substituted 1*H*-pyrazolyl, optionally substituted 1,3,4-thiadiazolyl, optionally substituted quinolinyl, optionally substituted [1,2,4]triazolo[4,3-a]pyridinyl, optionally substituted thiophenyl, optionally substituted 1,2,4-thiadiazolyl, optionally substituted pyrimidinyl, optionally substituted 1*H*-1,2,3-triazolyl, optionally substituted 1,3,4-oxadiazolyl or optionally substituted imidazo[1,2-b]pyridazinyl.

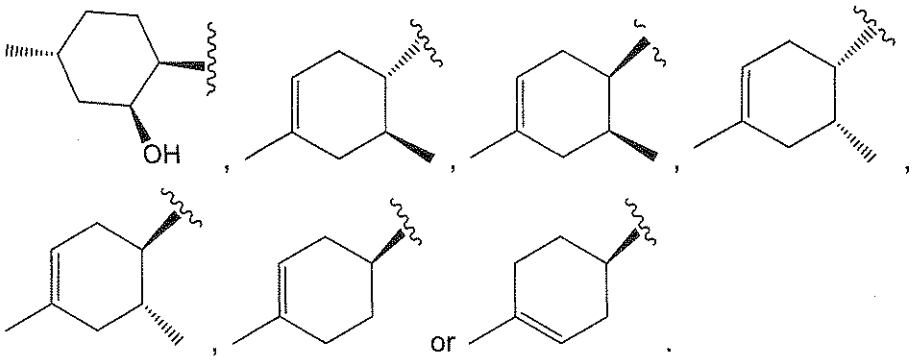
~~8~~5. The compound of any one of claims 1-~~7~~4 represented by Formula II:



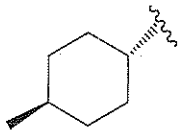
Formula II

or pharmaceutically acceptable salts ~~and esters~~ thereof, wherein:
R^2 is optionally substituted 4-methylcyclohexyl or optionally substituted methylcyclohexenyl.

~~9~~6. The compound of any one of claims 1-~~8~~5, wherein R^2 is



~~10~~7. The compound of any one of claims 1-~~8~~6, wherein R^2 is



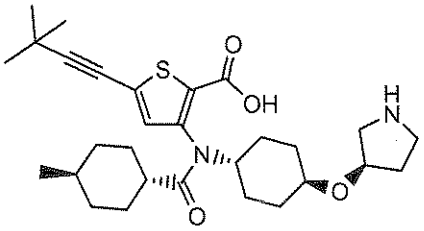
8. The compound of any one of claims 1-7, wherein R^3 is selected from the group consisting of optionally substituted C_{1-6} alkylene, C_{4-6} cycloalkylene, substituted C_{4-6} cycloalkylene, and optionally substituted 5-6 membered heterocyclylene, wherein said optionally substituted 5-6 membered heterocyclylene comprises one to six heteroatoms selected from O, S, or N.

9. The compound of any one of claims 1-8, wherein R^3 is selected from the group consisting of C_{4-6} cycloalkylene and substituted C_{4-6} cycloalkylene.

~~11~~10. The compound of any one of claims 1-~~10~~9, wherein R^3 is optionally substituted cyclohexylene.

11. The compound of any one of claims 1-8, wherein R^3 is optionally substituted 5-6 membered nitrogen containing heterocyclylene.

