INHIBITORS OF *FLAVIVIRIDAE* VIRUSES

FIELD OF THE INVENTION

The present application includes novel inhibitors of *Flaviviridae* viruses, compositions containing such compounds, therapeutic methods that include the administration of such compounds.

BACKGROUND OF THE INVENTION

Viruses comprising the *Flaviviridae* family include at least three distinguishable genera including *pestiviruses*, *flaviviruses*, and *hepaciviruses* (Calisher, *et al.*, J. Gen. Virol., 1993, 70, 37-43). While *pestiviruses* cause many economically important animal diseases such as bovine viral diarrhea virus (BVDV), classical swine fever virus (CSFV, hog cholera) and border disease of sheep (BDV), their importance in human disease is less well characterized (Moennig, V., *et al.*, Adv. Vir. Res. 1992, 48, 53-98). *Flaviviruses* are responsible for important human diseases such as dengue fever and yellow fever while *hepaciviruses* cause hepatitis C virus infections in humans. Other important viral infections caused by the *Flaviviridae* family include West Nile virus (WNV) Japanese encephalitis virus (JEV), tick-borne encephalitis virus, Junjin virus, Murray Valley encephalitis, St Louis enchaplitis, Omsk hemorrhagic fever virus and Zika virus.

The hepatitis C virus (HCV) is the leading cause of chronic liver disease worldwide (Boyer, N. et al. J Hepatol. 32:98-112, 2000) so a significant focus of current antiviral research is directed toward the development of improved methods of treatment of chronic HCV infections in humans (Di Besceglie, A.M. and Bacon, B. R., Scientific American, Oct.: 80-85, (1999); Gordon, C. P., et al., *J. Med. Chem.* **2005**, *48*, 1-20; Maradpour, D.; et al., *Nat. Rev. Micro.* **2007**, *5*(6), 453-463). A number of HCV treatments are reviewed by Bymock et al. in Antiviral Chemistry & Chemotherapy, 11:2; 79-95 (2000). Virologic cures of patients with chronic HCV infection are difficult to achieve because of the prodigious amount of daily virus production in chronically infected patients and the high spontaneous mutability of HCV virus (Neumann, et al., *Science* **1998**, *282*, 103-7; Fukimoto, et al., *Hepatology*,

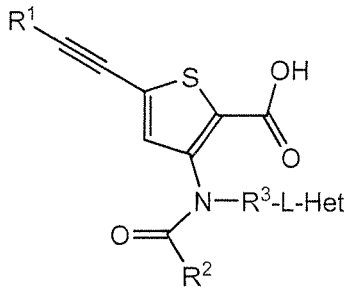
1996, *24*, 1351-4; Domingo, et al., *Gene*, **1985**, *40*, 1-8; Martell, et al., *J. Virol.* **1992**, *66*, 3225-9.

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

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,

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, -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 $-OC(O)NR^{11}R^{12}$;

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 $-S(O)_2R^{14}$;

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;

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, independently, is selected from the group consisting of halogen, oxo, oxide, $-NO_2$, $-N(=O)$, $-SR^{20}$, $-S(O)R^{20}$, $-S(O)_2R^{20}$, $-S(O)_2 NR^{20}R^{21}$, $-NR^{20}C(O)R^{21}$, $-NR^{20}C(O)NR^{21}R^{22}$, $-NR^{20}S(O)R^{21}$, $-NR^{20}S(O)_2R^{21}$, $-OP(O)R^{21}R^{22}$, $-P(O)R^{21}R^{22}$, $-P(O)OR^{21}R^{22}$, $-P(O)(OR^{21})OR^{22}$, $-C(O)NR^{21}R^{22}$, 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, -OH, $-NR^{21}R^{22}$, $-C(O)OR^{20}$, -CN, $-N_3$, $-C(=NR^{23})NR^{21}R^{22}$, $-C(=NR^{23})OR^{20}$, $-NR^{20}C(=NR^{23})N\ R^{21}R^{22}$, $-NR^{21}C(O)OR^{20}$, 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 C_{4-12} cycloalkylalkylene or substituted C_{4-12} cycloalkylalkylene;

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), $-SR^{30}$, $-S(O)R^{30}$, $-S(O)_2R^{30}$, $-S(O)_2\ NR^{30}R^{31}$, $-NR^{30}C(O)R^{31}$, $-NR^{30}C(O)NR^{31}R^{32}$, $-NR^{30}S(O)R^{31}$, $-NR^{30}S(O)_2R^{31}$, $-OP(O)R^{31}R^{32}$, $-P(O)R^{31}R^{32}$, $-P(O)OR^{31}R^{32}$, $-P(O)(OR^{31})OR^{32}$, $-C(O)NR^{31}R^{32}$, 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, -OH, $-NR^{31}R^{32}$, $-C(O)OR^{30}$, -CN, $-N_3$, $-C(=NR^{33})NR^{31}R^{32}$, $-C(=NR^{33})OR^{30}$, $-NR^{30}C(=NR^{33})N\ R^{31}R^{32}$, $-NR^{31}C(O)OR^{30}$, 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;

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 membered heteroaryl;

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), $-SR^{40}$, $-S(O)R^{40}$, $-S(O)_2R^{40}$, $-S(O)_2NR^{40}R^{41}$, $-NR^{40}C(O)R^{41}$, $-NR^{40}C(O)NR^{41}R^{42}$, $-NR^{40}S(O)R^{41}$, $-NR^{40}S(O)_2R^{41}$, $-OP(O)R^{41}R^{42}$, $-P(O)R^{41}R^{42}$, $-P(O)OR^{41}R^{42}$, $-P(O)(OR^{41})OR^{42}$, $-C(O)NR^{41}R^{42}$, 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, $-NR^{41}R^{42}$, $-C(O)OR^{40}$, -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 $-OC(O)NR^{41}R^{42}$;

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, optionally substituted 3-12 membered heterocyclyl, optionally substituted 3-18 membered heteroarylalkyl, and optionally substituted C_{6-18} arylalkyl;

or R^{41} and R^{42} taken together with the atoms to which they are attached form a 3 to 10 membered heterocyclyl;

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}, 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, $-NR^{51}R^{52}$, $-C(O)OR^{50}$, -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 $-OC(O)NR^{51}R^{52}$;

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, $-C(O)R^{54}$, -CHO and $-S(O)_2R^{54}$;

each R^{54}, independently, is optionally substituted C_{1-12} alkyl;

wherein, each substituted Q^5, substituted R^{50}, substituted R^{51}, substituted R^{52}, substituted R^{53}, or substituted R^{54} 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), $-SR^{60}$, $-S(O)R^{60}$, $-S(O)_2R^{60}$, $-S(O)_2 NR^{60} R^{61}$, $-NR^{60}C(O)R^{61}$, $-NR^{60}C(O)NR^{61}R^{62}$, $-NR^{60}S(O)R^{61}$,$-NR^{60}S(O)_2R^{61}$, $-OP(O)R^{61}R^{62}$, $-P(O)R^{61}R^{62}$, $-P(O)OR^{61}R^{62}$, $-P(O)(OR^{61})OR^{62}$, $-C(O)NR^{61}R^{62}$, 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, $-NR^{61}R^{62}$, $-C(O)OR^{60}$, -CN, $-N_3$, $-C(=NR^{63})NR^{61}R^{62}$, $-C(=NR^{63})OR^{60}$, $-NR^{60}C(=NR^{63})N R^{61}R^{62}$, $-NR^{61}C(O)OR^{60}$, and $-OC(O)NR^{61}R^{62}$;

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.

In another embodiment, a method for treating *Flaviviridae* viral infections is provided comprising administering an effective amount of a compound of Formula I to a patient 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 RNA in the 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 thereof.

In another embodiment, provided is the use of a compound of Formula I for the manufacture of a medicament for the treatment of *Flaviviridae* viral infections. In another aspect of this embodiment, the *Flaviviridae* viral infection is an HCV infection.

In another embodiment, provided is a compound of Formula I for use in treating a *Flaviviridae* viral infection. In another aspect of this embodiment, the *Flaviviridae* viral infection is an acute or chronic HCV infection. In another aspect of this embodiment, the treatment results in the reduction of one or more of the viral loads or clearance of RNA in the patient. In another aspect of this embodiment, the treatment results in the reduction of the HCV viral load or clearance of HCV viral RNA in the patient.

In another embodiment, 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. In another embodiment, provided is the use of a compound

of the present invention for the manufacture of a medicament for the treatment or prevention of HCV.

In another embodiment, provided is a pharmaceutical composition comprising a compound of Formula I 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, alpha-glucosidase 1 inhibitors, hepatoprotectants, nucleoside or nucleotide inhibitors of HCV NS5B polymerase, non-nucleoside inhibitors of HCV NS5B polymerase, HCV NS5A inhibitors, TLR-7 agonists, cyclophilin inhibitors, HCV IRES inhibitors, pharmacokinetic enhancers, and other drugs for treating HCV, or mixtures thereof.

In another embodimentt, 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 thereof and all racemates, enantiomers, diastereomers, tautomers, polymorphs, pseudopolymorphs and amorphous forms thereof.

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

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

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

DETAILED DESCRIPTION

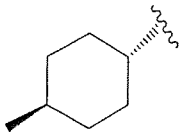
Reference will now be made in detail to certain embodiments of the invention, examples of which are illustrated in the accompanying structures and formulas. While the invention will be described in conjunction with the enumerated

embodiments, it will be understood that they are not intended to limit the invention to those embodiments. On the contrary, the invention is intended to cover all alternatives, modifications, and equivalents, which may be included within the scope of the present invention as defined herein.

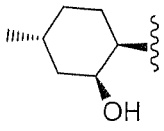
All documents referenced herein are each incorporated by reference in their entirety for all purposes.

In one embodiment of Formula I, R^1 is optionally substituted C_{1-12} alkyl, optionally substituted C_{2-12} alkenyl, optionally substituted C_{2-12} alkynyl, or optionally substituted C_{3-12} cycloalkyl. In another aspect of this embodiment, R^1 is optionally substituted C_1-C_{12} alkyl. In another aspect of this embodiment, R^1 is optionally substituted C_3-C_7 secondary or tertiary alkyl. In another aspect of this embodiment, R^1 is prop-2-yl (isopropyl) or 2-methylprop-2-yl (*t*-butyl).

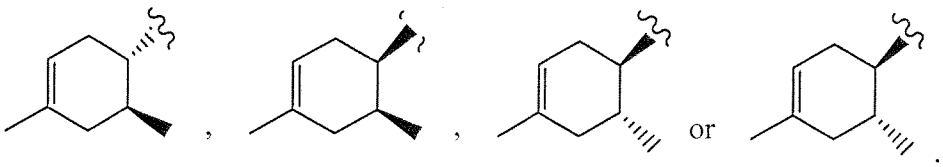
In another embodiment of Formula I, R^2 is optionally substituted C_{1-12} alkyl, optionally substituted C_{2-12} alkenyl, optionally substituted C_{2-12} alkynyl, optionally substituted C_{3-12} cycloalkyl, or optionally substituted C_{6-18} arylalkyl. In another aspect of this embodiment, R^2 is optionally substituted C_{3-12} cycloalkyl. In another aspect of this embodiment, R^2 is optionally substituted methylcyclohexyl or optionally substituted methylcyclohexenyl. In another aspect of this embodiment, R^2 is optionally substituted 4-methylcyclohexyl. In another aspect of this embodiment, R^2 is optionally substituted 4-methylcyclohexenyl. In a preferred aspect of this embodiment, R^2 is



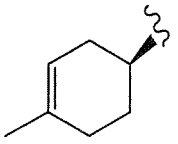
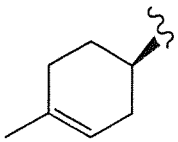
In another preferred aspect of this embodiment, R^2 is



In another preferred aspect of this embodiment, R^2 is



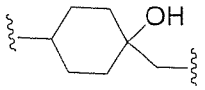
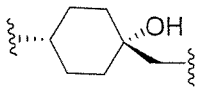
In another preferred aspect of this embodiment, R^2 is


or


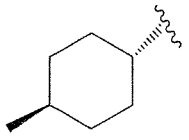
In another embodiment of Formula I, R^1 is optionally substituted C_1-C_{12} alkyl, and R^2 is optionally substituted C_{3-12} cycloalkyl. In another aspect of this embodiment, L is –O-, -S-, -S(O)-, or -$S(O)_2$-. In another aspect of this embodiment, L is –O-. In another aspect of this embodiment, L is –S-. In another aspect of this embodiment, L is –S(O)-. In another aspect of this embodiment, L is –$S(O)_2$-. In another aspect of this embodiment, R^3 is optionally substituted cycloalkylmethylene or optionally substituted cycloalkylethylene. In another aspect of this embodiment, R^3 is optionally substituted cyclopropylmethylene. In another aspect of this embodiment, R^3 is optionally substituted cyclobutylmethylene. In another aspect of this embodiment, R^3 is optionally substituted cyclopentylmethylene. In another aspect of this embodiment, R^3 is optionally substituted cyclohexylmethylene. In another aspect of this embodiment, R^3 is optionally substituted cycloheptylmethylene. In another aspect of this embodiment, 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. In another aspect of this embodiment, Het is an optionally substituted 3-12 membered heterocyclyl comprising one or two heteroatoms selected from O, S, or N. In another aspect of this embodiment, Het is an optionally substituted 5-10 membered heteroaryl comprising one to four hetroatoms selected from O, S, or N. In another aspect of this embodiment, Het is optionally substituted tetrahydrofuranyl. In another aspect of this embodiment, Het is optionally substituted tetrahydrofuran-3-yl.

In another embodiment of Formula I, R^1 is optionally substituted C_3-C_7 secondary or tertiary alkyl, R^2 is optionally substituted C_6 cycloalkyl and R^3 is optionally substituted cycloalkylmethylene or optionally substituted cycloalkylethylene. In another aspect of this embodiment, L is –O-, -S-, -S(O)-, or -$S(O)_2$-. In another aspect of this embodiment, L is –O-. In another aspect of this embodiment, L is –S-. In another aspect of this embodiment, L is –S(O)-. In another aspect of this embodiment, L is –$S(O)_2$-. In another aspect of this embodiment, R^3 is optionally substituted cyclopropylmethylene. In another aspect of this embodiment, R^3 is optionally substituted cyclobutylmethylene. In another aspect of this embodiment, R^3

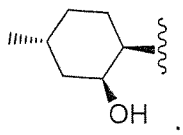
is optionally substituted cyclopentylmethylene. In another aspect of this embodiment, R^3 is optionally substituted cyclohexylmethylene. In another aspect of this embodiment, R^3 is optionally substituted cycloheptylmethylene. In another aspect of this embodiment, Het is an optionally substituted 3-12 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. In another aspect of this embodiment, Het is an optionally substituted 3-12 membered heterocyclyl comprising one or two heteroatoms selected from O, S, or N. In another aspect of this embodiment, Het is an optionally substituted 5-10 membered heteroaryl comprising one to four hetroatoms selected from O, S, or N. In another aspect of this embodiment, Het is optionally substituted tetrahydrofuranyl. In another aspect of this embodiment, Het is optionally substituted tetrahydrofuran-3-yl.

In another embodiment of Formula I, R^1 is optionally substituted C_3-C_7 tertiary alkyl, R^2 is optionally substituted methylcyclohexyl or optionally substituted methylcyclohexenyl and R^3 is optionally substituted cyclohexylmethylene. In another aspect of this embodiment, R^3 is . In another aspect of this embodiment, R^3 is . In another aspect of this embodiment, R^1 is 2-methylprop-2-yl (*t*-butyl). In another aspect of this embodiment, L is –O-, -S-, -S(O)-, or -$S(O)_2$-. In another aspect of this embodiment, L is –O-. In another aspect of this embodiment, L is –S-. In another aspect of this embodiment, L is –S(O)-. In another aspect of this embodiment, 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. In another aspect of this embodiment, Het is optionally substituted pyridinyl. In another aspect of this embodiment, Het is optionally substituted pyridazinyl. In another aspect of this embodiment, Het is optionally substituted tetrahydro-2*H*-pyranyl. In another aspect of this embodiment, Het is optionally substituted piperidinyl. In another aspect of this embodiment, Het is optionally substituted pyrrolidinyl. In another aspect of this embodiment, Het is optionally substituted

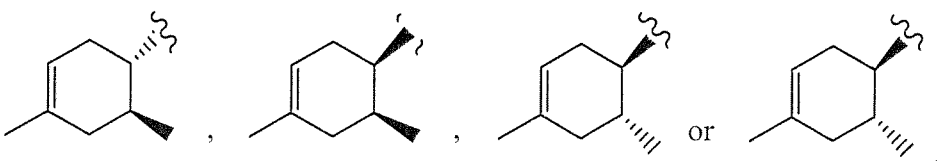
tetrahydrothiophenyl. In another aspect of this embodiment, Het is optionally substituted pyrazinyl. In another aspect of this embodiment, Het is optionally substituted 1*H*-tetrazolyl. In another aspect of this embodiment, Het is optionally substituted azetidinyl. In another aspect of this embodiment, Het is optionally substituted tetrahydrofuranyl. In another aspect of this embodiment, Het is optionally substituted tetrahydrofuran-3(*S*)-yl. In another aspect of this embodiment, Het is optionally substituted tetrahydrofuran-3(*R*)-yl. In another aspect of this embodiment, Het is optionally substituted tetrahydro-2*H*-furo[2,3-b]furanyl. In another aspect of this embodiment, Het is optionally substituted thiazoyl. In another aspect of this embodiment, Het is optionally substituted 1*H*-imidazolyl. In another aspect of this embodiment, Het is optionally substituted 4*H*-1,2,4-triazolyl. In another aspect of this embodiment, Het is optionally substituted 1*H*-pyrazolyl. In another aspect of this embodiment, Het is optionally substituted 1,3,4-thiadiazolyl. In another aspect of this embodiment, Het is optionally substituted quinolinyl. In another aspect of this embodiment, Het is optionally substituted [1,2,4]triazolo[4,3-a]pyridinyl. In another aspect of this embodiment, Het is optionally substituted thiophenyl. In another aspect of this embodiment, Het is optionally substituted 1,2,4-thiadiazolyl. In another aspect of this embodiment, Het is optionally substituted pyrimidinyl. In another aspect of this embodiment, Het is optionally substituted 1*H*-1,2,3-triazolyl. In another aspect of this embodiment, Het is optionally substituted 1,3,4-oxadiazolyl. In another aspect of this embodiment, Het is optionally substituted imidazo[1,2-b]pyridazinyl. In a preferred aspect of this embodiment, R^2 is



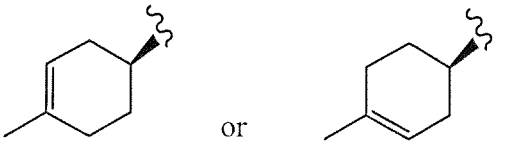
In another preferred aspect of this embodiment, R^2 is



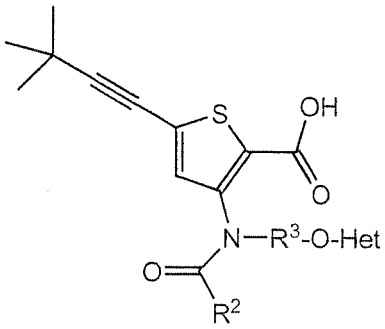
In another preferred aspect of this embodiment, R^2 is



In another preferred aspect of this embodiment, R^2 is



In another embodiment, compounds of Formula I comprise compounds of Formula II:

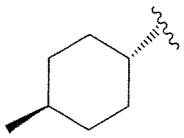


Formula II

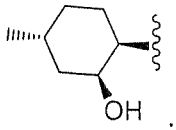
or pharmaceutically acceptable salts and esters thereof, wherein:

R^2 is optionally substituted 4-methylcyclohexyl or optionally substituted 4-methylcyclohexenyl and the remaining variables are defined as for Formula I.

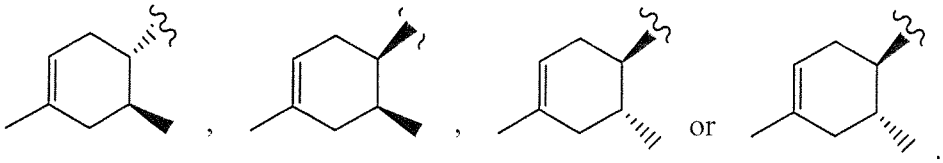
In one embodiment of Formula II, R^2 is



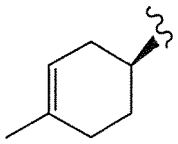
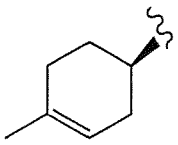
In another embodiment of Formula II, R^2 is

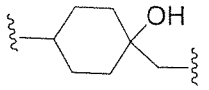


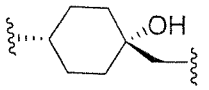
In another embodiment of Formula II, R^2 is



In another embodiment of Formula II, R^2 is


or


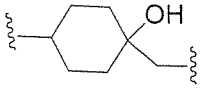
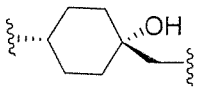
In another embodiment of Formula II, R^3 is .

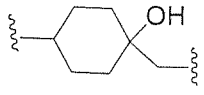
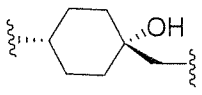
In another embodiment of Formula II, R^3 is .

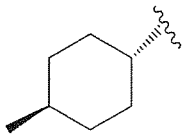
In another embodiment of Formula II, Het is an optionally substituted 3-12 membered heterocyclyl or optionally substituted 3-14 membered heteroaryl wherein said optionally substituted 3-12 membered heterocyclyl or optionally substituted 3-14 membered heteroaryl comprises one to four heteroatoms selected from O, S, or N. In another aspect of this embodiment, Het is an optionally substituted 3-12 membered heterocyclyl comprising one or two heteroatoms selected from O, S, or N. In another aspect of this embodiment, Het is an optionally substituted 5-10 membered heteroaryl comprising one to four hetroatoms selected from O, S, or N. In another aspect of this embodiment, Het is optionally substituted pyridinyl. In another aspect of this embodiment, Het is optionally substituted pyridazinyl. In another aspect of this embodiment, Het is optionally substituted tetrahydro-*2H*-pyranyl. In another aspect of this embodiment, Het is optionally substituted piperidinyl. In another aspect of this embodiment, Het is optionally substituted pyrrolidinyl. In another aspect of this embodiment, Het is optionally substituted tetrahydrothiophenyl. In another aspect of this embodiment, Het is optionally substituted pyrazinyl. In another aspect of this embodiment, Het is optionally substituted 1*H*-tetrazolyl. In another aspect of this embodiment, Het is optionally substituted azetidinyl. In another aspect of this embodiment, Het is optionally substituted tetrahydrofuranyl. In another aspect of this embodiment, Het is optionally substituted tetrahydrofuran-3-yl. In another aspect of this embodiment, Het is optionally substituted tetrahydrofuran-3(*S*)-yl. In another aspect of this embodiment, Het is optionally substituted tetrahydrofuran-3(*R*)-yl. In another aspect of this embodiment, Het is optionally substituted tetrahydro-2*H*-furo[2,3-b]furanyl. In another aspect of this embodiment, Het is optionally substituted thiazoyl. In another aspect of this embodiment, Het is optionally substituted 1*H*-imidazolyl. In another aspect of this embodiment, Het is optionally substituted 4*H*-1,2,4-triazolyl. In another

aspect of this embodiment, Het is optionally substituted 1*H*-pyrazolyl. In another aspect of this embodiment, Het is optionally substituted 1,3,4-thiadiazolyl. In another aspect of this embodiment, Het is optionally substituted quinolinyl. In another aspect of this embodiment, Het is optionally substituted [1,2,4]triazolo[4,3-a]pyridinyl. In another aspect of this embodiment, Het is optionally substituted thiophenyl. In another aspect of this embodiment, Het is optionally substituted 1,2,4-thiadiazolyl. In another aspect of this embodiment, Het is optionally substituted pyrimidinyl. In another aspect of this embodiment, Het is optionally substituted 1*H*-1,2,3-triazolyl. In another aspect of this embodiment, Het is optionally substituted 1,3,4-oxadiazolyl. In another aspect of this embodiment, Het is optionally substituted imidazo[1,2-b]pyridazinyl.