12. The compound of claim 1 that is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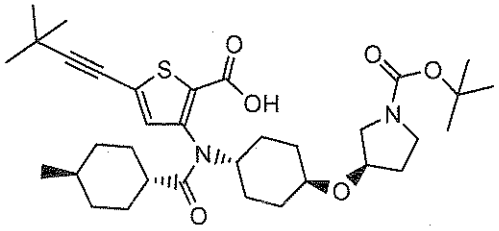
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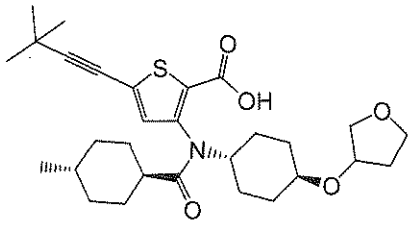
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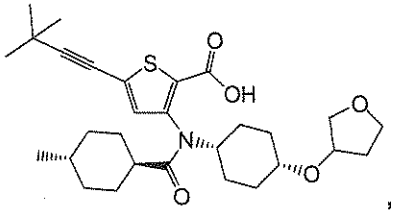
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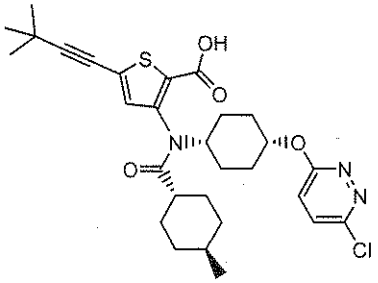
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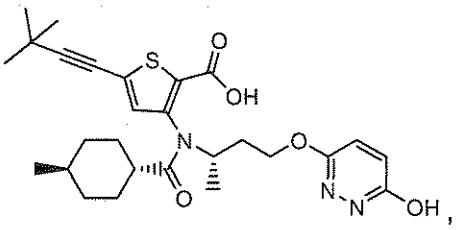
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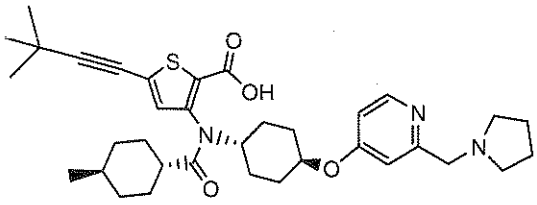
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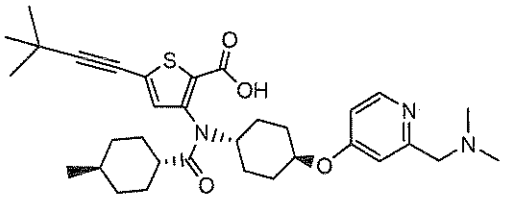
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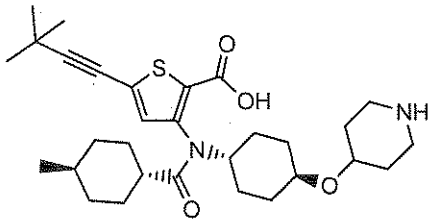
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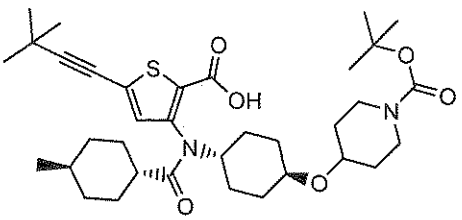
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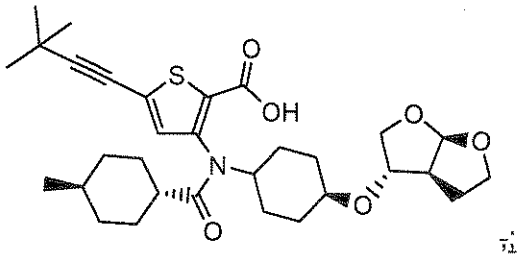
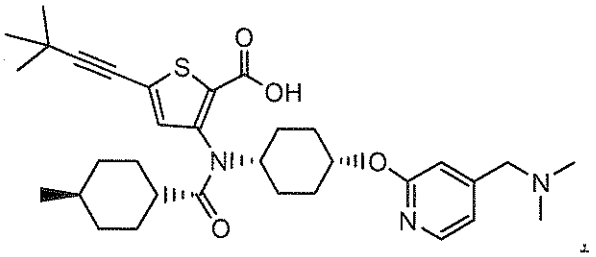
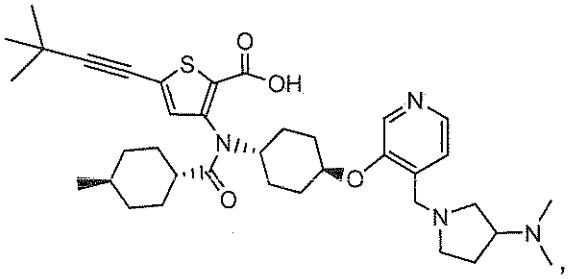
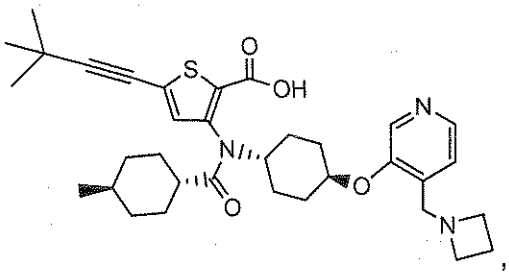


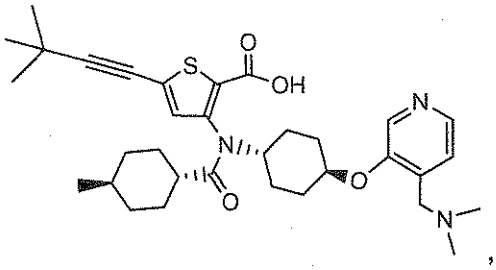
or a pharmaceutically acceptable salt thereof.

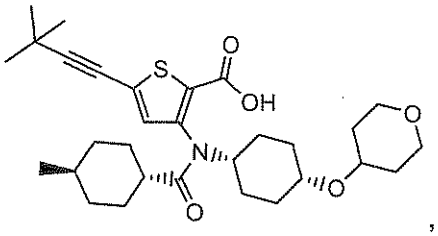
13. The compound of claim 1 that is

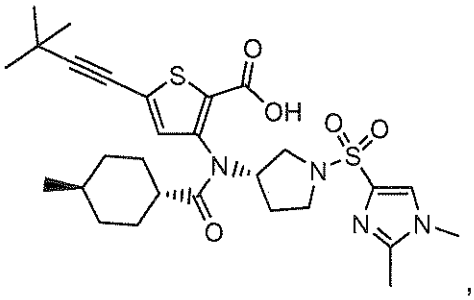








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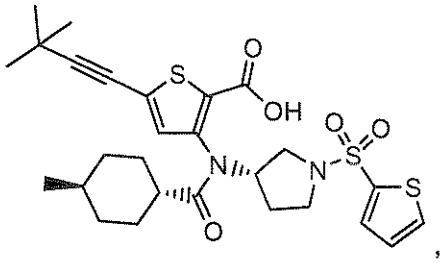
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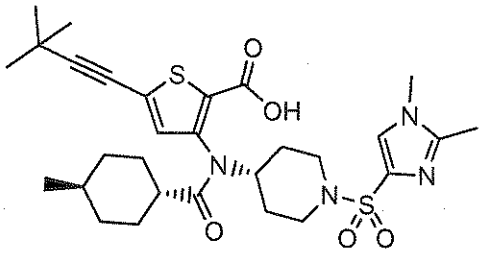
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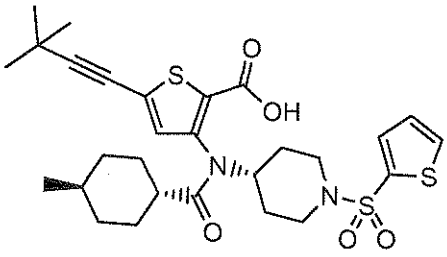
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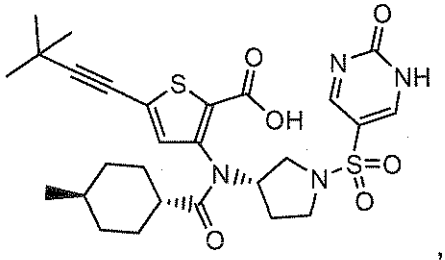
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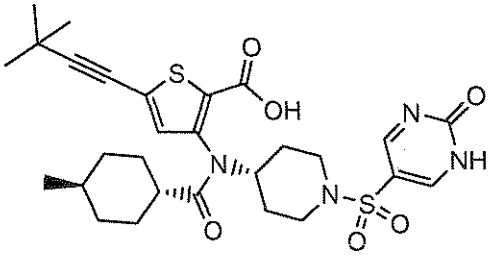
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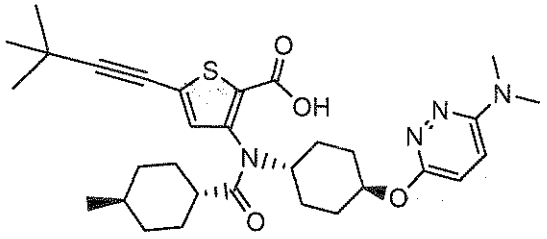
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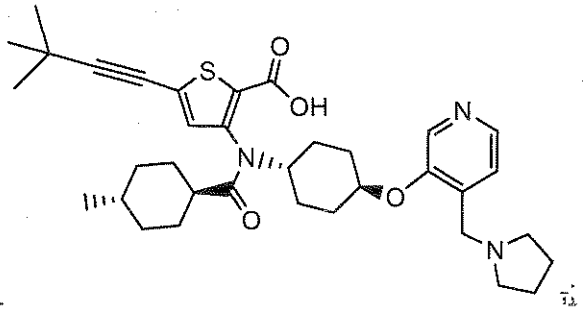
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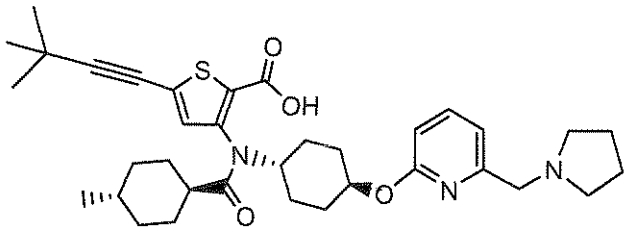
or a pharmaceutically acceptable salt thereof.