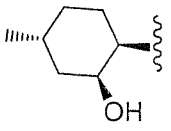
In another embodiment of Formula II, R^3 is optionally substituted cycloalkylmethylene or optionally substituted cycloalkylethylene. In another aspect of this embodiment, R^3 is optionally substituted cyclopropylmethylene. In another aspect of this embodiment, R^3 is optionally substituted cyclobutylmethylene. In another aspect of this embodiment, R^3 is optionally substituted cyclopentylmethylene. In another aspect of this embodiment, R^3 is optionally substituted cyclohexylmethylene. In another aspect of this embodiment, R^3 is optionally substituted cycloheptylmethylene. In another aspect of this embodiment, Q^3 is OH.

In another aspect of this embodiment, R^3 is . In another aspect of this embodiment, R^3 is .

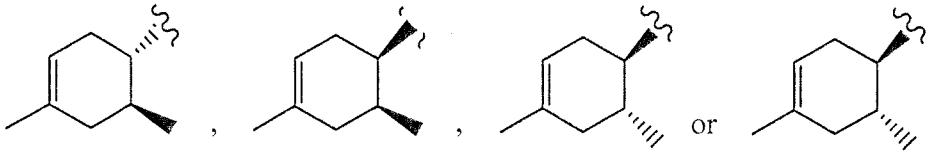
In another embodiment of Formula II, Het is optionally substituted tetrahydrofuranyl and R^3 is optionally substituted cyclohexylmethylene. In another aspect of this embodiment, Q^3 is OH. In another aspect of this embodiment, R^3 is . In another aspect of this embodiment, R^3 is . In another aspect of this embodiment, Het is optionally substituted tetrahydrofuran-3-yl. In another aspect of this embodiment, Het is tetrahydrofuran-3-yl. In another aspect of this embodiment, R^2 is



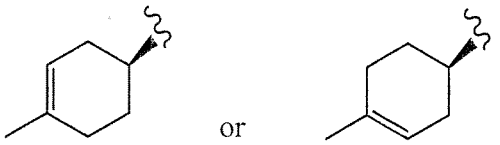
In another aspect of this embodiment, R^2 is



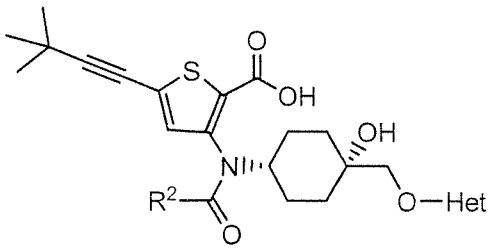
In another aspect of this embodiment, R^2 is



In another aspect of this embodiment, R^2 is

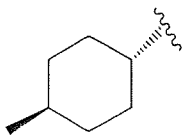


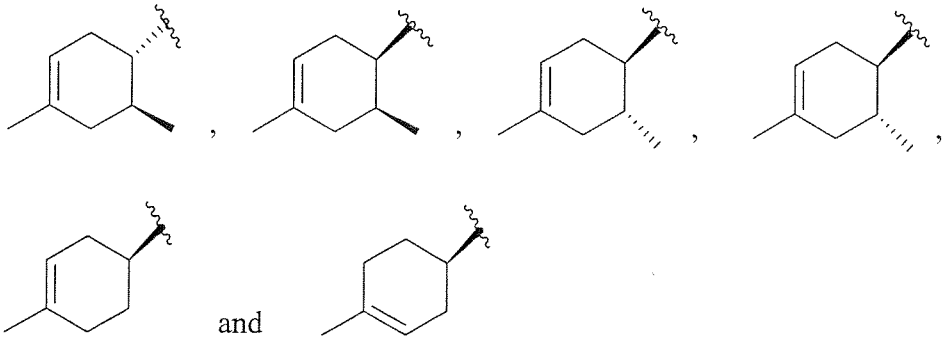
In another embodiment, compounds of Formula I are represented by Formula III:



Formula III

wherein R^2 is selected from the group consisting of



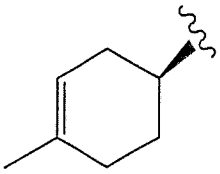
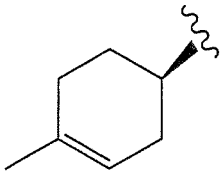


; or a pharmaceutically acceptable salt or ester thereof, wherein the remaining variables are defined as for Formula I.

In another embodiment of Formula III, 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. In another aspect of this embodiment, 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 or N. In another aspect of this embodiment, Het is an optionally substituted 3-12 membered heterocyclyl comprising one or two heteroatoms selected from O, S, or N. In another aspect of this embodiment, Het is an optionally substituted 3-12 membered heterocyclyl comprising one or two heteroatoms selected from O or N. In another aspect of this embodiment, Het is an optionally substituted 5-10 membered heteroaryl comprising one to four hetroatoms selected from O, S, or N. In another aspect of this embodiment, Het is optionally substituted pyridinyl. In another aspect of this embodiment, Het is optionally substituted pyridazinyl. In another aspect of this embodiment, Het is optionally substituted tetrahydro-2*H*-pyranyl. In another aspect of this embodiment, Het is optionally substituted piperidinyl. In another aspect of this embodiment, Het is optionally substituted pyrrolidinyl. In another aspect of this embodiment, Het is optionally substituted tetrahydrothiophenyl. In another aspect of this embodiment, Het is optionally substituted pyrazinyl. In another aspect of this embodiment, Het is optionally substituted 1*H*-tetrazolyl. In another aspect of this embodiment, Het is optionally substituted azetidinyl. In another aspect of this embodiment, Het is optionally substituted tetrahydrofuranyl. In another aspect of this embodiment, Het is optionally

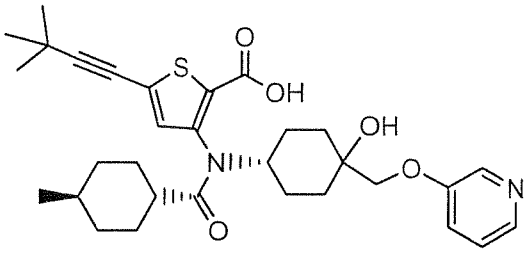
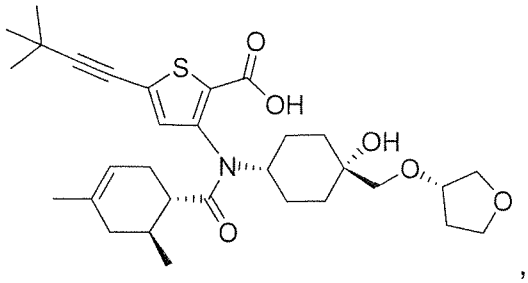
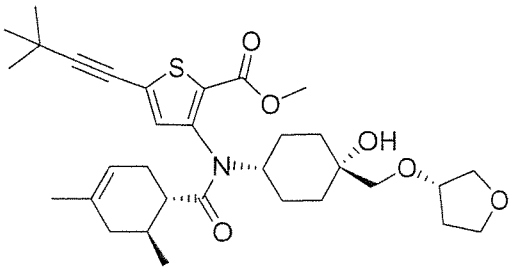
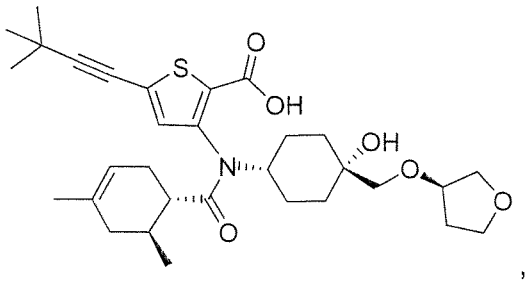
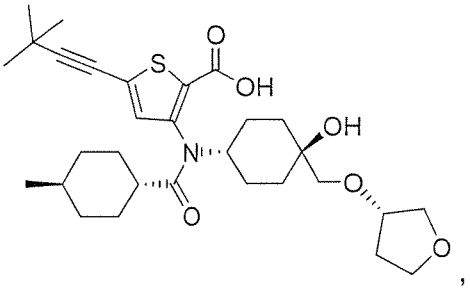
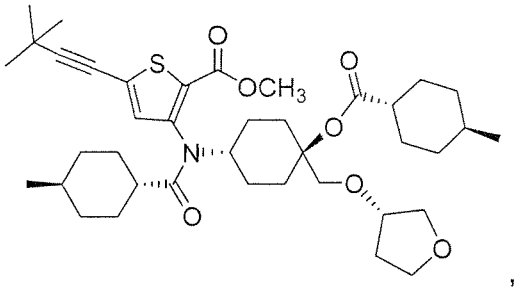
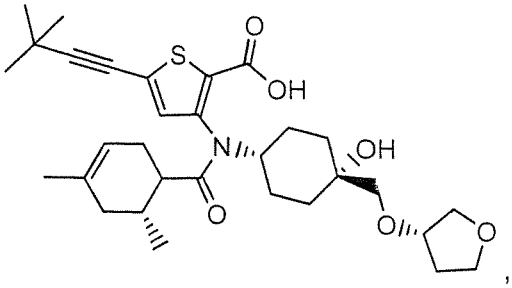
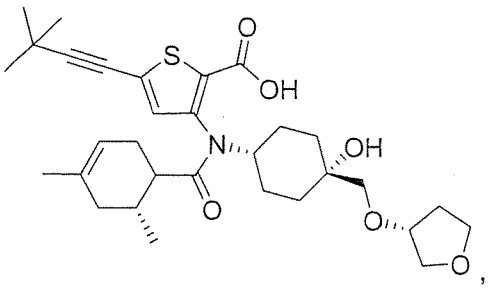
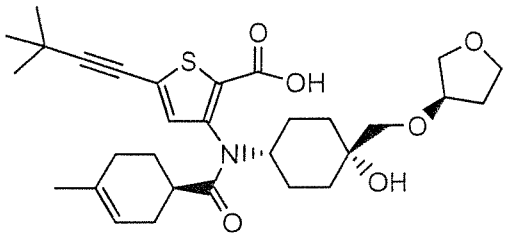
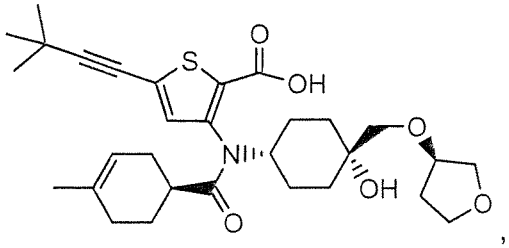
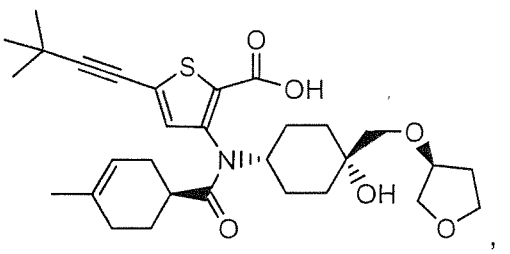
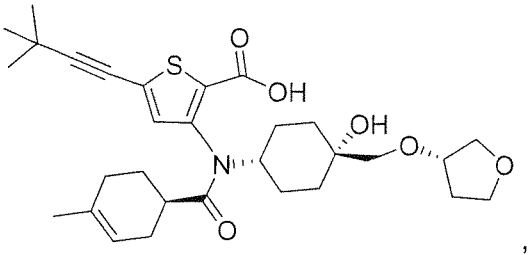
substituted tetrahydrofuran-3-yl. In another aspect of this embodiment, Het is optionally substituted tetrahydrofuran-3(*S*)-yl. In another aspect of this embodiment, Het is optionally substituted tetrahydrofuran-3(*R*)-yl. In another aspect of this embodiment, Het is optionally substituted tetrahydro-2*H*-furo[2,3-b]furanyl. In another aspect of this embodiment, Het is optionally substituted thiazoyl. In another aspect of this embodiment, Het is optionally substituted 1*H*-imidazolyl. In another aspect of this embodiment, Het is optionally substituted 4*H*-1,2,4-triazolyl. In another aspect of this embodiment, Het is optionally substituted 1*H*-pyrazolyl. In another aspect of this embodiment, Het is optionally substituted 1,3,4-thiadiazolyl. In another aspect of this embodiment, Het is optionally substituted quinolinyl. In another aspect of this embodiment, Het is optionally substituted [1,2,4]triazolo[4,3-a]pyridinyl. In another aspect of this embodiment, Het is optionally substituted thiophenyl. In another aspect of this embodiment, Het is optionally substituted 1,2,4-thiadiazolyl. In another aspect of this embodiment, Het is optionally substituted pyrimidinyl. In another aspect of this embodiment, Het is optionally substituted 1*H*-1,2,3-triazolyl. In another aspect of this embodiment, Het is optionally substituted 1,3,4-oxadiazolyl. In another aspect of this embodiment, Het is optionally substituted imidazo[1,2-b]pyridazinyl.

In another embodiment of Formula III, R^2 is

 or . In another aspect of this embodiment, 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. In another aspect of this embodiment, 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 or N. In another aspect of this embodiment, Het is an optionally substituted 3-12 membered heterocyclyl comprising one or two heteroatoms selected from O, S, or N. In another aspect of this embodiment, Het is an optionally substituted 3-12 membered heterocyclyl comprising one or two

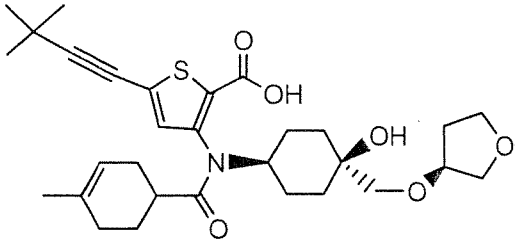
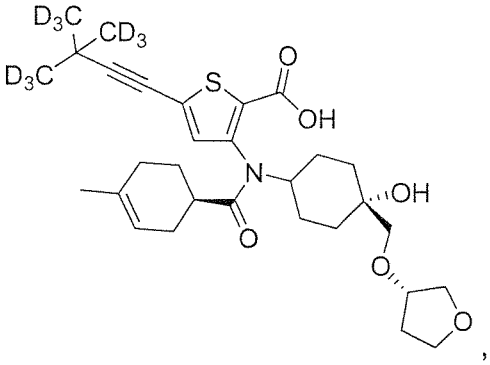
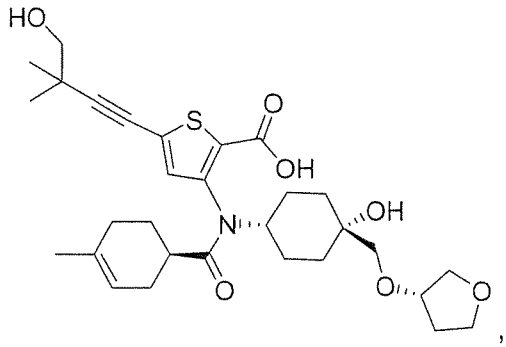
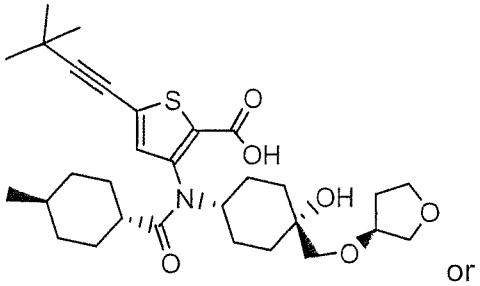
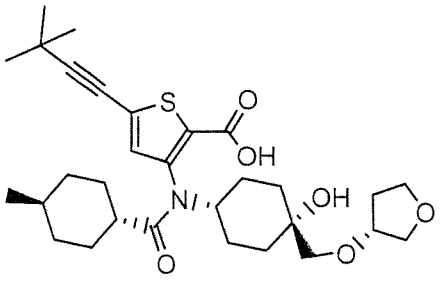
heteroatoms selected from O or N. In another aspect of this embodiment, Het is an optionally substituted 5-10 membered heteroaryl comprising one to four hetroatoms selected from O, S, or N. In another aspect of this embodiment, Het is optionally substituted pyridinyl. In another aspect of this embodiment, Het is optionally substituted pyridazinyl. In another aspect of this embodiment, Het is optionally substituted tetrahydro-2*H*-pyranyl. In another aspect of this embodiment, Het is optionally substituted piperidinyl. In another aspect of this embodiment, Het is optionally substituted pyrrolidinyl. In another aspect of this embodiment, Het is optionally substituted tetrahydrothiophenyl. In another aspect of this embodiment, Het is optionally substituted pyrazinyl. In another aspect of this embodiment, Het is optionally substituted 1*H*-tetrazolyl. In another aspect of this embodiment, Het is optionally substituted azetidinyl. In another aspect of this embodiment, Het is optionally substituted tetrahydrofuranyl. In another aspect of this embodiment, Het is optionally substituted tetrahydrofuran-3-yl. In another aspect of this embodiment, Het is optionally substituted tetrahydrofuran-3(*S*)-yl. In another aspect of this embodiment, Het is optionally substituted tetrahydrofuran-3(*R*)-yl. In another aspect of this embodiment, Het is optionally substituted tetrahydro-2*H*-furo[2,3-b]furanyl. In another aspect of this embodiment, Het is optionally substituted thiazoyl. In another aspect of this embodiment, Het is optionally substituted 1*H*-imidazolyl. In another aspect of this embodiment, Het is optionally substituted 4*H*-1,2,4-triazolyl. In another aspect of this embodiment, Het is optionally substituted 1*H*-pyrazolyl. In another aspect of this embodiment, Het is optionally substituted 1,3,4-thiadiazolyl. In another aspect of this embodiment, Het is optionally substituted quinolinyl. In another aspect of this embodiment, Het is optionally substituted [1,2,4]triazolo[4,3-a]pyridinyl. In another aspect of this embodiment, Het is optionally substituted thiophenyl. In another aspect of this embodiment, Het is optionally substituted 1,2,4-thiadiazolyl. In another aspect of this embodiment, Het is optionally substituted pyrimidinyl. In another aspect of this embodiment, Het is optionally substituted 1*H*-1,2,3-triazolyl. In another aspect of this embodiment, Het is optionally substituted 1,3,4-oxadiazolyl. In another aspect of this embodiment, Het is optionally substituted imidazo[1,2-b]pyridazinyl.

In another embodiment, the compound of Formula I-III is


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or

; or a pharmaceutically acceptable salt or ester thereof.

Definitions

Unless stated otherwise, the following terms and phrases as used herein are intended to have the following meanings. The fact that a particular term or phrase is not specifically defined should not be correlated to indefiniteness or lacking clarity, but rather terms herein are used within their ordinary meaning. When trade names are used herein, applicants intend to independently include the tradename product and the active pharmaceutical ingredient(s) of the tradename product.

The term "treating", and grammatical equivalents thereof, when used in the context of treating a disease, means slowing or stopping the progression of a disease, or ameliorating at least one symptom of a disease, more preferably ameliorating more than one symptom of a disease. For example, treatment of a hepatitis C virus

infection can include reducing the HCV viral load in an HCV infected human being, and/or reducing the severity of jaundice present in an HCV infected human being.

"Alkyl" is hydrocarbon containing normal, secondary, tertiary or cyclic carbon atoms. For example, an alkyl group can have 1 to 20 carbon atoms (i.e, C_1-C_{20} alkyl), 1 to 10 carbon atoms (i.e., C_1-C_{10} alkyl), or 1 to 6 carbon atoms (i.e., C_1-C_6 alkyl). Examples of suitable alkyl groups include, but are not limited to, methyl (Me, $-CH_3$), ethyl (Et, $-CH_2CH_3$), 1-propyl (n-Pr, n-propyl, $-CH_2CH_2CH_3$), 2-propyl (i-Pr, i-propyl, $-CH(CH_3)_2$), 1-butyl (n-Bu, n-butyl, $-CH_2CH_2CH_2CH_3$), 2-methyl-1-propyl (i-Bu, i-butyl, $-CH_2CH(CH_3)_2$), 2-butyl (s-Bu, s-butyl, $-CH(CH_3)CH_2CH_3$), 2-methyl-2-propyl (t-Bu, t-butyl, $-C(CH_3)_3$), 1-pentyl (n-pentyl, $-CH_2CH_2CH_2CH_2CH_3$), 2-pentyl ($-CH(CH_3)CH_2CH_2CH_3$), 3-pentyl ($-CH(CH_2CH_3)_2$), 2-methyl-2-butyl ($-C(CH_3)_2CH_2CH_3$), 3-methyl-2-butyl ($-CH(CH_3)CH(CH_3)_2$), 3-methyl-1-butyl ($-CH_2CH_2CH(CH_3)_2$), 2-methyl-1-butyl ($-CH_2CH(CH_3)CH_2CH_3$), 1-hexyl ($-CH_2CH_2CH_2CH_2CH_2CH_3$), 2-hexyl ($-CH(CH_3)CH_2CH_2CH_2CH_3$), 3-hexyl ($-CH(CH_2CH_3)(CH_2CH_2CH_3)$), 2-methyl-2-pentyl ($-C(CH_3)_2CH_2CH_2CH_3$), 3-methyl-2-pentyl ($-CH(CH_3)CH(CH_3)CH_2CH_3$), 4-methyl-2-pentyl ($-CH(CH_3)CH_2CH(CH_3)_2$), 3-methyl-3-pentyl ($-C(CH_3)(CH_2CH_3)_2$), 2-methyl-3-pentyl ($-CH(CH_2CH_3)CH(CH_3)_2$), 2,3-dimethyl-2-butyl ($-C(CH_3)_2CH(CH_3)_2$), 3,3-dimethyl-2-butyl ($-CH(CH_3)C(CH_3)_3$, and octyl ($-(CH_2)_7CH_3$).