14. The compound of claim 1 that is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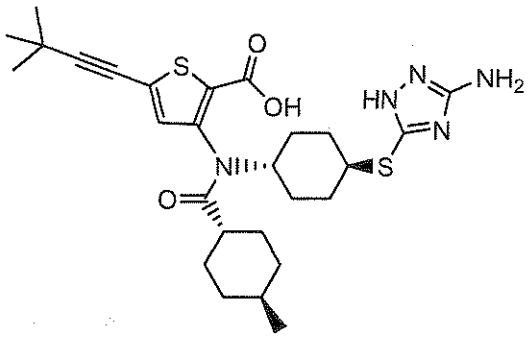
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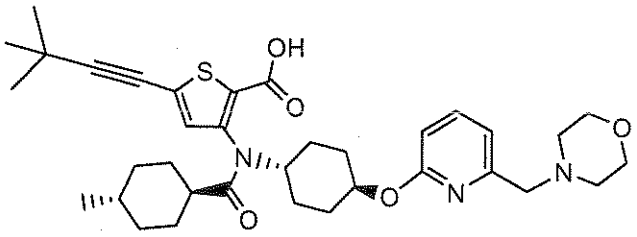
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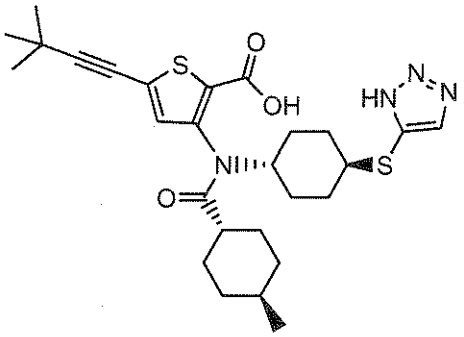
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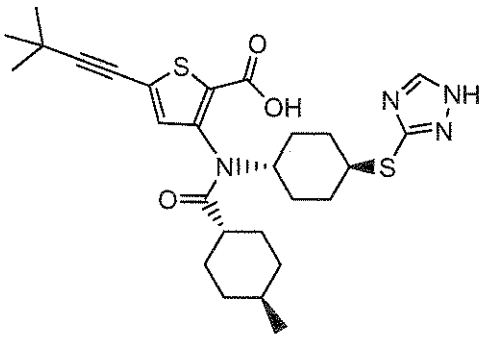
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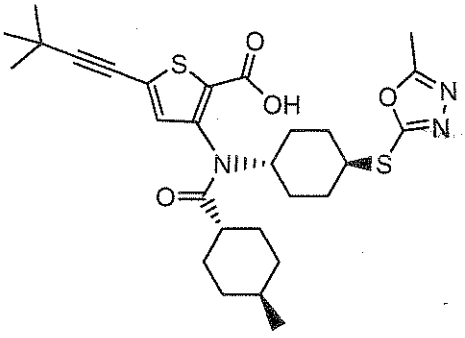
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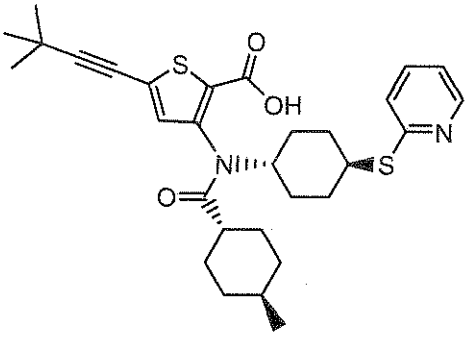
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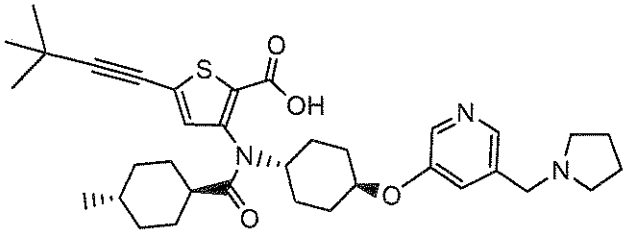

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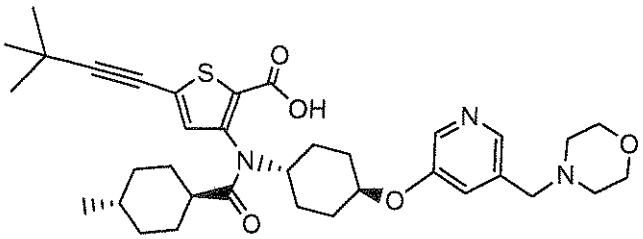

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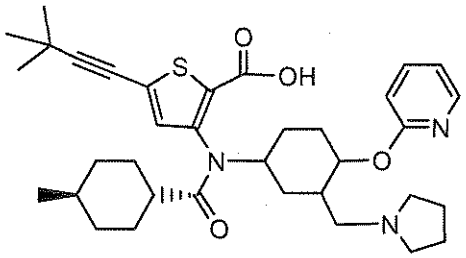

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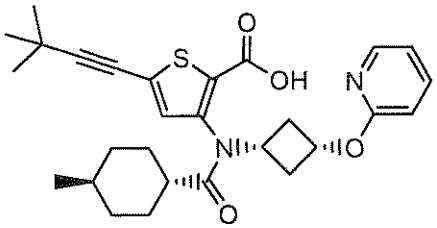

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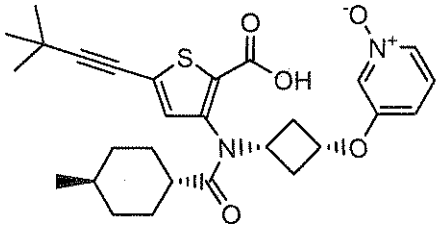

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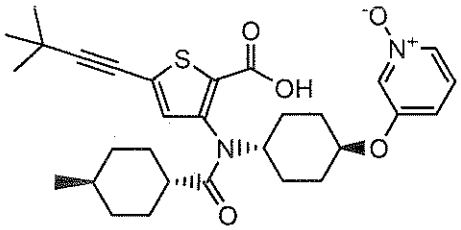

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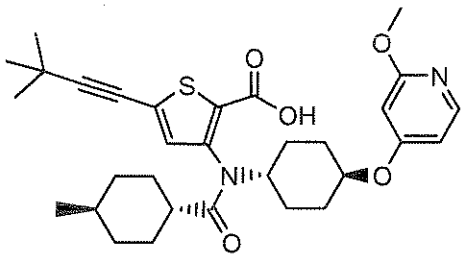
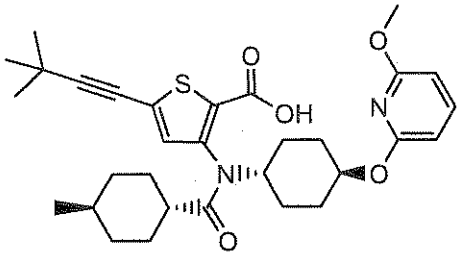


or a pharmaceutically acceptable salt thereof.

15. The compound of claim 1 that is



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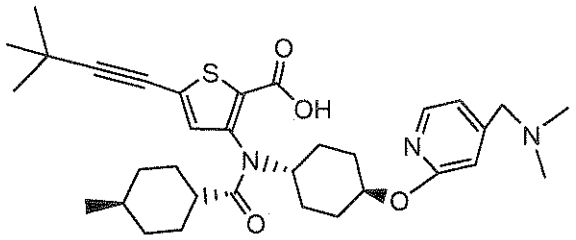

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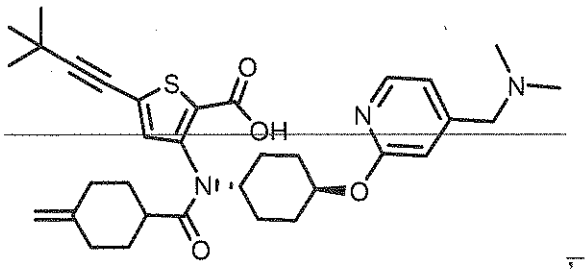
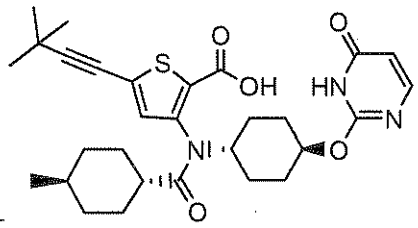
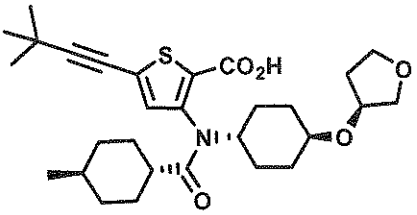
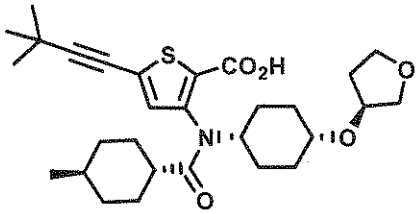
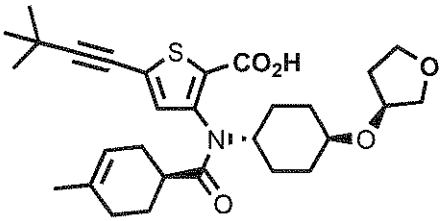
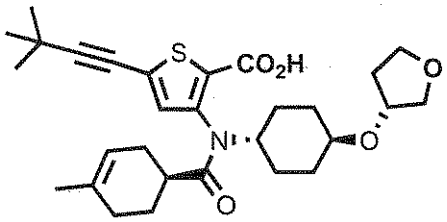