"Alkoxy" means a group having the formula –O-alkyl, in which an alkyl group, as defined above, is attached to the parent molecule via an oxygen atom. The alkyl portion of an alkoxy group can have 1 to 20 carbon atoms (i.e., C_1-C_{20} alkoxy), 1 to 12 carbon atoms (i.e., C_1-C_{12} alkoxy), or 1 to 6 carbon atoms(i.e., C_1-C_6 alkoxy). Examples of suitable alkoxy groups include, but are not limited to, methoxy ($-O-CH_3$ or –OMe), ethoxy ($-OCH_2CH_3$ or -OEt), t-butoxy ($-O-C(CH_3)_3$ or –OtBu), and the like.

"Haloalkyl" is an alkyl group, as defined above, in which one or more hydrogen atoms of the alkyl group is replaced with a halogen atom. The alkyl portion of a haloalkyl group can have 1 to 20 carbon atoms (i.e., C_1-C_{20} haloalkyl), 1 to 12 carbon atoms(i.e., C_1-C_{12} haloalkyl), or 1 to 6 carbon atoms (i.e., C_1-C_6 alkyl). Examples of suitable haloalkyl groups include, but are not limited to, $-CF_3$, $-CHF_2$, $-CFH_2$, $-CH_2CF_3$, and the like.

"Alkenyl" is a hydrocarbon containing normal, secondary, tertiary, or cyclic carbon atoms with at least one site of unsaturation, i.e. a carbon-carbon, sp2 double bond. For example, an alkenyl group can have 2 to 20 carbon atoms (i.e., C_2-C_{20}

alkenyl), 2 to 12 carbon atoms (i.e., C_2-C_{12} alkenyl), or 2 to 6 carbon atoms (i.e., C_2-C_6 alkenyl). Examples of suitable alkenyl groups include, but are not limited to, vinyl (-CH=CH_2), allyl (-CH_2CH=CH_2), cyclopentenyl (-C_5H_7), and 5-hexenyl (-$CH_2CH_2CH_2CH_2$CH=CH_2).

"Alkynyl" is a hydrocarbon containing normal, secondary, tertiary or cyclic carbon atoms with at least one site of unsaturation, i.e. a carbon-carbon, sp triple bond. For example, an alkynyl group can have 2 to 20 carbon atoms (i.e., C_2-C_{20} alkynyl), 2 to 12 carbon atoms (i.e., C_2-C_{12} alkyne,), or 2 to 6 carbon atoms (i.e., C_2-C_6 alkynyl). Examples of suitable alkynyl groups include, but are not limited to, acetylenic (-C≡CH), propargyl (-CH_2C≡CH), and the like.

"Alkylene" refers to a saturated, branched or straight chain radical or or cyclic hydrocarbon radical having two monovalent radical centers derived by the removal of two hydrogen atoms from the same or two different carbon atoms of a parent alkane. For example, an alkylene group can have 1 to 20 carbon atoms, 1 to 10 carbon atoms, or 1 to 6 carbon atoms. Typical alkylene radicals include, but are not limited to, methylene (-CH_2-), 1,1-ethylene (-CH(CH_3)-), 1,2-ethylene (-CH_2CH_2-), 1,1-propylene (-CH(CH_2CH_3)-), 1,2-propylene (-CH_2CH(CH_3)-), 1,3-propylene (-$CH_2CH_2CH_2$-), 1,4-butylene (-$CH_2CH_2CH_2CH_2$-), and the like.

"Alkenylene" refers to an unsaturated, branched or straight chain or cyclic hydrocarbon radical having two monovalent radical centers derived by the removal of two hydrogen atoms from the same or two different carbon atoms of a parent alkene. For example, and alkenylene group can have 1 to 20 carbon atoms, 1 to 10 carbon atoms, or 1 to 6 carbon atoms. Typical alkenylene radicals include, but are not limited to, 1,2-ethylene (-CH=CH-).

"Alkynylene" refers to an unsaturated, branched or straight chain or cyclic hydrocarbon radical having two monovalent radical centers derived by the removal of two hydrogen atoms from the same or two different carbon atoms of a parent alkyne. For example, an alkynylene group can have 1 to 20 carbon atoms, 1 to 10 carbon atoms, or 1 to 6 carbon atoms. Typical alkynylene radicals include, but are not limited to, acetylene (-C≡C-), propargyl (-CH_2C≡C-), and 4-pentynyl (-$CH_2CH_2CH_2$C≡C-).

"Alkylyne" refers to a saturated, branched or straight chain radical having two radical centers derived by the removal of three hydrogen atoms from two carbon atoms of a parent alkane. For example, an alkylyne group can have 2 to 20 carbon atoms, 2 to 10 carbon atoms, or 2 to 6 carbon atoms. Typical alkylyne radicals include, but are

not limited to, 1,2-ethylyne (-CH_2CH=), 1,2-propylyne (-$CH_2C(CH_3)$=), 1,3-propylyne (-CH_2CH_2CH=), 1,4-butylyne (-$CH_2CH_2CH_2CH$=), and the like.

"Aryl" means a monovalent aromatic hydrocarbon radical derived by the removal of one hydrogen atom from a single carbon atom of a parent aromatic ring system. For example, an aryl group can have 6 to 20 carbon atoms, 6 to 14 carbon atoms, or 6 to 12 carbon atoms. Typical aryl groups include, but are not limited to, radicals derived from benzene (e.g., phenyl), substituted benzene, naphthalene, anthracene, biphenyl, and the like.

"Arylene" refers to an aryl as defined above having two monovalent radical centers derived by the removal of two hydrogen atoms from the same or two different carbon atoms of a parent aryl. Typical arylene radicals include, but are not limited to, phenylene.

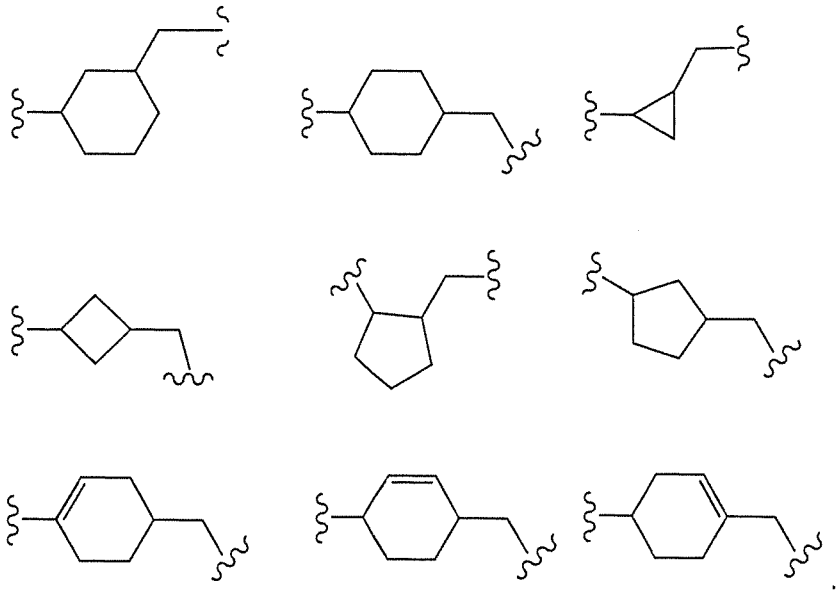
"Arylalkyl" refers to an acyclic alkyl radical in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or sp3 carbon atom, is replaced with an aryl radical. Typical arylalkyl groups include, but are not limited to, benzyl, 2-phenylethan-1-yl, naphthylmethyl, 2-naphthylethan-1-yl, naphthobenzyl, 2-naphthophenylethan-1-yl and the like. The arylalkyl group can comprise 6 to 20 carbon atoms, e.g., the alkyl moiety is 1 to 6 carbon atoms and the aryl moiety is 6 to 14 carbon atoms.

"Cycloalkyl" refers to a saturated or partially unsaturated ring having 3 to 7 carbon atoms as a monocycle, 7 to 12 carbon atoms as a bicycle, and up to about 20 carbon atoms as a polycycle. Monocyclic cycloalkyl groups have 3 to 6 ring atoms, still more typically 5 or 6 ring atoms. Bicyclic cycloalkyl groups have 7 to 12 ring atoms, e.g., arranged as a bicyclo (4,5), (5,5), (5,6) or (6,6) system, or 9 or 10 ring atoms arranged as a bicyclo (5,6) or (6,6) system. Cycloalkyl groups include hydrocarbon mono-, bi-, and poly-cyclic rings, whether fused, bridged, or spiro. Non-limiting examples of monocyclic carbocycles include cyclopropyl, cyclobutyl, cyclopentyl, 1-cyclopent-1-enyl, 1-cyclopent-2-enyl, 1-cyclopent-3-enyl, cyclohexyl, 1-cyclohex-1-enyl, 1-cyclohex-2-enyl, 1-cyclohex-3-enyl, bicyclo[3.1.0]hex-6-yl and the like.

"Cycloalkylene" refers to a cycloalkyl as defined above having two monovalent radical centers derived by the removal of two hydrogen atoms from the same or two different carbon atoms of a parent cycloalkyl. Typical cycloalkylene radicals include, but are not limited to, cyclopropylene, cyclobutylene, cyclopentylene and cyclohexylene.

"Cycloalkylalkyl" refers to an acyclic alkyl radical in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or sp3 carbon atom, is replaced with a cycloalkyl radical as defined above. Typical cycloalkylalkyl groups include, but are not limited to, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, cyclohexenyllmethyl, 2-cyclohexylethan-1-yl, 2-cyclohexenylethan-1-yl, 2-cyclopropylethan-1-yl, 2-cyclopentylethan-1-yl and the like. The cycloalkylalkyl group can comprise 4 to 26 carbon atoms, e.g., the alkyl moiety is 1 to 6 carbon atoms and the cycloalkyl moiety is as defined above.

"Cycloalkylalkylene" refers to a cycloalkylalkyl as defined above having two monovalent radical centers derived by the removal of one hydrodgen atom from the alkyl portion of the cycloalkylalkyl and another hydrogen atom removed from the cycloalkyl portion of the cycloalkylalkyl. Non-limiting examples of cycloalkylalkylene radicals are:



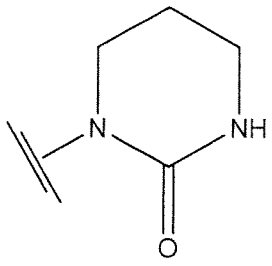
"Halogen" refers to F, Cl, Br, or I.

As used herein the term "haloalkyl" refers to an alkyl group, as defined herein, that is substituted with at least one halogen. Examples of branched or straight chained "haloalkyl" groups as used herein include, but are not limited to, methyl, ethyl, propyl, isopropyl, n-butyl, and t-butyl substituted independently with one or more halogens, for example, fluoro, chloro, bromo, and iodo. The term "haloalkyl" should be interpreted to include such substituents as perfluoroalkyl groups such as $-CF_3$.

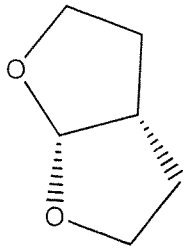
As used herein, the term "haloalkoxy" refers to a group $-OR^a$, where R^a is a haloalkyl group as herein defined. As non-limiting examples, haloalkoxy groups include $-O(CH_2)F$, $-O(CH)F_2$, and $-OCF_3$.

"Heterocycle" or "heterocyclyl" refers to a saturated or partially saturated cyclic group having from 1 to 14 carbon atoms and from 1 to 6 heteroatoms selected from N, S, P, or O, and includes single ring and multiple ring systems including, fused, bridged, and spiro ring systems. "Heterocycle" or "heterocyclyl" as used herein includes by way of example and not limitation those heterocycles described in Paquette, Leo A.; Principles of Modern Heterocyclic Chemistry (W.A. Benjamin, New York, 1968), particularly Chapters 1, 3, 4, 6, 7, and 9; The Chemistry of Heterocyclic Compounds, A Series of Monographs" (John Wiley & Sons, New York, 1950 to present), in particular Volumes 13, 14, 16, 19, and 28; and J. Am. Chem. Soc. (1960) 82:5566. In one embodiment, the carbon, nitrogen, phosphorous, or sulfur atom(s) of the heterocyclic group may be oxidized to provide for C(=O), N-oxide, phosphinane oxide, sulfinyl, or sulfonyl moieties.

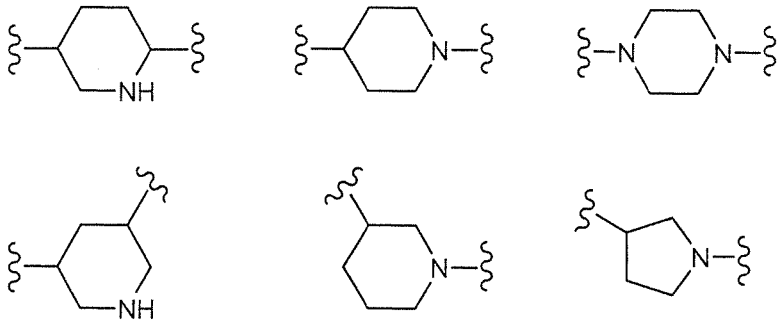
As one example, substituted heterocyclyls include, for example, heterocyclic rings substituted with any of the substituents disclosed herein including oxo groups. A non-limiting example of a carbonyl substituted heterocyclyl is:



Examples of heterocycles include by way of example and not limitation dihydroypyridyl, tetrahydropyridyl (piperidyl), tetrahydrothiophenyl, sulfur oxidized tetrahydrothiophenyl, piperidinyl, 4-piperidonyl, pyrrolidinyl, azetidinyl, 2-pyrrolidonyl, tetrahydrofuranyl, decahydroquinolinyl, octahydroisoquinolinyl, pyranyl, morpholinyl, and bis-tetrahydrofuranyl:



"Heterocyclene" or "heterocyclylene" refers to a "heterocycle" or "heterocyclyl" as defined above having two monovalent radical centers derived by the removal of two hydrogen atoms from the same or two different carbon atoms of a parent heterocycle, the removal of two hydrogen atoms from two nitrogen atoms of a parent heterocycle, or the removal of a hydrogen atom from a nitrogen and the removal of a hydrogen atom from a carbon atome of a parent heterocycle. Non-limiting examples of heterocyclene or heterocyclylenes are:



"Heteroaryl" refers to a monovalent aromatic heterocyclyl having at least one heteroatom in the ring. Thus, "heteroaryl" refers to an aromatic group of from 1 to 14 carbon atoms and 1 to 6 heteroatoms selected from oxygen, nitrogen, sulfur, or phosphorous. For multiple ring systems, by way of example, the term "heteroaryl" includes fused, bridged, and spiro ring systems having aromatic and non-aromatic rings. . In one embodiment, the carbon, nitrogen, or sulfur ring atom(s) of the heteroaryl group may be oxidized to provide for C(=O), N-oxide, sulfinyl, or sulfonyl moieties.

Examples of heteroaryls include by way of example and not limitation pyridyl, thiazolyl, pyrimidinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, tetrazolyl, benzofuranyl, thianaphthalenyl, indolyl, quinolinyl, isoquinolinyl, benzimidazolyl,

tetrahydroquinolinyl, tetrahydroisoquinolinyl, 6H-1,2,5-thiadiazinyl, 2H,6H-1,5,2-dithiazinyl, thienyl, thianthrenyl, isobenzofuranyl, chromenyl, xanthenyl, phenoxathinyl, 2H-pyrrolyl, isothiazolyl, isoxazolyl, pyrazinyl, pyridazinyl, indolizinyl, isoindolyl, 3H-indolyl, 1H-indazoly, purinyl, 4H-quinolizinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, pteridinyl, 4aH-carbazolyl, carbazolyl, ß-carbolinyl, phenanthridinyl, acridinyl, pyrimidinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, furazanyl, phenoxazinyl, isochromanyl, chromanyl, imidazolidinyl, imidazolinyl, pyrazolidinyl, pyrazolinyl, piperazinyl, indolinyl, isoindolinyl, quinuclidinyl, morpholinyl, oxazolidinyl, benzotriazolyl, benzisoxazolyl, oxindolyl, benzoxazolinyl, and isatinoyl. "Heterocyclylene" refers to a heterocyclyl, as defined herein, derived by replacing a hydrogen atom from a carbon atom or heteroatom of a heterocyclyl, with an open valence. Similarly, "heteroarylene" refers to an aromatic heterocyclylene.

"Heterocyclylalkyl" refers to an acyclic alkyl radical in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or sp3 carbon atom, is replaced with a heterocyclyl radical (i.e., a heterocyclyl-alkylene- moiety). Typical heterocyclyl alkyl groups include, but are not limited to heterocyclyl-CH_2-, 2-(heterocyclyl)ethan-1-yl, and the like, wherein the "heterocyclyl" portion includes any of the heterocyclyl groups described above, including those described in Principles of Modern Heterocyclic Chemistry. One skilled in the art will also understand that the heterocyclyl group can be attached to the alkyl portion of the heterocyclyl alkyl by means of a carbon-carbon bond or a carbon-heteroatom bond, with the proviso that the resulting group is chemically stable. The heterocyclylalkyl group comprises 2 to 20 carbon atoms and 1-6 heteroatoms, e.g., the alkyl portion of the heterocyclylalkyl group comprises 1 to 6 carbon atoms and the heterocyclyl moiety comprises 1 to 14 carbon atoms. Examples of heterocyclylalkyls include by way of example and not limitation 5-membered sulfur, oxygen, phosphorus, and/or nitrogen containing heterocycles such as pyrrolidiylmethyl, 2-tetrahydrofuranylylethan-1-yl, and the like, 6-membered sulfur, oxygen, and/or nitrogen containing heterocycles such as piperidinylmethyl, morpholinylmethyl, piperidinylethyl, teterahydropyranylethyl, and the like.

"Heteroarylalkyl" refers to an alkyl group, as defined herein, in which a hydrogen atom has been replaced with a heteroaryl group as defined herein. Non-limiting examples of heteroaryl alkyl include -CH_2-pyridinyl, -CH_2-pyrrolyl, -CH_2-oxazolyl, -CH_2-indolyl, -CH_2-isoindolyl, -CH_2-purinyl, -CH_2-furanyl, -CH_2-thienyl, -CH_2-

benzofuranyl, -CH_2-benzothiophenyl, -CH_2-carbazolyl, -CH_2-imidazolyl, -CH_2-thiazolyl, -CH_2-isoxazolyl, -CH_2-pyrazolyl, -CH_2-isothiazolyl, -CH_2-quinolyl, -CH_2-isoquinolyl, -CH_2-pyridazyl, -CH_2-pyrimidyl, -CH_2-pyrazyl, -$CH(CH_3)$-pyridinyl, -$CH(CH_3)$-pyrrolyl, -$CH(CH_3)$-oxazolyl,

-$CH(CH_3)$-indolyl, -$CH(CH_3)$-isoindolyl, -$CH(CH_3)$-purinyl, -$CH(CH_3)$-furanyl, -$CH(CH_3)$-thienyl, -$CH(CH_3)$-benzofuranyl, -$CH(CH_3)$-benzothiophenyl, -$CH(CH_3)$-carbazolyl,

-$CH(CH_3)$-imidazolyl, -$CH(CH_3)$-thiazolyl, -$CH(CH_3)$-isoxazolyl, -$CH(CH_3)$-pyrazolyl, -$CH(CH_3)$-isothiazolyl, -$CH(CH_3)$-quinolyl, -$CH(CH_3)$-isoquinolyl, -$CH(CH_3)$-pyridazyl, -$CH(CH_3)$-pyrimidyl, -$CH(CH_3)$-pyrazyl, and the like.

The term "heterocyclyloxy" represents a heterocyclyl group attached to the adjacent atom by an oxygen.

When there is a sulfur atom present, the sulfur atom can be at different oxidation levels, namely, S, SO, SO_2, or SO_3. All such oxidation levels are within the scope of the present invention.

When there is a phosphorous atom present, the phosphorous atom can be at different oxidation levels, namely, $POR^aR^bR^c$, $PO_2R^aR^b$, or $PO_3R^aR^b$, where R^a, R^b, and R^c each independently is chosen from H, $C_{1\text{-}12}$ alkyl, $C_{2\text{-}12}$ alkenyl, $C_{2\text{-}12}$ alkynyl, $C_{6\text{-}14}$ aryl, 3-12 membered heterocycle, 3-18 membered heteroarylalkyl, $C_{6\text{-}18}$ arylalkyl; or two taken together (with or without oxygens) form a 5 to 10 membered heterocycle. All such oxidation levels are within the scope of the present invention

The term "optionally substituted" in reference to a particular moiety of the compound of the Formulae of the invention, for example an "optionally substituted aryl group", refers to a moiety having none, one, or more substituents.

The term "substituted" in reference to alkyl, alkylene, aryl, arylalkyl, alkoxy, heterocyclyl, heteroaryl, carbocyclyl, etc. , for example, "substituted alkyl", "substituted alkylene", "substituted aryl", "substituted arylalkyl", "substituted heterocyclyl", and "substituted carbocyclyl" means alkyl, alkylene, aryl, arylalkyl, heterocyclyl, carbocyclyl respectively, in which one or more hydrogen atoms are each independently replaced with a non-hydrogen substituent. Divalent groups may also be similarly substituted. Unless otherwise indicated, typical substituents include, but are not limited to, -X, -R^b, -O^-, =O, -OR^b, -SR^b, -S^-, -NR^b_2, -$N^+R^b_3$, =NR^b, -CX_3, -CN, -OCN, -SCN, -N=C=O, -NCS, -NO, -NO_2, =N_2, -N_3, -$NHC(=O)R^b$, -$OC(=O)R^b$, -$NHC(=O)NR^b_2$, -$S(=O)_2$-, -$S(=O)_2OH$, -$S(=O)_2R^b$, -

$OS(=O)_2OR^b$, $-S(=O)_2NR^b{}_2$, $-S(=O)R^b$, $-OP(=O)(OR^b)_2$, $-P(=O)(OR^b)_2$, $-P(=O)(O^-)_2$, $-P(=O)(OH)_2$, $-P(O)(OR^b)(O^-)$, $-C(=O)R^b$, -C(=O)X, $-C(S)R^b$, $-C(O)OR^b$, $-C(O)O^-$, $-C(S)OR^b$, $-C(O)SR^b$, $-C(S)SR^b$, $-C(O)NR^b{}_2$, $-C(S)NR^b{}_2$, $-C(=NR^b)NR^b{}_2$, where each X is independently a halogen: F, Cl, Br, or I; and each R^b is independently H, alkyl, aryl, arylalkyl, a heterocycle, or a protecting group or prodrug moiety. Alkylene, alkenylene, and alkynylene groups may also be similarly substituted. Unless otherwise indicated, when the term "substituted" is used in conjunction with groups such as arylalkyl, which have two or more moieties capable of substitution, the substituents can be attached to the aryl moiety, the alkyl moiety, or both.