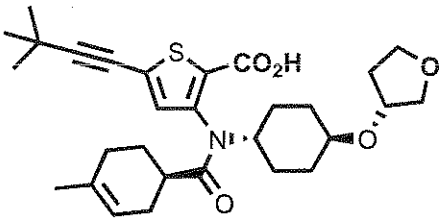


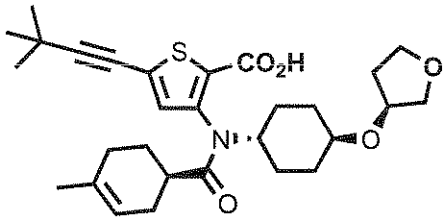


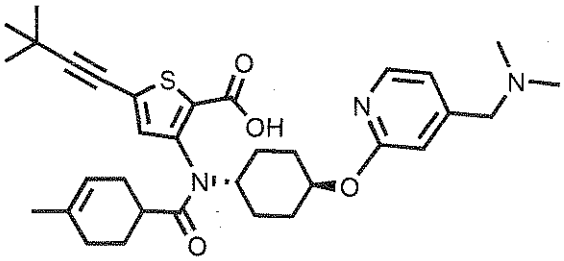


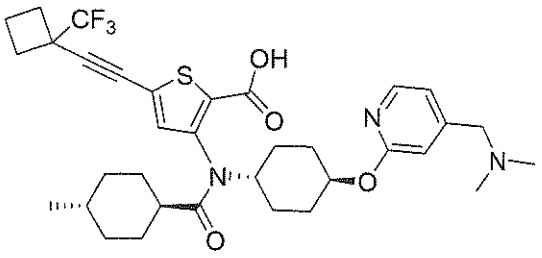


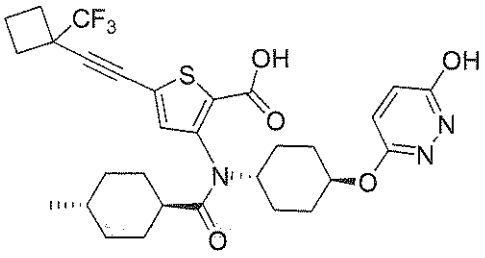


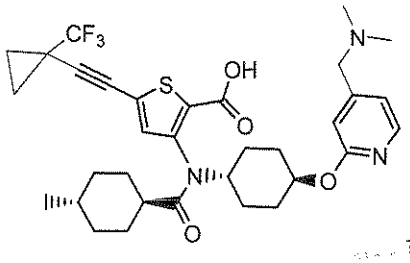






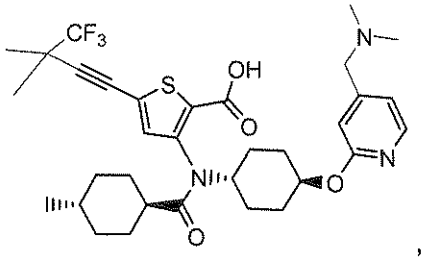






or a pharmaceutically acceptable salt thereof.

16. The compound of claim 1 that is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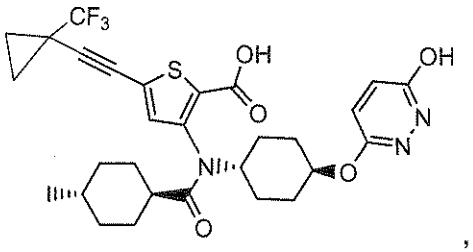
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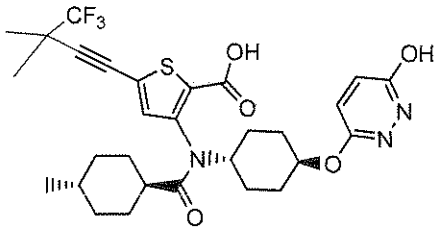
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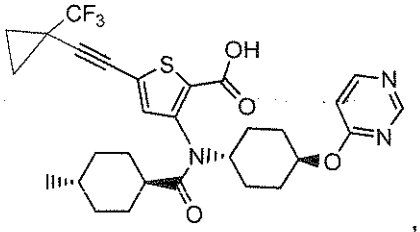
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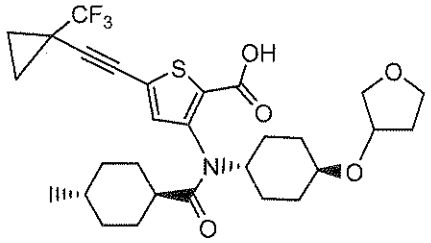
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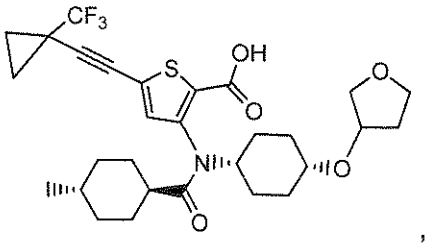
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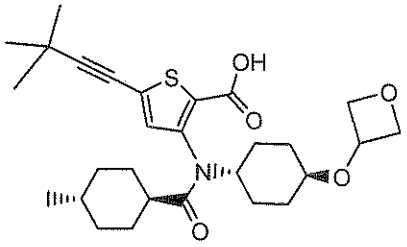
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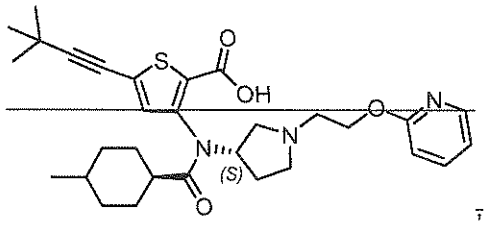
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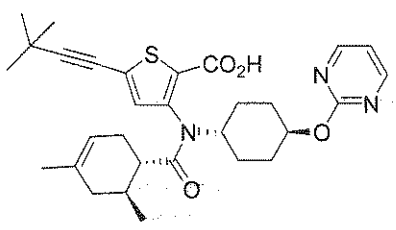
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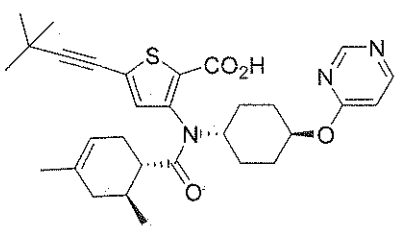
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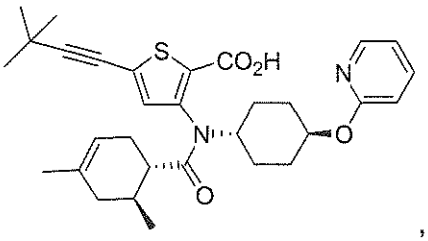
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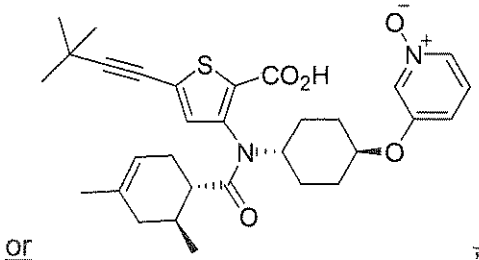

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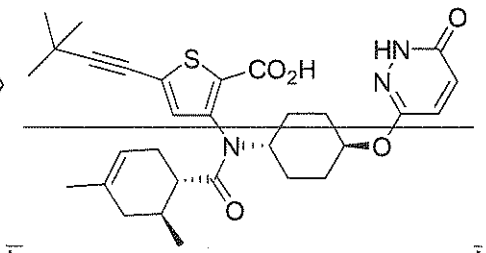

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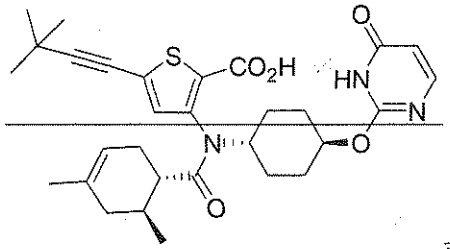

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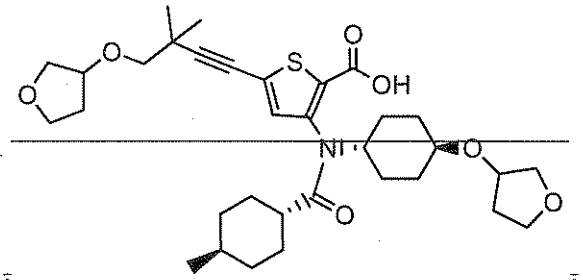

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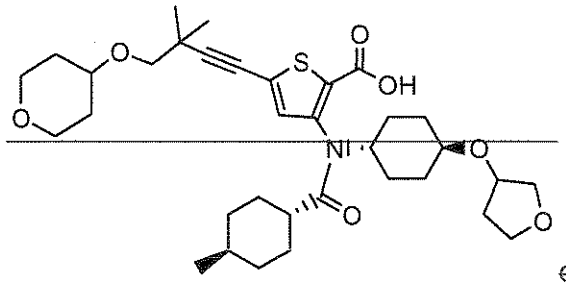

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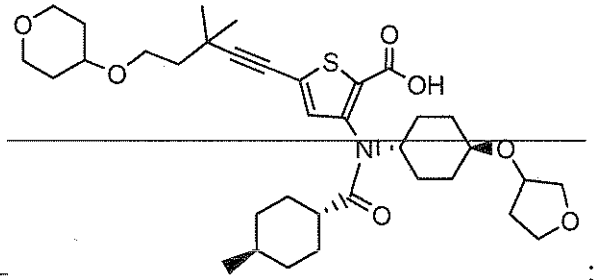
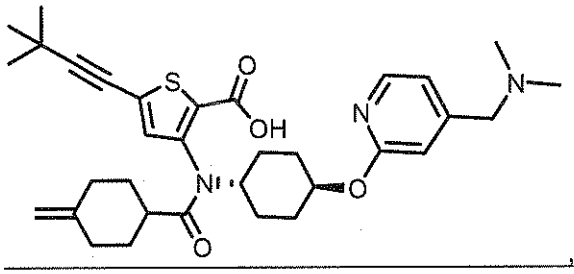
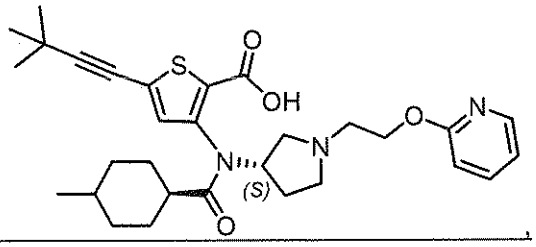
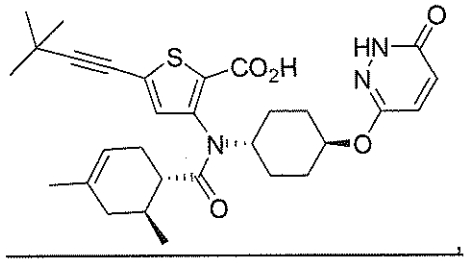