Those skilled in the art will recognize that when moieties such as “alkyl”, “aryl”, “heterocyclyl”, etc. are substituted with one or more substituents, they could alternatively be referred to as “alkylene”, “arylene”, “heterocyclylene”, etc. moieties (i.e., indicating that at least one of the hydrogen atoms of the parent “alkyl”, “aryl”, “heterocyclyl” moieties has been replaced with the indicated substituent(s)). When moieties such as “alkyl”, “aryl”, “heterocyclyl”, etc. are referred to herein as “substituted” or are shown diagrammatically to be substituted (or optionally substituted, e.g., when the number of substituents ranges from zero to a positive integer), then the terms “alkyl”, “aryl”, “heterocyclyl”, etc. are understood to be interchangeable with “alkylene”, “arylene”, “heterocyclylene”, etc.

As will be appreciated by those skilled in the art, the compounds of the present invention may exist in solvated or hydrated form. The scope of the present invention includes such forms. Again, as will be appreciated by those skilled in the art, the compounds may be capable of esterification. The scope of the present invention includes esters and other physiologically functional derivatives. The scope of the present invention includes prodrug forms of the compound herein described.

“Ester” means any ester of a compound in which any of the --COOH functions of the molecule is replaced by a –C(O)OR function, or in which any of the –OH functions of the molecule are replaced with a –OC(O)R function, in which the R moiety of the ester is any carbon-containing group which forms a stable ester moiety, including but not limited to alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclyl, heterocyclylalkyl and substituted derivatives thereof.

The term “prodrug” as used herein refers to any compound that when administered to a biological system generates the drug substance, i.e., active ingredient, as a result of spontaneous chemical reaction(s), enzyme catalyzed chemical reaction(s),

photolysis, and/or metabolic chemical reaction(s). A prodrug is thus a covalently modified analog or latent form of a therapeutically active compound. Example of prodrugs include ester moieties, quaternary ammonium moieties, glycol moieties, and the like.

One skilled in the art will recognize that substituents and other moieties of the compounds of Formula I-III should be selected in order to provide a compound which is sufficiently stable to provide a pharmaceutically useful compound which can be formulated into an acceptably stable pharmaceutical composition. Compounds of Formula I which have such stability are contemplated as falling within the scope of the present invention.

As will be appreciated by those skilled in the art, the compounds of the present invention may contain one or more chiral centers. The scope of the present invention includes such forms. Again, as will be appreciated by those skilled in the art, the compound is capable of esterification. The scope of the present invention includes esters and other physiologically functional derivatives. In addition, the scope of the present invention includes prodrug forms of the compound herein described.

A compound of Formula I-III and its pharmaceutically acceptable salts may exist as different polymorphs or pseudopolymorphs. As used herein, crystalline polymorphism means the ability of a crystalline compound to exist in different crystal structures. Polymorphism generally can occur as a response to changes in temperature, pressure, or both. Polymorphism can also result from variations in the crystallization process. Polymorphs can be distinguished by various physical characteristics known in the art such as x-ray diffraction patterns, solubility, and melting point. The crystalline polymorphism may result from differences in crystal packing (packing polymorphism) or differences in packing between different conformers of the same molecule (conformational polymorphism). As used herein, crystalline pseudopolymorphism means the ability of a hydrate or solvate of a compound to exist in different crystal structures. The pseudopolymorphs of the instant invention may exist due to differences in crystal packing (packing pseudopolymorphism) or due to differences in packing between different conformers of the same molecule (conformational pseudopolymorphism). The instant invention comprises all polymorphs and pseudopolymorphs of the compounds of Formula I-II and their pharmaceutically acceptable salts.

A compound of Formula I-III and its pharmaceutically acceptable salts may also exist as an amorphous solid. As used herein, an amorphous solid is a solid in which there is no long-range order of the positions of the atoms in the solid. This definition applies as well when the crystal size is two nanometers or less. Additives, including solvents, may be used to create the amorphous forms of the instant invention. The instant invention comprises all amorphous forms of the compounds of Formula I-II and their pharmaceutically acceptable salts.

Certain of the compounds described herein contain one or more chiral centers, or may otherwise be capable of existing as multiple stereoisomers. The scope of the present invention includes mixtures of stereoisomers as well as purified enantiomers or enantiomerically/diastereomerically enriched mixtures. Also included within the scope of the invention are the individual isomers of the compounds represented by the formulae of the present invention, as well as any wholly or partially equilibrated mixtures thereof. The present invention also includes the individual isomers of the compounds represented by the formulas above as mixtures with isomers thereof in which one or more chiral centers are inverted.

The term "chiral" refers to molecules which have the property of non-superimposability of the mirror image partner, while the term "achiral" refers to molecules which are superimposable on their mirror image partner.

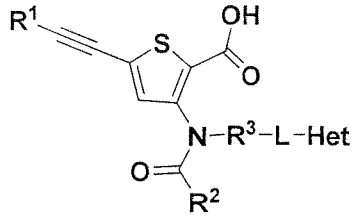
The term "stereoisomers" refers to compounds which have identical chemical constitution, but differ with regard to the arrangement of the atoms or groups in space.

"Diastereomer" refers to a stereoisomer with two or more centers of chirality and whose molecules are not mirror images of one another. Diastereomers have different physical properties, e.g., melting points, boiling points, spectral properties, and reactivities. Mixtures of diastereomers may separate under high resolution analytical procedures such as electrophoresis and chromatography.

"Enantiomers" refer to stereoisomers of a compound which are non-superimposable mirror images of one another.

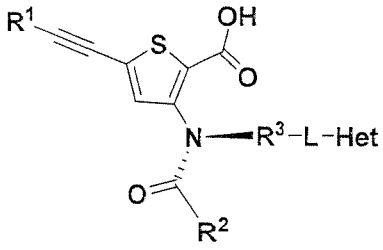
"Atropisomers" refer to stereoisomers of a compound resulting from hindered rotation about single bonds where the steric strain barrier to rotation is high enough to allow for the isolation of the individual conformer. Atropisomers display axial chirality. Atropisomers may be equilibrated thermally and the interconversion barrier may be measured kinetically. Atropisomerism may occur apart from the presence of

other forms of chiral isomerism. Thus, as illustrated, the depicted nitrogen atom is planar and compounds of Formula I are capable of existing as atropisomers:



(I).

In one embodiment of the present invention, the compounds exist in a conformeric form of Formula Ia:



(Ia).

Stereochemical definitions and conventions used herein generally follow S. P. Parker, Ed., McGraw-Hill Dictionary of Chemical Terms (1984) McGraw-Hill Book Company, New York; and Eliel, E. and Wilen, S., Stereochemistry of Organic Compounds (1994) John Wiley & Sons, Inc., New York.

Many organic compounds exist in optically active forms, i.e., they have the ability to rotate the plane of plane-polarized light. In describing an optically active compound, the prefixes D and L or R and S are used to denote the absolute configuration of the molecule about its chiral center(s). The prefixes d and l or (+) and (-) are employed to designate the sign of rotation of plane-polarized light by the compound, with (-) or 1 meaning that the compound is levorotatory. A compound prefixed with (+) or d is dextrorotatory.

A specific stereoisomer may also be referred to as an enantiomer, and a mixture of such isomers is often called an enantiomeric mixture. A 50:50 mixture of enantiomers is referred to as a racemic mixture or a racemate, which may occur where there has been no stereoselection or stereospecificity in a chemical reaction or process. The terms "racemic mixture" and "racemate" refer to an equimolar mixture of two enantiomeric species, devoid of optical activity.

The present invention includes a salt or solvate of the compounds herein described, including combinations thereof such as a solvate of a salt. The compounds of the present invention may exist in solvated, for example hydrated, as

well as unsolvated forms, and the present invention encompasses all such forms.

Typically, but not absolutely, the salts of the present invention are pharmaceutically acceptable salts. Salts encompassed within the term "pharmaceutically acceptable salts" refer to non-toxic salts of the compounds of this invention.

Examples of suitable pharmaceutically acceptable salts include inorganic acid addition salts such as chloride, bromide, sulfate, phosphate, and nitrate; organic acid addition salts such as acetate, galactarate, propionate, succinate, lactate, glycolate, malate, tartrate, citrate, maleate, fumarate, methanesulfonate, p-toluenesulfonate, and ascorbate; salts with acidic amino acid such as aspartate and glutamate; alkali metal salts such as sodium salt and potassium salt; alkaline earth metal salts such as magnesium salt and calcium salt; ammonium salt; organic basic salts such as trimethylamine salt, triethylamine salt, pyridine salt, picoline salt, dicyclohexylamine salt, and N,N'-dibenzylethylenediamine salt; and salts with basic amino acid such as lysine salt and arginine salt. The salts may be in some cases hydrates or ethanol solvates.

The modifier "about" used in connection with a quantity is inclusive of the stated value and has the meaning dictated by the context (e.g., includes the degree of error associated with measurement of the particular quantity).

Whenever a compound described herein is substituted with more than one of the same designated group, e.g., "R" or "R^1", then it will be understood that the groups may be the same or different, i.e., each group is independently selected. Wavy lines,



indicate the site of covalent bond attachments to the adjoining substructures, groups, moieties, or atoms.

The compounds of the invention can also exist as tautomeric isomers in certain cases. Although only one delocalized resonance structure may be depicted, all such forms are contemplated within the scope of the invention. For example, ene-amine tautomers can exist for purine, pyrimidine, imidazole, guanidine, amidine, and tetrazole systems and all their possible tautomeric forms are within the scope of the invention.

Selected substituents comprising the compounds of Formula I-III may be

present to a recursive degree. In this context, "recursive substituent" means that a substituent may recite another instance of itself. The multiple recitations may be direct or indirect through a sequence of other substituents. Because of the recursive nature of such substituents, theoretically, a large number of compounds may be present in any given embodiment. One of ordinary skill in the art of medicinal chemistry understands that the total number of such substituents is reasonably limited by the desired properties of the compound intended. Such properties include, by way of example and not limitation, physical properties such as molecular weight, solubility or log P, application properties such as activity against the intended target, and practical properties such as ease of synthesis. Recursive substituents may be an intended aspect of the invention. One of ordinary skill in the art of medicinal chemistry understands the versatility of such substituents. To the degree that recursive substituents are present in an embodiment of the invention, they may recite another instance of themselves, 0, 1, 2, 3, or 4 times.

The compounds of Formula I-III also include molecules that incorporate isotopes of the atoms specified in the particular molecules. Non-limiting examples of these isotopes include D, T, ^{14}C, ^{13}C, ^{18}O and ^{15}N.

Protecting Groups

In the context of the present invention, protecting groups include prodrug moieties and chemical protecting groups.

Protecting groups are available, commonly known and used, and are optionally used to prevent side reactions with the protected group during synthetic procedures, i.e. routes or methods to prepare the compounds of the invention. For the most part the decision as to which groups to protect, when to do so, and the nature of the chemical protecting group "PG" will be dependent upon the chemistry of the reaction to be protected against (e.g., acidic, basic, oxidative, reductive or other conditions) and the intended direction of the synthesis. The PG groups do not need to be, and generally are not, the same if the compound is substituted with multiple PG. In general, PG will be used to protect functional groups such as carboxyl, hydroxyl, thio, or amino groups and to thus prevent side reactions or to otherwise facilitate the synthetic efficiency. The order of deprotection to yield free, deprotected groups is dependent upon the intended direction of the synthesis and the reaction conditions to be encountered, and may occur in any order as determined by the

artisan.

Various functional groups of the compounds of the invention may be protected. For example, protecting groups for -OH groups (whether hydroxyl, carboxylic acid, phosphonic acid, or other functions) include "ether- or ester-forming groups". Ether- or ester-forming groups are capable of functioning as chemical protecting groups in the synthetic schemes set forth herein. However, some hydroxyl and thio protecting groups are neither ether- nor ester-forming groups, as will be understood by those skilled in the art, and are included with amides, discussed below.

A very large number of hydroxyl protecting groups and amide-forming groups and corresponding chemical cleavage reactions are described in Protective Groups in Organic Synthesis, Theodora W. Greene and Peter G. M. Wuts (John Wiley & Sons, Inc., New York, 1999, ISBN 0-471-16019-9) ("Greene"). See also Kocienski, Philip J.; Protecting Groups (Georg Thieme Verlag Stuttgart, New York, 1994), which is incorporated by reference in its entirety herein. In particular Chapter 1, Protecting Groups: An Overview, pages 1-20, Chapter 2, Hydroxyl Protecting Groups, pages 21-94, Chapter 3, Diol Protecting Groups, pages 95-117, Chapter 4, Carboxyl Protecting Groups, pages 118-154, Chapter 5, Carbonyl Protecting Groups, pages 155-184. For protecting groups for carboxylic acid, phosphonic acid, phosphonate, sulfonic acid and other protecting groups for acids see Greene as set forth below. Such groups include by way of example and not limitation, esters, amides, hydrazides, and the like.

Ether- and Ester-forming protecting groups

Ester-forming groups include: (1) phosphonate ester-forming groups, such as phosphonamidate esters, phosphorothioate esters, phosphonate esters, and phosphon-bis-amidates; (2) carboxyl ester-forming groups, and (3) sulphur ester-forming groups, such as sulphonate, sulfate, and sulfinate.

Metabolites of the Compounds of the Invention

Also falling within the scope of this invention are the in vivo metabolic products of the compounds described herein. Such products may result for example from the oxidation, reduction, hydrolysis, amidation, esterification and the like of the administered compound, primarily due to enzymatic processes. Accordingly, the invention includes compounds produced by a process comprising contacting a

compound of this invention with a mammal for a period of time sufficient to yield a metabolic product thereof. Such products typically are identified by preparing a radiolabelled (e.g., C^{14} or H^3) compound of the invention, administering it parenterally in a detectable dose (e.g., greater than about 0.5 mg/kg) to an animal such as rat, mouse, guinea pig, monkey, or to man, allowing sufficient time for metabolism to occur (typically about 30 seconds to 30 hours) and isolating its conversion products from the urine, blood or other biological samples. These products are easily isolated since they are labeled (others are isolated by the use of antibodies capable of binding epitopes surviving in the metabolite). The metabolite structures are determined in conventional fashion, e.g., by MS or NMR analysis. In general, analysis of metabolites is done in the same way as conventional drug metabolism studies well-known to those skilled in the art. The conversion products, so long as they are not otherwise found in vivo, are useful in diagnostic assays for therapeutic dosing of the compounds of the invention even if they possess no anti-infective activity of their own.

The definitions and substituents for various genus and subgenus of the present compounds are described and illustrated herein. It should be understood by one skilled in the art that any combination of the definitions and substituents described above should not result in an inoperable species or compound. "Inoperable species or compounds" means compound structures that violates relevant scientific principles (such as, for example, a carbon atom connecting to more than four covalent bonds) or compounds too unstable to permit isolation and formulation into pharmaceutically acceptable dosage forms.

Pharmaceutical Formulations

The compounds of this invention are formulated with conventional carriers and excipients, which will be selected in accord with ordinary practice. Tablets will contain excipients, glidants, fillers, binders and the like. Aqueous formulations are prepared in sterile form, and when intended for delivery by other than oral administration generally will be isotonic. All formulations will optionally contain excipients such as those set forth in the Handbook of Pharmaceutical Excipients (1986), herein incorporated by reference in its entirety. Excipients include ascorbic acid and other antioxidants, chelating agents such as EDTA, carbohydrates such as dextrin, hydroxyalkylcellulose, hydroxyalkylmethylcellulose, stearic acid and the like.

The pH of the formulations ranges from about 3 to about 11, but is ordinarily about 7 to 10.

While it is possible for the active ingredients to be administered alone it may be preferable to present them as pharmaceutical formulations. The formulations of the invention, both for veterinary and for human use, comprise at least one active ingredient, together with one or more acceptable carriers and optionally other therapeutic ingredients. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and physiologically innocuous to the recipient thereof.

The formulations include those suitable for the foregoing administration routes. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. Techniques and formulations generally are found in Remington's Pharmaceutical Sciences (Mack Publishing Co., Easton, Pa.), herein incorporated by reference in its entirety. Such methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more accessory ingredients. In general the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be administered as a bolus, electuary or paste.

A tablet is made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, preservative, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered active ingredient moistened with an inert liquid diluent. The tablets may optionally be coated or scored and optionally are formulated so as to provide slow or controlled release of the active ingredient.

For administration to the eye or other external tissues e.g., mouth and skin, the formulations are preferably applied as a topical ointment or cream containing the active ingredient(s) in an amount of, for example, 0.075 to 20% w/w (including active ingredient(s) in a range between 0.1% and 20% in increments of 0.1% w/w such as 0.6% w/w, 0.7% w/w, etc.), preferably 0.2 to 15% w/w and most preferably 0.5 to 10% w/w. When formulated in an ointment, the active ingredients may be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredients may be formulated in a cream with an oil-in-water cream base.

If desired, the aqueous phase of the cream base may include, for example, at least 30% w/w of a polyhydric alcohol, i.e. an alcohol having two or more hydroxyl groups such as propylene glycol, butane 1,3-diol, mannitol, sorbitol, glycerol and polyethylene glycol (including PEG 400) and mixtures thereof. The topical formulations may desirably include a compound which enhances absorption or penetration of the active ingredient through the skin or other affected areas. Examples of such dermal penetration enhancers include dimethyl sulphoxide and related analogs.

The oily phase of the emulsions of this invention may be constituted from known ingredients in a known manner. While the phase may comprise merely an emulsifier (otherwise known as an emulgent), it desirably comprises a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil. Preferably, a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stabilizer. It is also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabilizer(s) make up the so-called emulsifying wax, and the wax together with the oil and fat make up the so-called emulsifying ointment base which forms the oily dispersed phase of the cream formulations.

Emulgents and emulsion stabilizers suitable for use in the formulation of the invention include Tween® 60, Span® 80, cetostearyl alcohol, benzyl alcohol, myristyl alcohol, glyceryl mono-stearate and sodium lauryl sulfate.

The choice of suitable oils or fats for the formulation is based on achieving the desired cosmetic properties. The cream should preferably be a non-greasy, non-staining and washable product with suitable consistency to avoid leakage from tubes or other containers. Straight or branched chain, mono- or dibasic alkyl esters such as di-isoadipate, isocetyl stearate, propylene glycol diester of coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-ethylhexyl

palmitate or a blend of branched chain esters known as Crodamol CAP may be used, the last three being preferred esters. These may be used alone or in combination depending on the properties required. Alternatively, high melting point lipids such as white soft paraffin and/or liquid paraffin or other mineral oils are used.

Pharmaceutical formulations according to the present invention comprise one or more compounds of the invention together with one or more pharmaceutically acceptable carriers or excipients and optionally other therapeutic agents. Pharmaceutical formulations containing the active ingredient may be in any form suitable for the intended method of administration. When used for oral use for example, tablets, troches, lozenges, aqueous or oil suspensions, dispersible powders or granules, emulsions, hard or soft capsules, syrups or elixirs may be prepared. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents including sweetening agents, flavoring agents, coloring agents and preserving agents, in order to provide a palatable preparation. Tablets containing the active ingredient in admixture with non-toxic pharmaceutically acceptable excipient which are suitable for manufacture of tablets are acceptable. These excipients may be, for example, inert diluents, such as calcium or sodium carbonate, lactose, lactose monohydrate, croscarmellose sodium, povidone, calcium or sodium phosphate; granulating and disintegrating agents, such as maize starch, or alginic acid; binding agents, such as cellulose, microcrystalline cellulose, starch, gelatin or acacia; and lubricating agents, such as magnesium stearate, stearic acid or talc. Tablets may be uncoated or may be coated by known techniques including microencapsulation to delay disintegration and adsorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate alone or with a wax may be employed.

Formulations for oral use may be also presented as hard gelatin capsules where the active ingredient is mixed with an inert solid diluent, for example calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, such as peanut oil, liquid paraffin or olive oil.

Aqueous suspensions of the invention contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients include a suspending agent, such as sodium carboxymethylcellulose,

methylcellulose, hydroxypropyl methylcelluose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia, and dispersing or wetting agents such as a naturally occurring phosphatide (e.g., lecithin), a condensation product of an alkylene oxide with a fatty acid (e.g., polyoxyethylene stearate), a condensation product of ethylene oxide with a long chain aliphatic alcohol (e.g., heptadecaethyleneoxycetanol), a condensation product of ethylene oxide with a partial ester derived from a fatty acid and a hexitol anhydride (e.g., polyoxyethylene sorbitan monooleate). The aqueous suspension may also contain one or more preservatives such as ethyl or n-propyl p-hydroxy-benzoate, one or more coloring agents, one or more flavoring agents and one or more sweetening agents, such as sucrose or saccharin.

Oil suspensions may be formulated by suspending the active ingredient in a vegetable oil, such as arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oral suspensions may contain a thickening agent, such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents, such as those set forth herein, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an antioxidant such as ascorbic acid.

Dispersible powders and granules of the invention suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, a suspending agent, and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those disclosed above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, such as olive oil or arachis oil, a mineral oil, such as liquid paraffin, or a mixture of these. Suitable emulsifying agents include naturally-occurring gums, such as gum acacia and gum tragacanth, naturally occurring phosphatides, such as soybean lecithin, esters or partial esters derived from fatty acids and hexitol anhydrides, such as sorbitan monooleate, and condensation products of these partial esters with ethylene oxide, such as polyoxyethylene sorbitan monooleate. The emulsion may also contain sweetening and flavoring agents. Syrups and elixirs may be formulated with

sweetening agents, such as glycerol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative, a flavoring or a coloring agent.

The pharmaceutical compositions of the invention may be in the form of a sterile injectable preparation, such as a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned herein. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, such as a solution in 1,3-butane-diol or prepared as a lyophilized powder. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile fixed oils may conventionally be employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid may likewise be used in the preparation of injectables.

The amount of active ingredient that may be combined with the carrier material to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a time-release formulation intended for oral administration to humans may contain approximately 1 to 1000 mg of active material compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95% of the total compositions (weight:weight). The pharmaceutical composition can be prepared to provide easily measurable amounts for administration. For example, an aqueous solution intended for intravenous infusion may contain from about 3 to 500 µg of the active ingredient per milliliter of solution in order that infusion of a suitable volume at a rate of about 30 mL/hr can occur.

Formulations suitable for administration to the eye include eye drops wherein the active ingredient is dissolved or suspended in a suitable carrier, especially an aqueous solvent for the active ingredient. The active ingredient is preferably present in such formulations in a concentration of 0.5 to 20%, advantageously 0.5 to 10% particularly about 1.5% w/w.

Formulations suitable for topical administration in the mouth include lozenges comprising the active ingredient in a flavored basis, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert basis such as gelatin

and glycerin, or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Formulations for rectal administration may be presented as a suppository with a suitable base comprising for example cocoa butter or a salicylate.

Formulations suitable for intrapulmonary or nasal administration have a particle size for example in the range of 0.1 to 500 μm (including particle sizes in a range between 0.1 and 500 μm in increments such as 0.5 μm, 1 μm, 30 μm, 35 μm, etc.), which is administered by rapid inhalation through the nasal passage or by inhalation through the mouth so as to reach the alveolar sacs. Suitable formulations include aqueous or oily solutions of the active ingredient. Formulations suitable for aerosol or dry powder administration may be prepared according to conventional methods and may be delivered with other therapeutic agents such as compounds heretofore used in the treatment or prophylaxis of infections as described herein.

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

Formulations suitable for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents.

The formulations are presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injection, immediately prior to use. Extemporaneous injection solutions and suspensions are prepared from sterile powders, granules and tablets of the kind previously described. Preferred unit dosage formulations are those containing a daily dose or unit daily sub-dose, as herein above recited, or an appropriate fraction thereof, of the active ingredient.

It should be understood that in addition to the ingredients particularly mentioned above the formulations of this invention may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavoring agents.

Compounds of the invention can also be formulated to provide controlled release of the active ingredient to allow less frequent dosing or to improve the pharmacokinetic or toxicity profile of the active ingredient. Accordingly, the invention also provided compositions comprising one or more compounds of the invention formulated for sustained or controlled release.

The effective dose of an active ingredient depends at least on the nature of the condition being treated, toxicity, whether the compound is being used prophylactically (lower doses) or against an active viral infection, the method of delivery, and the pharmaceutical formulation, and will be determined by the clinician using conventional dose escalation studies. The effective dose can be expected to be from about 0.0001 to about 100 mg/kg body weight per day; typically, from about 0.01 to about 10 mg/kg body weight per day; more typically, from about .01 to about 5 mg/kg body weight per day; most typically, from about .05 to about 0.5 mg/kg body weight per day. For example, the daily candidate dose for an adult human of approximately 70 kg body weight will range from 1 mg to 1000 mg, preferably between 5 mg and 500 mg, and may take the form of single or multiple doses.

In yet another embodiment, the present application discloses pharmaceutical compositions comprising a compound of Formula I or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or exipient.

Routes of Administration

One or more compounds of the invention (herein referred to as the active ingredients) are administered by any route appropriate to the condition to be treated. Suitable routes include oral, rectal, nasal, topical (including buccal and sublingual), vaginal and parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal and epidural), and the like. It will be appreciated that the preferred route may vary with for example the condition of the recipient. An advantage of the compounds of this invention is that they are orally bioavailable and can be dosed orally.

Combination Therapy, Including HCV Combination Therapy

In another embodiment, the compounds of the present invention may be combined with one or more active agents. Non-limiting examples of suitable combinations include combinations of one or more compounds of the present

invention with one or more 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, 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.

More specifically, one or more compounds of the present invention may be combined with one or more compounds selected from the group consisting of

1) interferons, *e.g.*, pegylated rIFN-alpha 2b (PEG-Intron), pegylated rIFN-alpha 2a (Pegasys), rIFN-alpha 2b (Intron A), rIFN-alpha 2a (Roferon-A), interferon alpha (MOR-22, OPC-18, Alfaferone, Alfanative, Multiferon, subalin), interferon alfacon-1 (Infergen), interferon alpha-n1 (Wellferon), interferon alpha-n3 (Alferon), interferon-beta (Avonex, DL-8234), interferon-omega (omega DUROS, Biomed 510), albinterferon alpha-2b (Albuferon), IFN alpha XL, BLX-883 (Locteron), DA-3021, glycosylated interferon alpha-2b (AVI-005), PEG-Infergen, PEGylated interferon lambda (PEGylated IL-29), and belerofon,

2) ribavirin and its analogs, *e.g.*, ribavirin (Rebetol, Copegus), and taribavirin (Viramidine),

3) HCV NS3 protease inhibitors, *e.g.*, boceprevir (SCH-503034 , SCH-7), telaprevir (VX-950), VX-813, TMC-435 (TMC435350), ABT-450, BI-201335, BI-1230, MK-7009, SCH-900518, VBY-376, VX-500, GS-9256, GS-9451, BMS-790052, BMS-605339, PHX-1766, AS-101, YH-5258, YH5530, YH5531, and ITMN-191 (R-7227),

4) alpha-glucosidase 1 inhibitors, *e.g.*, celgosivir (MX-3253), Miglitol, and UT-231B,

5) hepatoprotectants, *e.g.*, emericasan (IDN-6556), ME-3738, GS-9450 (LB-84451), silibilin, and MitoQ,

6) nucleoside or nucleotide inhibitors of HCV NS5B polymerase, *e.g.*, R1626, R7128 (R4048), IDX184, IDX-102, PSI-7851, BCX-4678, valopicitabine (NM-283), and MK-0608,

7) non-nucleoside inhibitors of HCV NS5B polymerase, *e.g.*, filibuvir (PF-868554), ABT-333, ABT-072, BI-207127, VCH-759, VCH-916, JTK-652, MK-3281, VBY-708, VCH-222, A848837, ANA-598, GL60667, GL59728, A-63890, A-48773, A-

48547, BC-2329, VCH-796 (nesbuvir), GSK625433, BILN-1941, XTL-2125, and GS-9190,

8) HCV NS5A inhibitors, *e.g.*, AZD-2836 (A-831), AZD-7295 (A-689), and BMS-790052,

9) TLR-7 agonists, *e.g.*, imiquimod, 852A, GS-9524, ANA-773, ANA-975, AZD-8848 (DSP-3025), PF-04878691, and SM-360320,

10) cyclophillin inhibitors, *e.g.*, DEBIO-025, SCY-635, and NIM811,

11) HCV IRES inhibitors, *e.g.*, MCI-067,

12) pharmacokinetic enhancers, *e.g.*, BAS-100, SPI-452, PF-4194477, TMC-41629, GS-9350, GS-9585, and roxythromycin,

13) other drugs for treating HCV, *e.g.*, thymosin alpha 1 (Zadaxin), nitazoxanide (Alinea, NTZ), BIVN-401 (virostat), PYN-17 (altirex), KPE02003002, actilon (CPG-10101), GS-9525, KRN-7000, civacir, GI-5005, XTL-6865, BIT225, PTX-111, ITX2865, TT-033i, ANA 971, NOV-205, tarvacin, EHC-18, VGX-410C, EMZ-702, AVI 4065, BMS-650032, BMS-791325, Bavituximab, MDX-1106 (ONO-4538), Oglufanide, FK-788, and VX-497 (merimepodib).

14) mevalonate decarboxylase antagonists, e.g., statins, HMGCoA synthase inhibitors (e.g., hymeglusin), squalene synthesis inhibitors (e.g., zaragozic acid);

15) angiotensin II receptor antagonists, e.g., losartan, irbesartan, olmesartan, candesartan, valsartan, telmisartan, eprosartan;

16) angiotensin-converting enzyme inhibitors, e.g., captopril, zofenopril, enalapril, ramipril, quinapril, perindopril, lisinopril, benazepril, fosinopril;

17) other anti-fibrotic agents, e.g., amiloride and

18) endothelin antagonists, e.g. bosentan and ambrisentan.

In yet another embodiment, the present application discloses pharmaceutical compositions comprising a compound of the present invention, or a pharmaceutically acceptable salt thereof, in combination with at least one additional active agent, and a pharmaceutically acceptable carrier or excipient. In yet another embodiment, the present application provides a combination pharmaceutical agent with two or more therapeutic agents in a unitary dosage form. Thus, it is also possible to combine any compound of the invention with one or more other active agents in a unitary dosage form.

The combination therapy may be administered as a simultaneous or sequential regimen. When administered sequentially, the combination may be administered in two or more administrations.

Co-administration of a compound of the invention with one or more other active agents generally refers to simultaneous or sequential administration of a compound of the invention and one or more other active agents, such that therapeutically effective amounts of the compound of the invention and one or more other active agents are both present in the body of the patient.

Co-administration includes administration of unit dosages of the compounds of the invention before or after administration of unit dosages of one or more other active agents, for example, administration of the compounds of the invention within seconds, minutes, or hours of the administration of one or more other active agents. For example, a unit dose of a compound of the invention can be administered first, followed within seconds or minutes by administration of a unit dose of one or more other active agents. Alternatively, a unit dose of one or more other active agents can be administered first, followed by administration of a unit dose of a compound of the invention within seconds or minutes. In some cases, it may be desirable to administer a unit dose of a compound of the invention first, followed, after a period of hours (e.g., 1-12 hours), by administration of a unit dose of one or more other active agents. In other cases, it may be desirable to administer a unit dose of one or more other active agents first, followed, after a period of hours (e.g., 1-12 hours), by administration of a unit dose of a compound of the invention.

The combination therapy may provide "synergy" and "synergistic effect", i.e. the effect achieved when the active ingredients used together is greater than the sum of the effects that results from using the compounds separately. A synergistic effect may be attained when the active ingredients are: (1) co-formulated and administered or delivered simultaneously in a combined formulation; (2) delivered by alternation or in parallel as separate formulations; or (3) by some other regimen. When delivered in alternation therapy, a synergistic effect may be attained when the compounds are administered or delivered sequentially, e.g., in separate tablets, pills or capsules, or by different injections in separate syringes. In general, during alternation therapy, an effective dosage of each active ingredient is administered sequentially, i.e. serially, whereas in combination therapy, effective dosages of two or more active ingredients are administered together.

In still yet another embodiment, the present application provides for methods of treating HCV in a patient, comprising: administering to the patient a therapeutically effective amount of a compound of Formula I-III, or a pharmaceutically acceptable salt, solvate, and/or ester thereof. In a preferred aspect of this embodiment, the compound of Formula I-III is, at least, 70% a single diastereomer, 80% a single diastereomer, 90% a single diastereomer or most preferably 95% a single diastereomer.

In still yet another embodiment, the present application provides for methods of treating HCV in a patient, comprising: administering to the patient a therapeutically effective amount of a compound of Formula I-III, or a pharmaceutically acceptable salt, solvate, and/or ester thereof, and at least one additional active therapeutic agent. In a preferred aspect of this embodiment, the compound of Formula I-III is, at least, 70% a single diastereomer, 80% a single diastereomer, 90% a single diastereomer or most preferably 95% a single diastereomer.

In still yet another embodiment, the present application provides for methods of treating HCV in a patient, comprising: administering to the patient a therapeutically effective amount of a compound of Formula I-III, or a pharmaceutically acceptable salt, solvate, and/or ester thereof, and at least one additional active therapeutic agent selected from the group consisting of one or more compounds of the present invention with one or more 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, 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. In a preferred aspect of this embodiment, the compound of Formula I-III is, at least, 70% a single diastereomer, 80% a single diastereomer, 90% a single diastereomer or most preferably 95% a single diastereomer.

In still yet another embodiment, the present application provides for the use of a compound of Formula I-III, or a pharmaceutically acceptable salt, solvate, and/or ester thereof, for the preparation of a medicament for treating an HCV infection in a patient. In a preferred aspect of this embodiment, the compound of Formula I-III is,

at least, 70% a single diastereomer, 80% a single diastereomer, 90% a single diastereomer or most preferably 95% a single diastereomer.

In still yet another embodiment, the present application provides for the use of a compound of Formula I-III, or a pharmaceutically acceptable salt, solvate, and/or ester thereof, for treating an HCV infection. In a preferred aspect of this embodiment, the compound of Formula I-III is, at least, 70% a single diastereomer, 80% a single diastereomer, 90% a single diastereomer or most preferably 95% a single diastereomer.

As will be appreciated by those skilled in the art, when treating a viral infection such as HCV, such treatment may be characterized in a variety of ways and measured by a variety of endpoints. The scope of the present invention is intended to encompass all such characterizations.

Synthetic Examples

Certain abbreviations and acronyms are used in describing the experimental details. Although most of these would be understood by one skilled in the art, Table 1 contains a list of many of these abbreviations and acronyms.

Table 1. List of abbreviations and acronyms.

Abbreviation	Meaning
Ac	acetyl
ACN	acetonitrile
AIBN	2,2'-azobis(2-methylpropionitrile)
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Bn	benzyl
BnBr	benzylbromide
BSA	bis(trimethylsilyl)acetamide
BzCl	benzoyl chloride
CDI	carbonyl diimidazole
DABCO	1,4-diazabicyclo[2.2.2]octane
dba	dibenzylideneacetone
DBN	1,5-diazabicyclo[4.3.0]non-5-ene
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone

DBU	1,5-diazabicyclo[5.4.0]undec-5-ene
DCA	dichloroacetamide
DCC	dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
DCM	dichloromethane
deg	degrees
DIAD	di-isopropylazodicarboxylate
DIEA	*N,N*-di-isopropylethylamine
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMTCl	dimethoxytrityl chloride
DMSO	dimethylsulfoxide
DMTr	4, 4'-dimethoxytrityl
DMF	dimethylformamide
EtOAc	ethyl acetate
ES, ESI	electrospray ionization
HMDS	hexamethyldisilazane
HPLC	high pressure liquid chromatography
LC	liquid chromatography
LDA	lithium diisopropylamide
LRMS	low resolution mass spectrum
MCPBA	meta-chloroperbenzoic acid
MeCN	acetonitrile
MeOH	methanol
MMTC	mono methoxytrityl chloride
m/z or m/e	mass to charge ratio
MH^+	mass plus 1
MH^-	mass minus 1
MsOH	methanesulfonic acid
MS or ms	mass spectrum
NBS	N-bromosuccinimide
NMP	N-methylpyrrolidine
Ph	phenyl

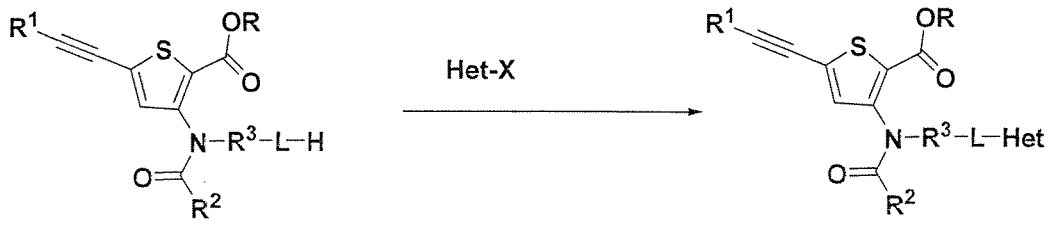
rt or r.t.	room temperature
TBAF	tetrabutylammonium fluoride
TES	triethylsilyl
THF	tetrahydrofuran
THP	tetrahydropyran
TMSCl	chlorotrimethylsilane
TMSBr	bromotrimethylsilane
TMSI	iodotrimethylsilane
TMSOTf	(trimethylsilyl)trifluoromethylsulfonate
TEA	triethylamine
TBA	tributylamine
TBAP	tributylammonium pyrophosphate
TBSCl	t-butyldimethylsilyl chloride
TEAB	triethylammonium bicarbonate
TFA	trifluoroacetic acid
TLC or tlc	thin layer chromatography
Tr	triphenylmethyl
Tol	4-methylbenzoyl
Turbo Grignard	1:1 mixture of isopropylmagnesium chloride and lithium chloride
xantphos	4,5-bis(diphenylphosphino)-9,9-dimethylxanthene
δ	parts per million down field from tetramethylsilane

General Schemes

The compounds of this invention may be synthesized by several routes with key bond-forming steps as indicated in Schemes A-C, in which the carboxylate substituent R indicates either a protecting group such as an alkyl ester (where necessary), or the free acid itself. Alkyl ester protecting groups are conveniently removed by saponification with an alkali metal hydroxide in a protic solvent such as water or an alcohol, and may be facilitated by use of ethereal solvent mixtures and/or heating. Alternatively they may be removed by dealkylation through heating with an alkali metal halide in an aprotic solvent. As will be appreciated, substituents on Het may be modified subsequent to other bond-forming steps by, for example, N-oxidation with a typical oxidant such as metachloroperbenzoic acid in a solvent such

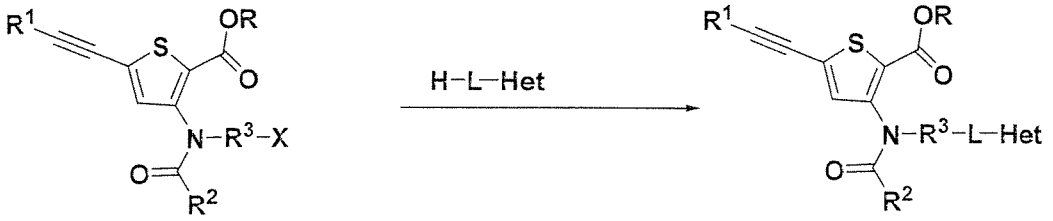
as dichloromethane, O-dealkylation through treatment with a reagent such as boron tribromide in a solvent such as dichloromethane, or hydrolysis.

Scheme A



The bond between L and Het may be formed by displacement of X on Het, where X is a leaving group such as a halide, sulfinate, sulfonate or phosphate moiety. The reaction is conveniently performed by deprotonation of L-H with a base such as sodium hydride or potassium hexamethyldisilazide, or is facilitated by the presence of a tertiary amine; it can be carried out in a variety of solvents such as THF, dioxane, dichloromethane, NMP, DMF or DMSO and may be accelerated by heating.

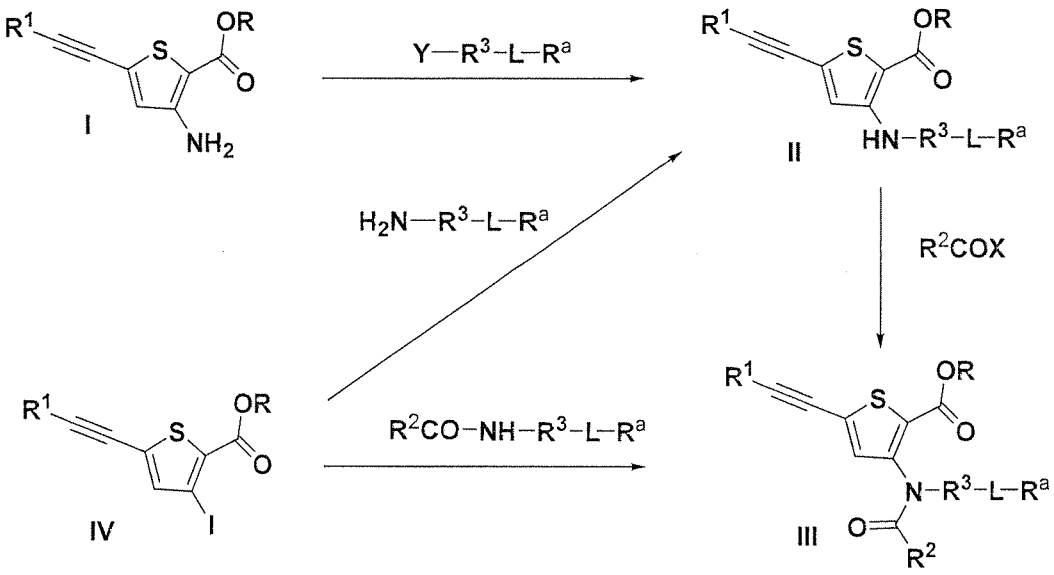
Scheme B



The bond between R^3 and L may be formed by nucleophilic displacement of a leaving group X on R^3. The leaving group may vary widely and includes, but is not limited to, halide, carboxylate, sulfinate, sulfonate or phosphate moieties, and it may be generated from the corresponding alcohol in situ through treatment with reagents such as dialkyl azodicarboxylates. The reaction may also be facilitated by deprotonation of Het-L-H with a base such as sodium hydride or potassium hexamethyldisilazide, or is facilitated by the presence of a tertiary amine; it can be

carried out in a variety of solvents such as THF, dioxane, dichloromethane, NMP, DMF or DMSO and may be accelerated by heating.

Scheme C



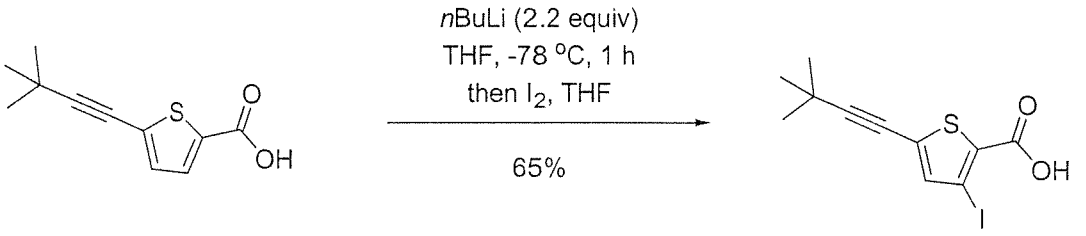
The starting material in Scheme A may be synthesized as depicted in Scheme C. Substituted 3-aminothiophenes II may be generated by reductive amination of Y-R^3-L-R (where Y indicates an aldehyde or ketone and R and R^a depict optional protecting groups), or by direct alkylation (where Y indicates a leaving group such as a halide, sulfinate, sulfonate or phosphate moiety) of the 3-aminothiophene I (see patent application WO2008/58393). In the latter case the alkylation may be facilitated by deprotonation of the amine with a base such as sodium hydride or potassium hexamethyldisilazide, and can be carried out in a variety of solvents such as THF, dioxane, dichloromethane, NMP, DMF or DMSO and may be accelerated by heating. In cases where R^3 is aromatic, the reaction may be catalyzed by Pd (*J. Org. Chem.*, **2000**, *65*, 1158-1174). Alternatively II may be generated by coupling of an amine with a 3-iodothiophene IV catalyzed by Pd (*J. Org. Chem.*, **2000**, *65*, 1158-1174). The amine II is converted to the amide III by acylation with a carboxylic acid derivative such as an acyl chloride or anhydride in the presence of a base such as pyridine or a tertiary amine in an inert solvent such as dichloromethane. Alternatively

IV may be converted to III directly by amidation catalyzed by Cu (*J. Am. Chem. Soc.*, **2002**, *124*, 7421-7428).

The starting material for Scheme B may be generated in an analogous fashion, with the leaving group X being generated in a final step by standard methods from the precursor alcohol.