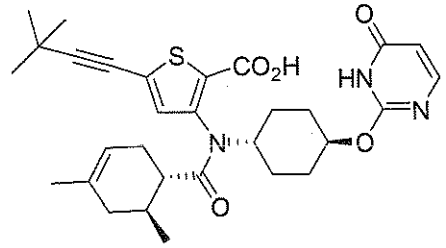
; or a pharmaceutically acceptable salt ~~or ester~~ thereof.

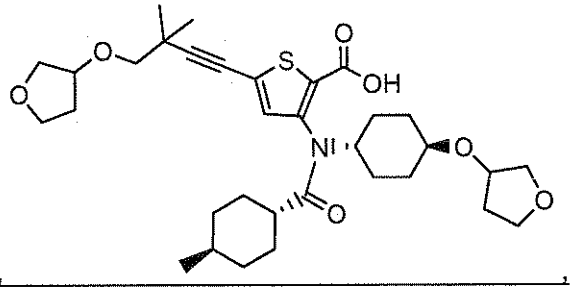
17. A compound that is

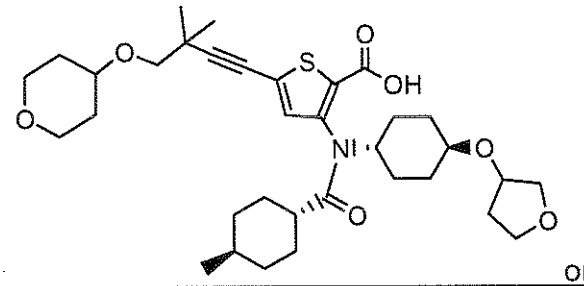












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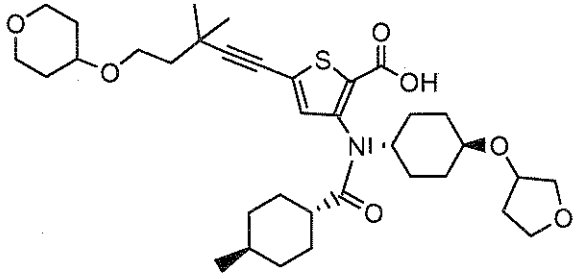

or a pharmaceutically acceptable salt thereof.

~~13~~18. A pharmaceutical composition comprising a therapeutically effective amount of a compound of any one of claims 1-~~12~~ 17 and a pharmaceutically acceptable carrier or excipient.

~~14~~19. The pharmaceutical composition of claim ~~13~~ 18 further comprising at least one additional therapeutic agent selected from the group consisting of interferons, ribavirin or its analogs, HCV NS3 protease inhibitors, NS5a inhibitors, alpha-glucosidase 1 inhibitors, hepatoprotectants, mevalonate decarboxylase antagonists,

antagonists of the renin-angiotensin system, endothelin antagonists, other anti-fibrotic agents, nucleoside or nucleotide inhibitors of HCV NS5B polymerase, non-nucleoside inhibitors of HCV NS5B polymerase, HCV NS5A inhibitors, TLR-7 agonists, cyclophillin inhibitors, HCV IRES inhibitors, pharmacokinetic enhancers and other drugs for treating HCV; or mixtures thereof.

~~15~~20. Use of a compound of any one of claims 1 to ~~12~~17 or a pharmaceutical composition of claim ~~13~~18 or claim 19 in the manufacture of a medicament for treating a *Flaviridae* viral infection in a mammal in need thereof.

~~16~~21. The use of claim ~~15~~20 wherein the viral infection is caused by a Hepatitis C virus.

~~17~~22. The use of claim ~~15~~20 or ~~16~~21, wherein the medicament is to be administered with at least one additional therapeutic agent selected from the group consisting of interferons, ribavirin or its analogs, HCV NS3 protease inhibitors, NS5a inhibitors, alpha-glucosidase 1 inhibitors, hepatoprotectants, mevalonate decarboxylase antagonists, antagonists of the renin-angiotensin system, endothelin antagonists, other anti-fibrotic agents, nucleoside or nucleotide inhibitors of HCV NS5B polymerase, non-nucleoside inhibitors of HCV NS5B polymerase, HCV NS5A inhibitors, TLR-7 agonists, cyclophillin inhibitors, HCV IRES inhibitors, pharmacokinetic enhancers and other drugs for treating HCV; or mixtures thereof.

~~18~~23. Use of a compound of any one of claims 1-~~12~~17 in the manufacture of a medicament for the treatment of Hepatitis C virus infection.

~~19~~24. A compound of any one of claims 1-~~12~~17 for use in therapy.