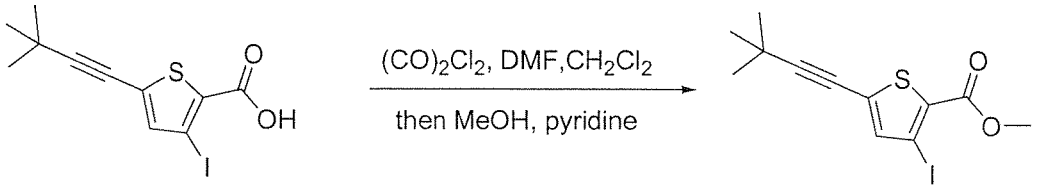
The synthesis of iodothiophene IV is illustrated below for the case where R^1 = tBu, and other variants may be synthesized in analogous fashion:

Scheme D



To a solution of 5-(3,3-Dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid (6.2 g, 30 mmol; see patent application US5861421) in THF (100 mL) was added a solution of nBuLi (2.0 M in pentane, 33 mL, 66 mmol) via an addition funnel at -78 °C. After addition, the reaction was stirred at -78 °C for 1 h. A solution of I_2 (7.7 g, 30 mmol) in THF (100 mL) was added slowly (ca. 15 min) to the flask. After a further 10 mins, the reaction was quenched with 1 N HCl (50 mL) and warmed to room temperature. The volatiles were removed in vacuo and the residue was dissolved in ether (500 mL). The organic solution was washed with 1 M $Na_2S_2O_3$ (100 mL x 2), brine (100 mL) and dried over Na_2SO_4. After concentrated in vacuo, the residue was purified by silica gel chromatography (EtOAc/hexanes) to give 5-(3,3-Dimethyl-but-1-ynyl)-3-iodo-thiophene-2-carboxylic acid (5.9 g, 65%) as a white solid.

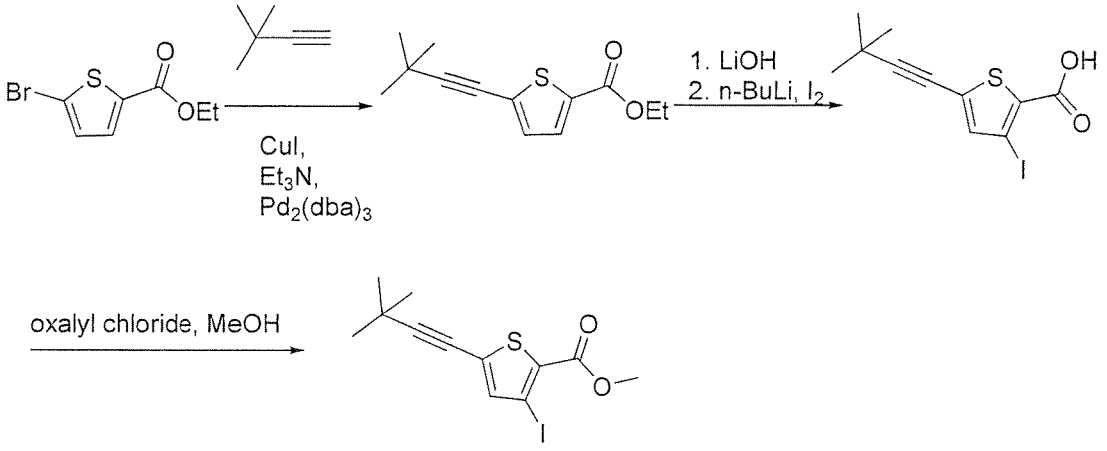
Scheme E



To a solution of 5-(3,3-Dimethyl-but-1-ynyl)-3-iodo-thiophene-2-carboxylic acid (1.0 g, 3.0 mmol) and DMF (20 μL) in dry dichloromethane (10 mL) was added oxalyl chloride (508 μL, 6.0 mmol) at room temperature. After stirring at room temperature for 90 min, the reaction was concentrated in vacuo to remove volatiles. The residue was dissolved in pyridine (5 mL) and methanol (5 mL) and stirred for 2 h. The volatiles were removed in vacuo and the residue was participated between ether (150 mL) and saturated NH_4Cl solution (50 mL). The organic layer was washed with saturated NH_4Cl solution (50 mL) and dried over Na_2SO_4. After concentration in vacuo, the residue was purified by silica gel chromatography (EtOAc/hexanes) to give the desired product (835 mg, 80%).

Synthesis of 5-(3,3-dimethyl-but-1-ynyl)-3-iodo-thiophene-2-carboxylic acid methyl ester

Scheme 8



A mixture of 5-bromo-thiophene-2-carboxylic acid ethyl ester (7g, 30 mmol), copper iodide (1.2g, 6 mmol), triethylamine (20 mL) in DMF (100 mL) was degassed in a 350mL pressure bottle. Then tris(dibenzylideneacetone)dipalladium(0) (2.1 g, 3 mmol) and 3,3-dimethyl-but-1-yne (18.3 mL, 150 mmol) were added and heated at 80 degree for 3 hours. The reaction mixture was filtered on celite and washed with

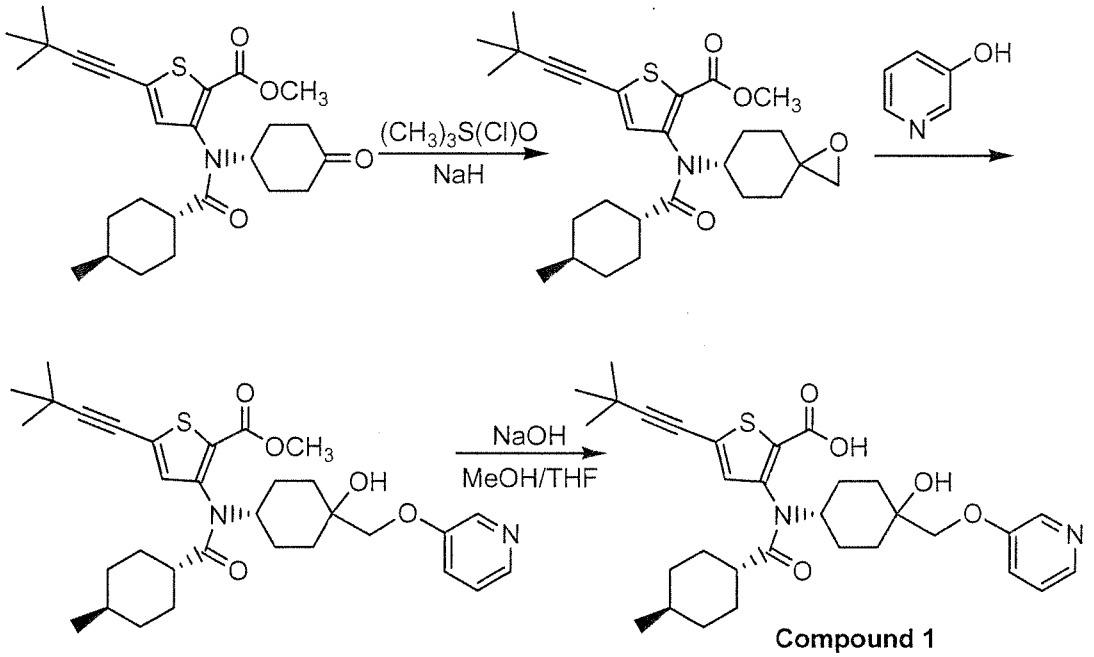
ethyl acetate. The solution was diluted with water and extracted twice with ethyl acetate. The organic phases were combined and washed with water. After drying and concentration, the crude residue was purified by flash chromatography to yield 6.9g (95%) of 5-(3,3-Dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid ethyl ester as a yellow oil.

A solution of 5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid ethyl ester (6.9g) in THF (100 mL) was added LiOH (1.5N, 100mL). The mixture was stirred at room temperature for 4 hours. Acidified reaction with HCl to pH =2, then remove volatiles under vacuo. The resulting beige color solid was collected by filtration, washed with water then dried overnight to give 6.2 g of product which was used without further purification.

To a solution of 5-(3,3-Dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid (6.2 g, 30 mmol; see patent application US5861421) in THF (100 mL) was added a solution of nBuLi (2.0 M in pentane, 33 mL, 66 mmol) via an addition funnel at -78 °C. After addition, the reaction was stirred at -78 °C for 1 h. A solution of I_2 (7.7 g, 30 mmol) in THF (100 mL) was added slowly (ca. 15 min) to the flask. After a further 10 mins, the reaction was quenched with 1 N HCl (50 mL) and warmed to room temperature. The volatiles were removed in vacuo and the residue was dissolved in ether (500 mL). The organic solution was washed with 1 M $Na_2S_2O_3$ (100 mL x 2), brine (100 mL) and dried over Na_2SO_4. After concentrated in vacuo, the residue was purified by silica gel chromatography (EtOAc/hexanes) to give 5-(3,3-Dimethyl-but-1-ynyl)-3-iodo-thiophene-2-carboxylic acid (5.9 g, 65%) as a white solid.

To a solution of 5-(3,3-dimethyl-but-1-ynyl)-3-iodo-thiophene-2-carboxylic acid (1.0 g, 3.0 mmol) and DMF (20 μL) in dry dichloromethane (10 mL) was added oxalyl chloride (508 μL, 6.0 mmol) at room temperature. After stirring at room temperature for 90 min, the reaction was concentrated in vacuo to remove volatiles. The residue was dissolved in pyridine (5 mL) and methanol (5 mL) and stirred for 2 h. The volatiles were removed in vacuo and the residue was participated between ether (150 mL) and saturated NH_4Cl solution (50 mL). The organic layer was washed with saturated NH_4Cl solution (50 mL) and dried over Na_2SO_4. After concentration in vacuo, the residue was purified by silica gel chromatography (EtOAc/hexanes) to give the desired product (835 mg, 80%).

Compound 1 - 5-(3,3-Dimethylbut-1-ynyl)-3-(N-(4-hydroxy-4-((pyridin-3-yloxy)methyl)cyclohexyl)-4-methylcyclohexanecarboxamido)thiophene-2-carboxylic acid.



Compound 1

NaH (36 mg of a 60% oil dispersion, 0.90 mmol) was added in portions to a solution of trimethylsulfoxonium chloride (116 mg, 0.90 mmol) in DMSO (2.0 mL) at room temperature. After 15 min, a solution of 5-(3,3-dimethyl-but-1-ynyl)-3-[(4-methyl-cyclohexanecarbonyl)-(4-oxo-cyclohexyl)-amino]-thiophene-2-carboxylic acid methyl ester (343 mg, 0.75 mmol) (WO 2008/058393) in THF (2.0 mL) was added dropwise. After 3 h, brine was added the reaction extracted with ethyl acetate. The combined organic layers were washed with water, brine, dried over Na_2SO_4 and concentrated to give a pale foam. Purification by flash column chromatography on silica gel with 5% methanol in dichloromethane provided the product (216 mg, 61%) as an off-white solid.

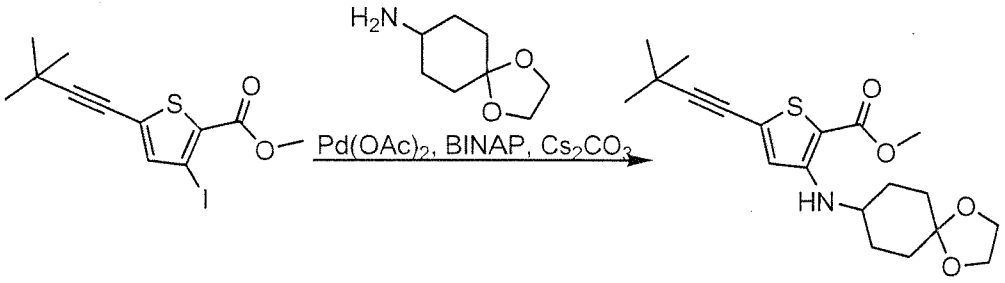
NaH (20 mg of a 60% oil dispersion, 0.50 mmol) was added to a solution of 3-hydroxy pyridine (48 mg, 0.50 mmol) in DMF(2.0 mL) at room temperature. After stirring for 10 min, a solution of the epoxide from the previous step (216 mg, 0.46 mmol) in DMF (2.0 mL) was added. The reaction was heated at 100 °C 6 h, cooled and partitioned between ethyl acetate and sat. NH_4Cl. The organic layer was separated, washed with 5% aqueous LiCl, brine, dried over Na_2SO_4 and concentrated to give a dark orange residue. Purification by flash column chromatography on silica

gel with 5% methanol in dichloromethane provided the desired product (87 mg) that was contaminated with an unidentified impurity. This material was carried on to the next step without any additional purification.

A solution of 1.0 N NaOH (0.50 mL) was added to a solution of the methyl ester from the previous step (87 mg, assume 0.15 mmol) in THF (0.75 mL) and methanol (0.75 mL) at 0 °C. After 1 h, the reaction was concentrated top dryness to give an orange gum that was purified by prep HPLC to provide the desired product (4 mg, 1.3% for two steps) as the trifluoroacetic acid salt. MS (m/z): 553.0 [M+H]; HPLC retention time: 3.36 min (2-98% acetonitrile:water with 0.05% tifluoroacetic acid).

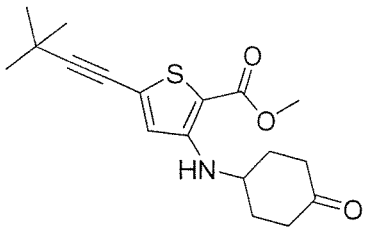
Example 15 – Compound 2: 5-(3,3-Dimethyl-but-1-ynyl)-3-[[4-hydroxy-4-(tetrahydrofuran-3*R*-yloxymethyl)-cyclohexyl]-(4-methyl-cyclohexanecarbonyl)-amino]-thiophene-2-carboxylic acid

Synthesis of 5-(3,3-dimethyl-but-1-ynyl)-3-(1,4-dioxa-spiro[4.5]dec-8-ylamino)-thiophene-2-carboxylic acid methyl ester



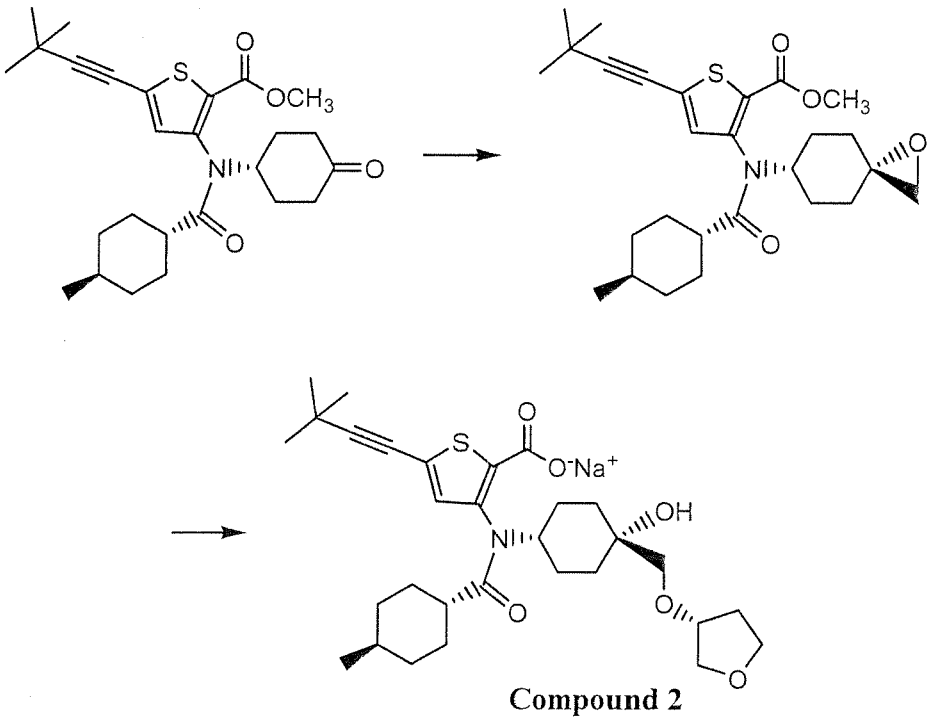
A mixture of 5-(3,3-dimethyl-but-1-ynyl)-3-iodo-thiophene-2-carboxylic acid methyl ester (0.5 g, 1.5 mmol), palladium acetate (0.033 g, 0.15 mmol), BINAP (0.093 g, 0.15 mmol), cesium carbonate (0.733 g, 2.25 mmol) and 1,4-Dioxa-spiro[4.5]dec-8-ylamine (0.706 g, 4.5 mmol) in toluene (8 mL) was degassed with N_2 then heated to 110 °C for 8 h. The reaction was diluted with ethyl acetate filtered through a Celite pad and purified by silica gel chromatography (0-40% hexane/ethylacetate) to give the title compound in 50% yield. MS (m/z): 378.1 [M+H]; HPLC retention time: 5.12 min (2-98% acetonitrile:water with 0.05% trifluoroacetic acid).

Synthesis of 5-(3,3-dimethyl-but-1-ynyl)-3-(4-oxo-cyclohexylamino)-thiophene-2-carboxylic acid methyl ester



A mixture of 5-(3,3-dimethyl-but-1-ynyl)-3-(4-oxo-cyclohexylamino)-thiophene-2-carboxylic acid methyl ester (0.5 g, 1.5 mmol) and HCl (24 mmol, 4M HCl) in THF/H_2O (6 mL) was heated to 45 °C for 2 h. The reaction was diluted with ethyl acetate (20 mL) and the organic phase was washed with H_2O (3X100 mL), $NaHCO_3$ sat. (1X100 mL) and dried over Na_2SO_4. The solution was filtered and concentrated to give the title compound in 96% yield. MS (m/z): 334.1 [M+H]; HPLC retention time: 4.530 min (2-98% acetonitrile:water with 0.05% trifluoroacetic acid).

Scheme 7

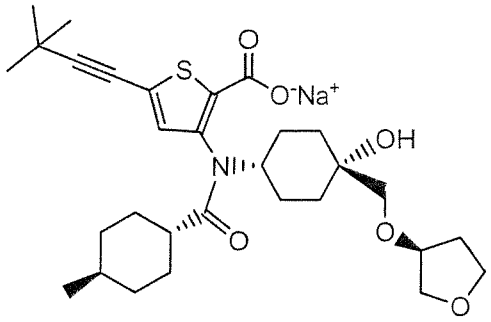


Compound 2

NaH (140 mg of a 60% oil dispersion, 3.50 mmol) was added in portions to a solution of trimethylsulfoxonium chloride (452 mg, 3.51 mmol) in DMSO (8.0 mL) at room temperature. After 15 min, a solution of 5-(3,3-dimethyl-but-1-ynyl)-3-[(4-methyl-cyclohexanecarbonyl)-(4-oxo-cyclohexyl)-amino]-thiophene-2-carboxylic acid methyl ester (1.34 g, 2.93 mmol) in THF (8.0 mL) was added dropwise. After 3 h, brine was added and the reaction extracted with ethyl acetate. The combined organic layers were washed with water, brine, dried over Na_2SO_4 and concentrated to give a viscous yellow oil. Trituration with ethyl ether and hexanes provided 5-(3,3-dimethyl-but-1-ynyl)-3-[(4-methyl-cyclohexanecarbonyl)-(1-oxa-spiro[2.5]oct-6-yl)-amino]-thiophene-2-carboxylic acid methyl ester (509 mg, 37%) as a colorless solid.

NaH (55 mg of a 60% oil dispersion, 1.37 mmol) was added to a solution of (*R*)-(-)-3-hydroxytetrahydrofuran (120 mg, 1.36 mmol) in dry THF (4.0 mL) at 0 °C. After 5 min, solid 5-(3,3-dimethyl-but-1-ynyl)-3-[(4-methyl-cyclohexanecarbonyl)-(1-oxa-spiro[2.5]oct-6-yl)-amino]-thiophene-2-carboxylic acid methyl ester (125 mg, 0.265 mmol) was added and the reaction was heated in a 75 °C oil bath for 2.5 days. The reaction was cooled and evaporated to dryness to give a brown residue that was purified by column chromatography on reverse phase C_{18} silica gel (100% water to 10% acetonitrile/water). Fractions containing product were pooled and evaporated to provide 5-(3,3-dimethyl-but-1-ynyl)-3-[[4-hydroxy-4-(tetrahydrofuran-3*R*-yloxymethyl)-cyclohexyl]-(4-methyl-cyclohexanecarbonyl)-amino]-thiophene-2-carboxylic acid (30 mg, 20%) as a colorless solid. MS (m/z): 546.0 $[M+H]^+$; HPLC retention time 4.32 min (2-98% acetonitrile: water with 0.05% trifluoroacetic acid).

Example 16 – Compound 3: 5-(3,3-Dimethyl-but-1-ynyl)-3-[[4-hydroxy-4-(tetrahydrofuran-3*S*-yloxymethyl)-cyclohexyl]-(4-methyl-cyclohexanecarbonyl)-amino]-thiophene-2-carboxylic acid

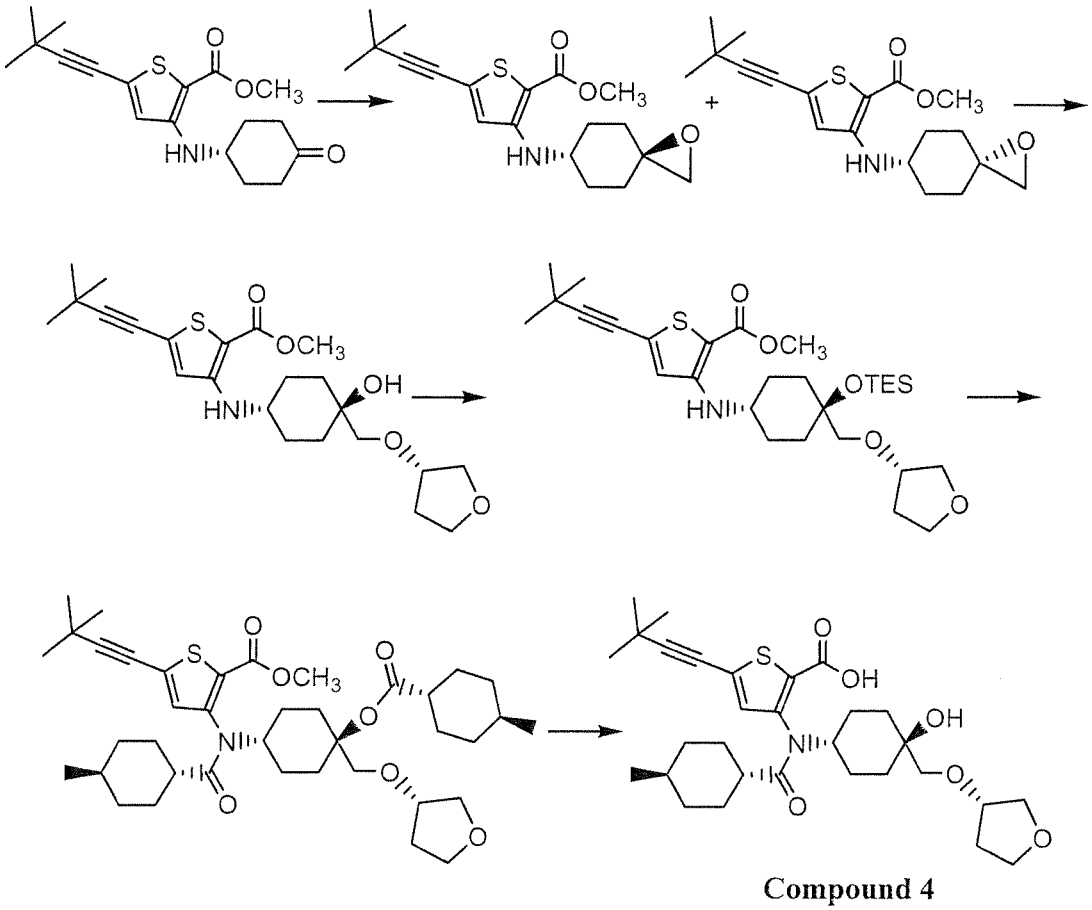


Compound 3

Compound 3 (32 mg, 21%) was synthesized in a manner analogous to Example 15, using (*S*)-(+)-3-hydroxytetrahydrofuran in place of (*R*)-(-)-3-hydroxytetrahydrofuran: MS (m/z): 546.0 [M+H]+; HPLC retention time 4.32 min (2-98% acetonitrile: water with 0.05% trifluoroacetic acid).

Example 20 – Compound 4: Synthesis of 5-(3,3-Dimethyl-but-1-ynyl)-3-{(4-methyl-cyclohexanecarbonyl)-[4-(4-methyl-cyclohexanecarbonyloxy)-4-(tetrahydro-furan-3-yloxymethy)-cyclohexyl]-amino}-thiophene-2-carboxylic acid

Scheme 11



Compound 4

NaH (370 mg of a 60% oil dispersion, 9.25 mmol) was added in portions to a solution of trimethylsulfonium iodide (1.88 g, 9.25 mmol) in DMSO (16.0 mL) at room

temperature. After 15 min, a solution of 5-(3,3-dimethyl-but-1-ynyl)-3-[(4-oxo-cyclohexylamino)-thiophene-2-carboxylic acid methyl ester (1.10 g, 3.30 mmol) in THF (16.0 mL) was added dropwise. After 3 h, brine was added and the reaction extracted with ethyl acetate. The combined organic layers were washed with water, brine, dried over Na_2SO_4 and concentrated to give a viscous yellow oil. Purification by column chromatography on silica gel (Teledyne Isco Redisep Rf Gold™) with dichloromethane gave the two epoxide isomers, the first of which to elute was isolated as the desired 5-(3,3-dimethyl-but-1-ynyl)-3-(1-oxa-spiro[2.5]oct-6-ylamino]-thiophene-2-carboxylic acid methyl ester (400 mg, 35%) as a colorless solid.

A solution of (*S*)-(+)-3-hydroxytetrahydrofuran (259 mg, 2.94 mmol) in dry NMP (1mL) was added to a solution of KOtBu (271 mg, 2.42mmol) in dry NMP (1mL). The reaction was stirred at room temperature for 15 min, then a solution of 5-(3,3-dimethyl-but-1-ynyl)-3-(1-oxa-spiro[2.5]oct-6-ylamino]-thiophene-2-carboxylic acid methyl ester (200 mg, 0.576 mmol) in dry NMP (4.0 mL) was added and the reaction heated in a 40 °C oil bath for 24 h. The reaction was poured into ice water, cooled to 0 °C, neutralized with 5% citric acid to pH = 5-6 and extracted with ethyl acetate. The organic layer was washed with 5% LiCl, brine, dried and concentrated to give a brown oil which was taken up in dichloromethane/MeOH (5.0 mL/1.0 mL) and treated with the dropwise addition of $TMSCH_2N_2$ (0.35mL, 0.692 mmol, 2M in hexane). After 20 min, volatiles were removed under vacuum and the crude residue was purified by column chromatography on silica gel (Teledyne Isco Redisep Rf Gold™) eluting with 100% dichloromethane to 20% ethyl acetate/dichloromethane to give 5-(3,3-dimethyl-but-1-ynyl)-3-[4-hydroxy-4-(tetrahydro-furan-3-yloxymethy)-cyclohexylamino]-thiophene-2-carboxylic acid methyl ester (120 mg, 48%) as a colorless solid.

Triethylamine (1.02 mL, 7.34 mmol) was added to a solution of 5-(3,3-dimethyl-but-1-ynyl)-3-[4-hydroxy-4-(tetrahydro-furan-3-yloxymethy)-cyclohexylamino]-thiophene-2-carboxylic acid methyl ester (200 mg, 0.459 mmol) in dichloromethane (12.0 mL). After 10 min, the solution was cooled to -78 °C and TESOTf (0.87 mL, 3.85 mmol) was added dropwise. The reaction was stirred for 30 min at -78 °C, quenched with the addition of ice, diluted with sat. $NaHCO_3$ and extracted with dichloromethane. The organic layer was separated, dried over Na_2SO_4, concentrated and purified by column chromatography with 0 to 20% ethyl acetate/hexane to give 5-(3,3-dimethyl-but-1-ynyl)-3-[4-hydroxy-4-(tetrahydro-furan-

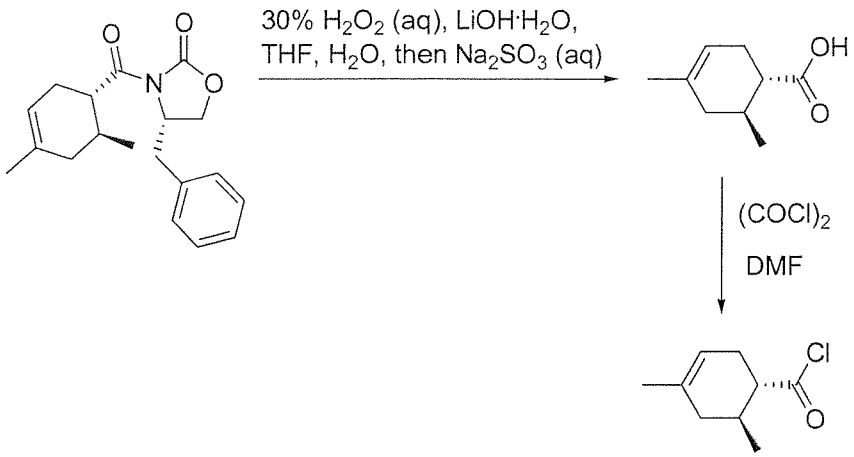
3-yloxymethy)-4-triethylsilanyloxy-cyclohexylamino]-thiophene-2-carboxylic acid methyl ester (200 mg, 79%) as a yellow oil.

5-(3,3-Dimethyl-but-1-ynyl)-3-[4-hydroxy-4-(tetrahydro-furan-3-yloxymethy)-4-triethylsilanyloxy-cyclohexylamino]-thiophene-2-carboxylic acid methyl ester (200 mg, 0.36 mmol) was dissolved in pyridine (2 mL). After 10 min, neat 4-methyl-cyclohexanecarbonyl chloride (233 mg, 1.44mmol) was added dropwise. The reaction solution was heated at 110 °C overnight and then concentrated to give a residue that was purified by column chromatography with ethyl acetate/ hexane (0 to 20%) to give 5-(3,3-dimethyl-but-1-ynyl)-3-{(4-methyl-cyclohexanecarbonyl)-[4-(4-methyl-cyclohexanecarbonyloxy)-4-(tetrahydro-furan-3-yloxymethy)-cyclohexyl]-amino}-thiophene-2-carboxylic acid methyl ester (80 mg, 32%) as a colorless solid.

NaOH (1.17 mL of a 1.0 N aqueous solution) was added dropwise to a solution of 5-(3,3-dimethyl-but-1-ynyl)-3-{(4-methyl-cyclohexanecarbonyl)-[4-(4-methyl-cyclohexanecarbonyloxy)-4-(tetrahydro-furan-3-yloxymethy)-cyclohexyl]-amino}-thiophene-2-carboxylic acid methyl ester (80 mg, 0.117mmol) in methanol (2mL)/THF (2mL)/ H_2O(2mL) at room temperature. The solution was heated at 70 °C overnight and then cooled to room temperature. Volatiles were removed under vacuum and the resulting residue purified by HPLC with CH_3CN(0.1% TFA)/H_2O(0.1% TFA) to provide the Compound 4 (23.3 mg, 36%) as colorless solid. MS (m/z): 546.0[M+H]+; HPLC retention time 4.169min (2-98% acetonitrile: water with 0.05% trifluoroacetic acid).

Synthesis of (1*S*,6*S*)-4,6-dimethyl-cyclohex-3-enecarboxylic acid and acid chloride

Scheme 2

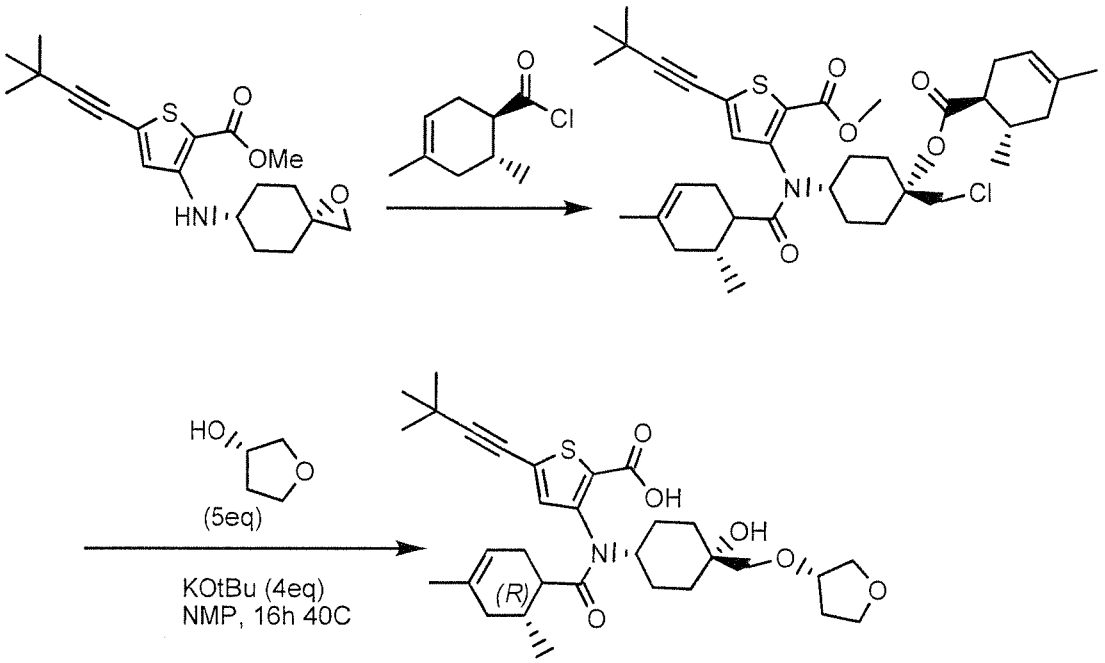


4*S*-benzyl-3-(4,6S-dimethyl-cyclohex-3-ene-1*S*-carbonyl)-oxazolidin-2-one, prepared in a method similar to that described in *J. Am. Chem. Soc.* 110(4), **1988**, 1238-1256, was dissolved in THF (1000mL) and H_2O (350mL). The solution was cooled in an ice bath and 30% H_2O_2 (36mL, 354mmol) was slowly added followed by $LiOH{*}H_2O_{(s)}$ (9.90g, 263mmol) in one portion. The reaction was allowed to slowly warm to rt and was stirred for 16h. The reaction was then cooled in an ice bath. Na_2SO_3 (60g, 472mmol) was dissolved H_2O (400mL) and very slowly added to the cooled reaction mixture. The solution was stirred for 1h, then the layers were separated. The organics were removed under reduced pressure. The aqueous was added back to the organics concentrate and was washed with CH_2Cl_2 (2 X 500mL). Adjust the aqueous pH to 2 with a slow addition of con HCl. Extract the aqueous with EtOAc (4 X 300mL) and dry over Na_2SO_4. Remove organics under reduced pressure and co-evaporate with hexanes to afford (1*S*,6*S*)-4,6-dimethyl-cyclohex-3-enecarboxylic acid (14.14g, 78%) as a white solid.

4,6-S-dimethyl-cyclohex-3-ene-1*S*-carboxylic acid (944mg, 6.17mmol) was dissolved in CH_2Cl_2 (10mL) and DMF (20µL) was added. The solution was cooled to 0 °C and then $(COCl)_2$ (700µL, 7.38mmol) was slowly added to the solution. The reaction was stirred in the ice bath for 1 hour and then concentrated. The residue was taken up in hexanes and concentrated; this hexanes coevaporation was repeated once more. The acid chloride was used without further purification.

Example 23 – Compound 5: 5-(3,3-dimethyl-but-1-ynyl)-3-{(4,6*R*-dimethyl-cyclohex-3-enecarbonyl)-[4-hydroxy-4-(tetrahydro-furan-3-yloxymethyl)-cyclohexyl]-amino}-thiophene-2-carboxylic acid

Scheme 12

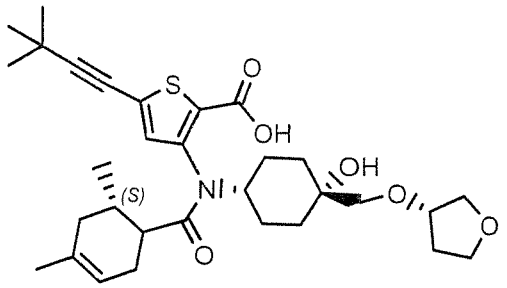


Compound 5

5-(3,3-dimethyl-but-1-ynyl)-3-(1-oxa-spiro[2.5]oct-6-ylamino)-thiophene-2-carboxylic acid methyl ester was prepared similarly to the process in Scheme 11 above using trimethylsulfoxonium chloride instead of trimethylsulfonium iodide. A solution of 5-(3,3-dimethyl-but-1-ynyl)-3-(1-oxa-spiro[2.5]oct-6-ylamino)-thiophene-2-carboxylic acid methyl ester (362 mg, 0.575 mmol) in pyridine (11 mL) was treated with 4,6*R*-dimethyl-cyclohex-3-enecarbonyl-1*R*-chloride (325 mg, 2.11 mmol, prepared in a manner analogous to Scheme 2) and heated to 85 °C for 22h. Upon cooling the reaction was concentrated, diluted with ethylacetate, washed with 1 M HCl (100 mL), and dried over $NaSO_4$. The solution was filtered and purified by silica gel to give 3-[[4-chloromethyl-4-(4,6-dimethyl-cyclohex-3-enecarbonyloxy)-cyclohexyl]-(4,6-dimethyl-cyclohex-3-enecarbonyl)-amino]-5-(3,3-dimethyl-but-1-ynyl)-thiophene-2-carboxylic acid methyl ester (34 mg, 0.05 mmol). The thick yellow oil was taken up in NMP (2 mL), treated with (*S*)-(+)-3-hydroxytetrahydrofuran (36 µL, 0.5 mmol) and K-OtBu (45 mg, 0.4 mmol) then heated to 75 °C for 1h. Upon cooling the reaction was neutralized with 1 M HCl, diluted with ethylacetate (100 mL), and the organic layer was washed with brine (100 mL) and dried over $NaSO_4$. The solution was filtered and the volatiles were removed under vacuum. The resulting

residue purified by HPLC with CH_3CN (0.1% TFA)/H_2O(0.1% TFA) to provide the desired products as colorless solid. Isomer A (Compound 5A): MS (m/z): 558.0 [M+H]+; HPLC retention time 7.95 min (2-98% acetonitrile: water with 0.05% trifluoroacetic acid) 30 min run. Isomer B (Compound 5B); MS (m/z): 558.2 [M+H]+; HPLC retention time 8.02 min (2-98% acetonitrile: water with 0.05% trifluoroacetic acid) 30 min run.

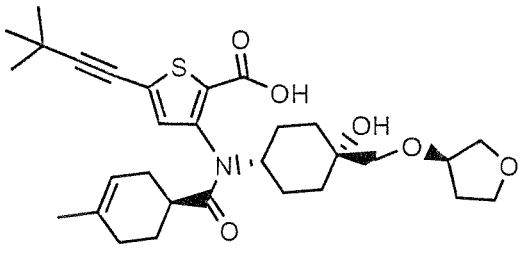
Example 24 – Compund 6: 5-(3,3-dimethyl-but-1-ynyl)-3-{(4,6*S*-dimethyl-cyclohex-3-enecarbonyl)-[4-hydroxy-4-(tetrahydro-furan-3(S)-yloxymethyl)-cyclohexyl]-amino}-thiophene-2-carboxylic acid



Compound 6

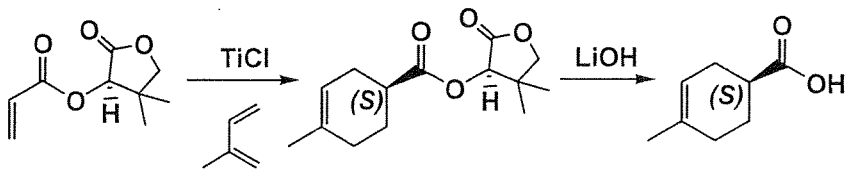
Compound 6 was synthesized in a manner analogous to Example 23, acylating with 4,6*S*-dimethyl-cyclohex-3-enecarbonyl-chloride. MS (m/z): 558.3 [M+H].

Example 27 – Compound 7: 5-(3,3-Dimethyl-but-1-ynyl)-3-[[4-hydroxy-4-(tetrahydro-furan-3(*R*)-yloxymethyl)-cyclohexyl]-(1*S*)-4-methyl-cyclohex-3-enecarbonyl)-amino]-thiophene-2-carboxylic acid



Compound 7

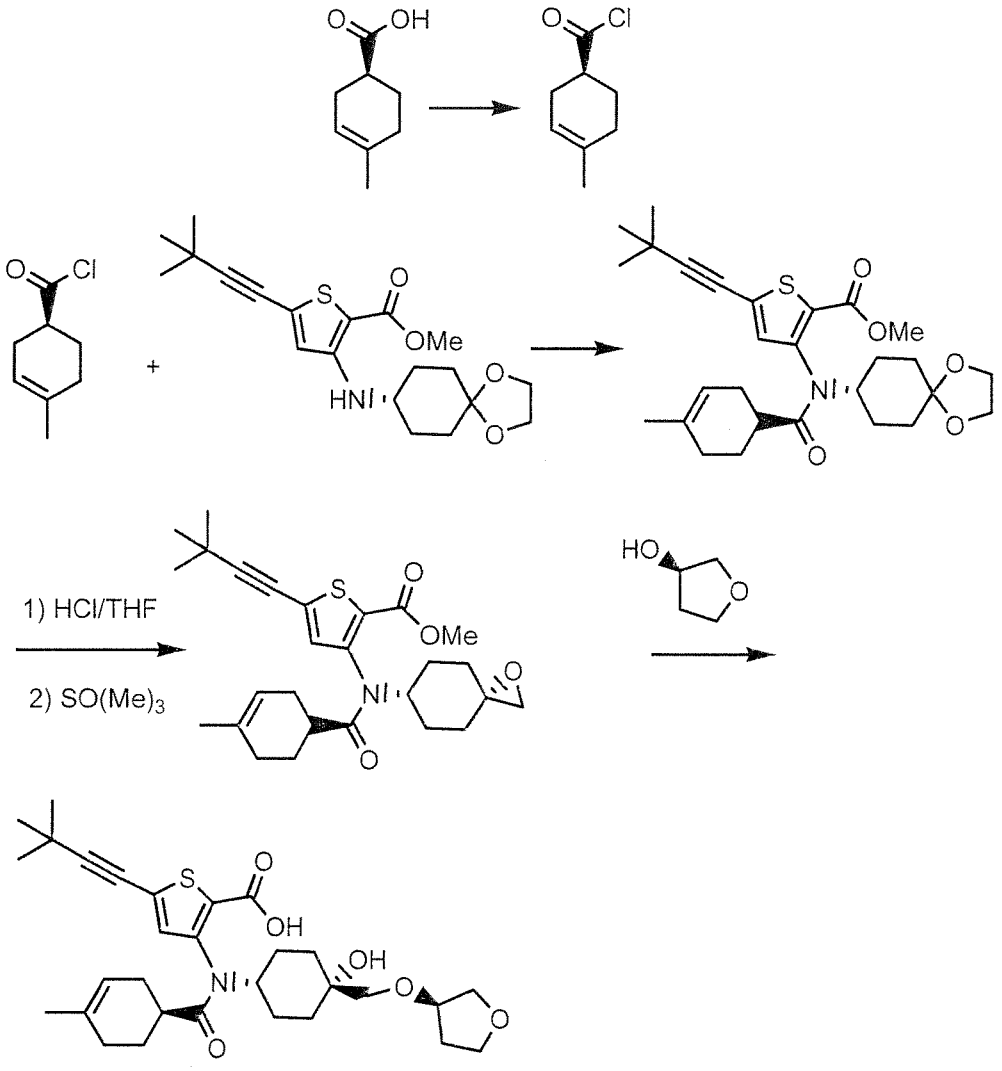
Scheme 15



Acrylic acid 4,4-dimethyl-2-oxo-tetrahydro-furan-3-yl ester (*R*) (2.92 g, 15.9 mmol) in dichloromethane (20 mL) and hexanes (3 mL) was cooled to -10 °C and treated with titanium tetrachloride (2.4 mL, 2.4 M in dichloromethane, 2.4 mmol). The red solution was stirred for 15 min and treated with isoprene (2.4 mL, 23.8 mmol) dropwise over 5 min. After stirring for 1.5 h, an additional portion of isoprene (2.4 mL, 23.8 mmol) was added and the reaction mixture was stirred at -10 to 0 °C for 2.5 h. After cooling to -10 °C, the reaction mixture was quenched with ammonium chloride (sat. aq.). Water and ethyl acetate: hexanes (1:1) were added. The organic layer was separated and the aqueous layer was extracted again with ethyl acetate:hexanes (1:1). The combined organic layers were dried over sodium sulfate, filtered and concentrated. The residue was purified by flash chromatography (10-40% EtOAc:Hex, 80 g column) to afford 3.35 g (84% yield) of 4-methyl-cyclohex-3-(*S*)-enecarboxylic acid 4,4-dimethyl-2-oxo-tetrahydro-furan-3-yl ester as a clear oil.

4-Methyl-cyclohex-3-(*S*)-enecarboxylic acid 4,4-dimethyl-2-oxo-tetrahydro-furan-3-yl ester (3.34 g, 13.2 mmol) in THF (25 mL), water (2.5 mL) and methanol (2.5 mL) was treated with lithium hydroxide monohydrate (2.8 g, 66.2 mmol) and warmed to 50 °C with stirring. After 1h, the reaction mixture treated with 1M HCl (about 25 mL). The mixture was extracted with hexanes:ethyl acetate (200 mL: 15 mL), dried over sodium sulfate, filtered and concentrated to 2.4 g of a white semi-solid. The residue was redissolved in hexanes:dichloromethane (100 mL, 95:5), washed with water, dried over sodium sulfate, filtered and concentrated to 1.68 g (91% yield) of (1*S*)-4-methyl-cyclohex-3-enecarboxylic acid as a white powder.

Scheme 16



Compound 7

(1*S*)-4-Methyl-cyclohex-3-enecarboxylic acid (209 mg, 1.5 mmol), azeotropically dried by evaporation from toluene, was treated with potassium phosphate tribasic (383 mg, 1.8 mmol), suspended in dichloromethane (4 mL) and treated with dimethylformamide (2 drops). The reaction mixture was cooled to 0 °C and treated dropwise with oxalyl chloride (0.3 mL, 3.2 mmol). The reaction mixture was allowed to warm to ambient temperature while stirring for 2 h. After filtering the solids, the solution was concentrated, treated with hexanes and concentrated again to afford 4-methyl-cyclohex-3-enecarbonyl chloride (*S*) as a light yellow oil which was used immediately in the next step.

(1*S*)-4-Methyl-cyclohex-3-enecarboxylic acid chloride (1.5 mmol), 5-(3,3-dimethyl-but-1-ynyl)-3-(1,4-dioxa-spiro[4.5]dec-8-ylamino)-thiophene-2-carboxylic

acid methyl ester (159 mg, 0.42 mmol) and potassium phosphate tribasic (266 mg, 1.25 mmol) was suspended in dichloroethane (1 mL), sealed with a cap and heated to 90 °C. After 16 h, the reaction mixture was cooled and partitioned between ethyl acetate and water. The organic layer was separated and the aqueous extracted again with ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered and concentrated. Flash chromatography (15-60% EtOAc:Hexanes) afforded 128 mg (61% yield) of the desired 5-(3,3-dimethyl-but-1-ynyl)-3-[(1,4-dioxa-spiro[4.5]dec-8-yl)-((1*S*)-4-methyl-cyclohex-3-enecarbonyl)-amino]-thiophene-2-carboxylic acid methyl ester as a white foam.

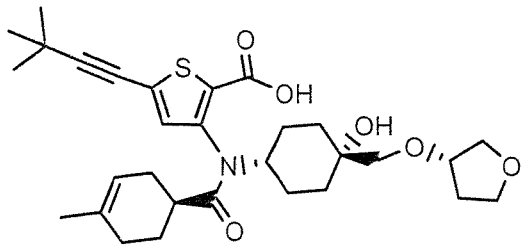
5-(3,3-Dimethyl-but-1-ynyl)-3-[(1,4-dioxa-spiro[4.5]dec-8-yl)-((1*S*)-4-methyl-cyclohex-3-enecarbonyl)-amino]-thiophene-2-carboxylic acid methyl ester (116 mg, 0.23 mmol) was dissolved in THF (1.8 mL) and treated with 4M HCl (0.9 mL). The reaction mixture was heated to 45 °C and stirred 4.5 h. An additional portion of 12M HCl (0.2 mL) and the solution was stirred 2h at 45 °C. Ethyl acetate was added and the organic layer was separated then washed with brine, sodium bicarbonate (sat aq) and brine. The organic layer was dried over sodium sulfate, filtered and concentrated to 98 mg of the desired 5-(3,3-dimethyl-but-1-ynyl)-3-[(1*S*)-4-methyl-cyclohex-3-enecarbonyl)-(4-oxo-cyclohexyl)-amino]-thiophene-2-carboxylic acid methyl ester as a white foam.

Trimethylsulfoxonium chloride (39 mg, 0.3 mmol) in DMSO (1.5 mL) was treated with sodium hydride (10 mg, 60% oil dispersion, 0.25 mmol) and stirred at ambient temperature for 10 min. 5-(3,3-Dimethyl-but-1-ynyl)-3-[(4-methyl-cyclohex-3-enecarbonyl)-(4-oxo-cyclohexyl)-amino]-thiophene-2-carboxylic acid methyl ester (*S*) in THF (1 mL + 0.5 mL) was added dropwise and the reaction mixture was stirred for 1 h. The orange solution was treated with 5% citric acid until pH~4 and partitioned between water and ethyl acetate. The organic layer was separated and the aqueous was extracted again with ethyl acetate. The combined organics were washed with water and brine, and dried over sodium sulfate. After filtration and concentration, the residue was purified by flash chromatography (25-75% EtOAc:hexanes) to afford 99 mg of the desired 5-(3,3-dimethyl-but-1-ynyl)-3-[(1*S*)-4-methyl-cyclohex-3-enecarbonyl)-(1-oxa-spiro[2.5]oct-6-yl)-amino]-thiophene-2-carboxylic acid methyl ester as a white solid.

(*R*)-Tetrahydro-furan-3-ol (89 mg, 1.01 mmol) in 1-methyl-pyrrolidin-2-one (1 mL) was treated with potassium *tert*-butoxide (90.5 mg, 0.81 mmol) and stirred at

ambient temperature for 15 minutes. This slightly cloudy solution was added to 5-(3,3-dimethyl-but-1-ynyl)-3-[(4-methyl-cyclohex-3-enecarbonyl)-(1-oxa-spiro[2.5]oct-6-yl)-amino]-thiophene-2-carboxylic acid methyl ester (*S*) (34 mg, 0.073 mmol). The reaction mixture was sealed at heated to 40 °C for 16 h. After cooling the mixture was treated with 2 M HCl until pH~3, partitioned between ethyl acetate and water and separated. The aqueous layer was extracted again with ethyl acetate and the combined organics were washed with water, brine and dried over sodium sulfate. After filtration and concentration the residue was purified by HPLC with CH_3CN (0.1% TFA)/H_2O(0.1% TFA) to afford 22 mg (55% yield) of Compound 7 as a white powder: MS (m/z): 544.0 [M+H]+; HPLC retention time 4.20 min (2-98% acetonitrile: water with 0.05% trifluoroacetic acid).

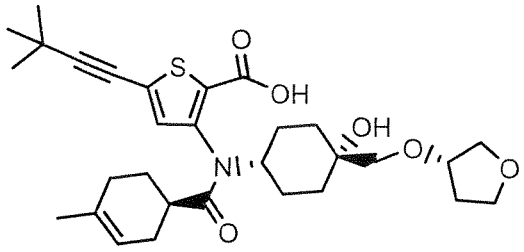
Example 28 – Compound 8: 5-(3,3-Dimethyl-but-1-ynyl)-3-[[4-hydroxy-4-(tetrahydro-furan-3(*S*)-yloxymethyl)-cyclohexyl]-(1*S*)-4-methyl-cyclohex-3-enecarbonyl)-amino]-thiophene-2-carboxylic acid



Compound 8

Compound 8 was synthesized in a manner similar to Example 27 using (*S*)-tetrahydro-furan-3-ol in place of (*R*)-tetrahydro-furan-3-ol: MS (m/z): 544.1 [M+H]+; HPLC retention time 4.20 min (2-98% acetonitrile: water with 0.05% trifluoroacetic acid).

Example 29 – Compound 9: 5-(3,3-Dimethyl-but-1-ynyl)-3-[[4-hydroxy-4-(tetrahydro-furan-3(*S*)-yloxymethyl)-cyclohexyl]-(1*R*)-4-methyl-cyclohex-3-enecarbonyl)-amino]-thiophene-2-carboxylic acid

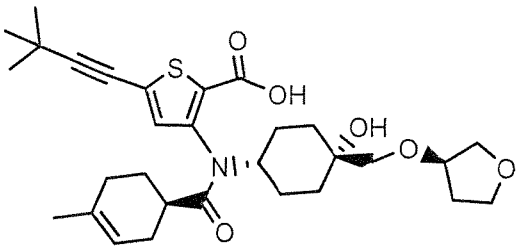


Compound 9

Acrylic acid 4,4-dimethyl-2-oxo-tetrahydro-furan-3-yl ester (*R)* was prepared in the following manner: 3-(*S)*-Hydroxy-4,4-dimethyl-dihydro-furan-2-one (2.60 g, 20 mmol) and diisopropylethylamine (5.2 mL, 30 mmol) in dichloromethane (25 mL) was cooled to -10 °C and treated dropwise with acryloyl chloride (2.03 mL, 25 mmol) and stirred for 2 h. 1M HCl (20 mL) was added and the organic layer was washed with sodium bicarbonate and water. The organic layer was dried over sodium sulfate, filtered and concentrated. Flash chromatography (10-40% EtOAc, hexanes) afforded 2.09 g (57% yield) of the desired acrylic acid 4,4-dimethyl-2-oxo-tetrahydro-furan-3-yl ester (*R*) as a clear oil. This substrate was used to prepare the acid chloride of (1*R*)-4-methyl-cyclohex-3-enecarboxylic acid analogous to the procedure described in Scheme 15 and Scheme 16.

Compound 9 was prepared in a manner similar to Example 27 using the acid chloride of (1*R*)-4-methyl-cyclohex-3-enecarboxylic acid in place of the acid chloride of (1*S*)-4-methyl-cyclohex-3-enecarboxylic acid and (*S*)-tetrahydro-furan-3-ol in place of (*R*)-tetrahydro-furan-3-ol: MS (m/z): 544.0 [M+H]+; HPLC retention time 4.22 min (2-98% acetonitrile: water with 0.05% trifluoroacetic acid).

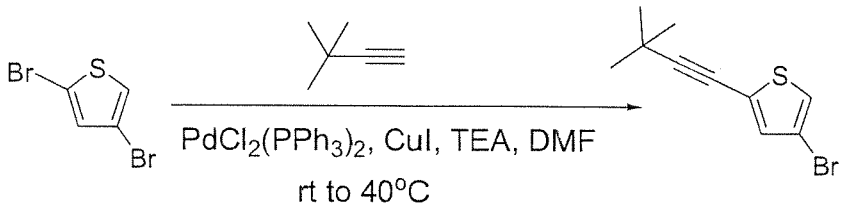
Example 30 – Compound 10: 5-(3,3-Dimethyl-but-1-ynyl)-3-[[4-hydroxy-4-(tetrahydro-furan-3(*R*)-yloxymethyl)-cyclohexyl]-(1*R*)-4-methyl-cyclohex-3-enecarbonyl)-amino]-thiophene-2-carboxylic acid



Compound 10

Compound 10 was prepared in a manner similar to Example 29 using (*R*)-tetrahydro-furan-3-ol in place of (*S*) tetrahydro-furan-3-ol: MS (m/z): 544.1 [M+H]+; HPLC retention time 4.20min (2-98% acetonitrile: water with 0.05% trifluoroacetic acid).

Example 31: Compounds 16, 17, and 18

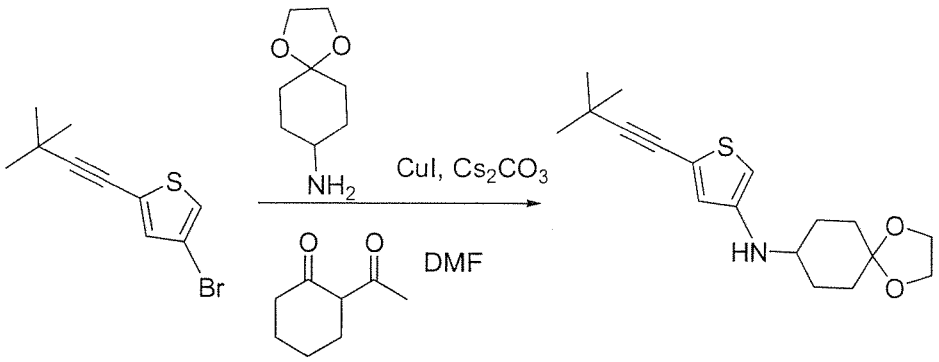


11

2,4-Dibromothiophene (6g, 24.8 mmol), $PdCl_2(PPh_3)_2$ (522 mg, 0.74 mmol) and CuI (283 mg, 1.49 mmol) were added to a 250 mL round bottom flask, which was then sealed with a rubber septa. The flask was degassed and backfilled with argon three times, followed by the addition of DMF (150ml) and TEA (30ml). 3,3-Dimethylbut-1-yne (2.87 mL, 23.56 mmol) was added. The reaction mixture was heated at 45°C for two hours, by which time 2,4-dibromothiophene had been completely consumed. Insoluble material was removed by filtration and the filtrate was concentrated in vacuo. The residue was partitioned between EtOAc (150 mL) and aqueous ammonium hydroxide (2 ml 28-30% wt solution, diluted into 100mL water). The organic phase was separated, washed with 5% LiCl aqueous solution and brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated. The residue was purified by silica gel chromatography eluting with hexane to afford **11** (5.1g) as a faintly yellow liquid.

HPLC retention time: 5.169 min (5-95% acetonitrile with 0.05% TFA: water with 0.05% TFA).

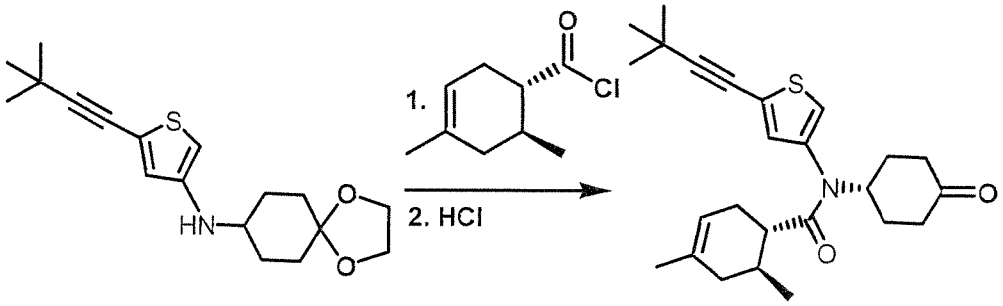
N-(5-(3,3-dimethylbut-1-ynyl)thiophen-3-yl)-1,4-dioxaspiro[4.5]decan-8-amine: **12**



12

A mixture of **11** (0.773g, 3.18 mmol), CuI (30 mg, 0.160 mmol), cesium carbonate (2.072g, 6.36 mmol), 2-acetylcyclohexanone (90mg, 0.636 mmol) and 1,4-dioxa-spiro[4.5]dec-8-ylamine (1.0g, 6.36 mmol) in DMF (1.6 mL) was degassed with N_2 then heated to 80 °C for 16 h in a sealed tube. The reaction was diluted with EtOAc, filtered through a pad of diatomaceous earth, washed with 5% LiCl aqueous solution, dried over sodium sulfate, filtered and concentrated. Flash chromatography (EtOAc:Hexanes) afforded **12**.

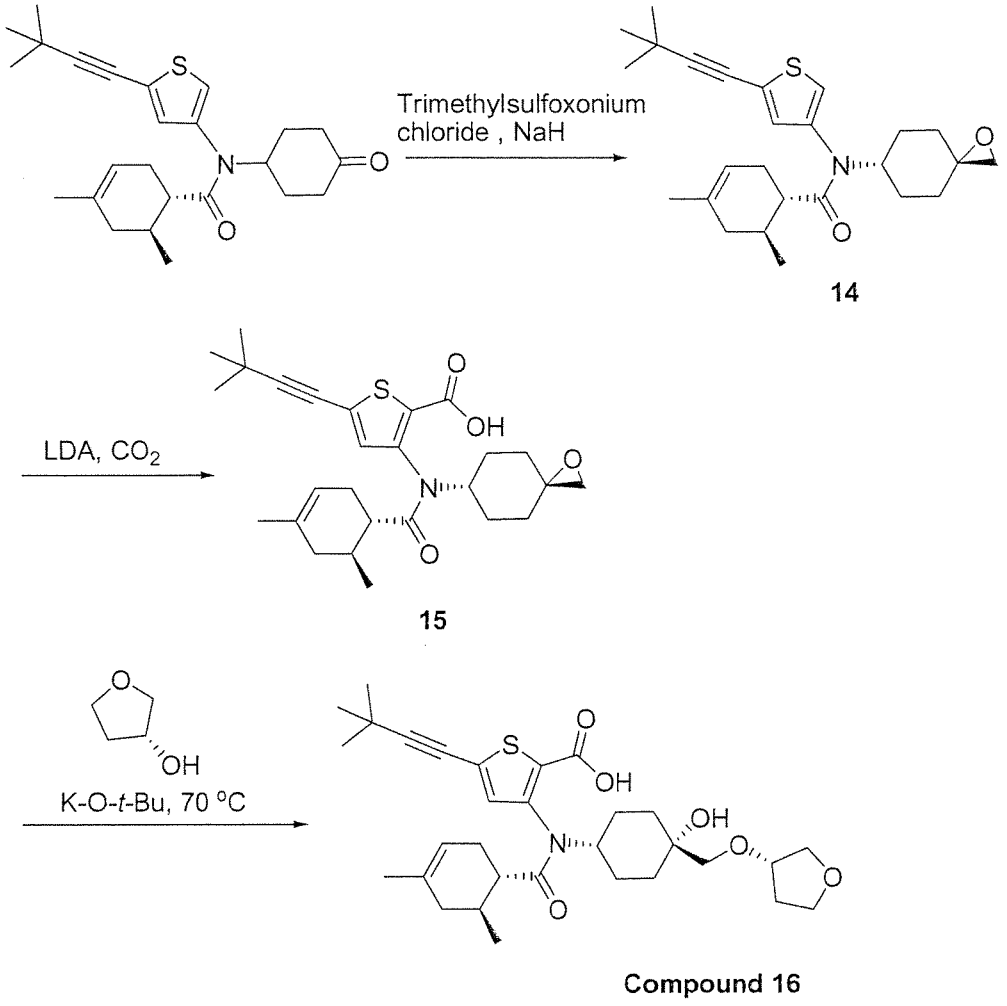
MS (m/z): 320.20 [M+H].



13

A solution of **12** (4.16 g, 13.0 mmol) in 1,2-dichloroethane (40 mL) was cool to 0 °C and treated with a solution of (1S,6S)-4,6-dimethylcyclohex-3-enecarbonyl chloride (3.88g, 24 mmol, prepared in a manner analogous to Scheme 2) in 20 mL 1,2-dichloroethane. The reaction mixture was allowed to gradually warm to room temperature and stirred for 17 hours, at which point it was diluted with DCM, twice washed with saturated $NH_4Cl_{(aq)}$, dried over $MgSO_4$, filtered and concentrated. The residue was purified by silica gel to give a mixture of (1S,6S)-N-(5-(3,3-dimethylbut-1-ynyl)thiophen-3-yl)-4,6-dimethyl-N-(1,4-dioxaspiro[4.5]decan-8-yl)cyclohex-3-enecarboxamide and the product of ketal hydrolysis (5.60 g, 12.3 mmol). This

mixture was taken up in THF (70 mL), treated with 4N $HCl_{(aq)}$, and stirred at 45 °C for 90 minutes. THF was removed under reduced pressure, and the resulting aqueous layer was thrice extracted with EtOAc. The combined organic layers were washed with saturated $NaHCO_{3(aq)}$, water, and brine, dried over $MgSO_4$, filtered, and concentrated to 5.05 g of ketone product **13**.



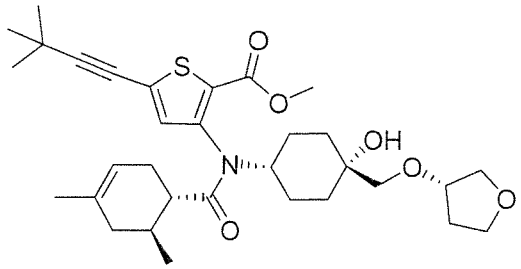
Compound 16

A solution of trimethylsulfoxonium chloride (0.47 g, 3.64 mmol) in THF (8mL)/ DMSO (8 mL) was treated with NaH (0.126 g, 3.16 mmol) at room temperature for 20 minutes. A solution of **13** (1 g, 2.43 mmol) in a THF (8mL) was added dropwise over a period of 7 min stirring was continued for 0.5h. The reaction mixture was cooled to 0 ° and was quenched with 10% citric acid (200 mL). The aqueous layer was extracted with ethyl acetate (300 mL) and the combined organic phases were washed with brine (500 mL), dried over Na_2SO_4, and concentrated. The crude

material was purified by silica gel chromatography to give (1S,6S)-N-(5-(3,3-dimethylbut-1-ynyl)thiophen-3-yl)-4,6-dimethyl-N-((3R,6s)-1-oxaspiro[2.5]octan-6-yl)cyclohex-3-enecarboxamide (**14**) (0.25 g, 0.58 mmol).

A solution of **14** (0.25 g, 0.58 mmol) in THF (3 mL) was cooled to -78 °C and treated with LDA (2M in THF, 2.35 mmol). After 2h, CO_2 (g) was bubbled through the reaction mixture for 15 min. The reaction mixture was allowed to warm to room temperature and quenched with NH_3Cl (sat). The aqueous layer was extracted with ethyl acetate (50 mL) and the combined organic phases were washed with brine (100 mL), dried over Na_2SO_4, and concentrated to give **15**. The crude material was dissolved in NMP (1 mL) and treated with potassium tert-butoxide (2.5 mmol) and (S)-tetrahydrofuran-3-ol (2.5 mmol). The reaction mixture was heated to 40 °C for 16 h. The reaction was then cooled and neutralized with aqueous HCl (1M). The product was extracted with ethyl acetate, concentrated and purified by HPLC with CH_3CN (0.1% TFA)/H_2O (0.1% TFA) to provide **Compound 16**. MS (m/z): 558.1 [M-H]-; HPLC retention time 4.47 min (2-98% acetonitrile: water with 0.1% trifluoroacetic acid) 6 min run.

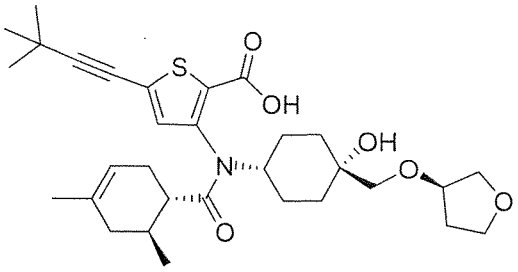
Compound 17



Compound 17

A solution of **16** (0.025 g, 0.044 mmol) in DCM/ MeOH (5 mL/ 1 mL) was treated with trimethylsilyldiazomethane (2 M in hexanes, 0.22 mL) for 30 min. The reaction was concentrated and purified by HPLC with CH_3CN (0.1% TFA)/H_2O(0.1% TFA) to provide the title compound as a solid. MS (m/z): 572.1 [M-H]-; HPLC retention time 5.08 min (2-98% acetonitrile: water with 0.1% trifluoroacetic acid) 6 min run.

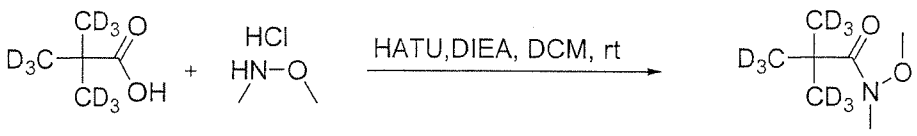
Compound 18



18

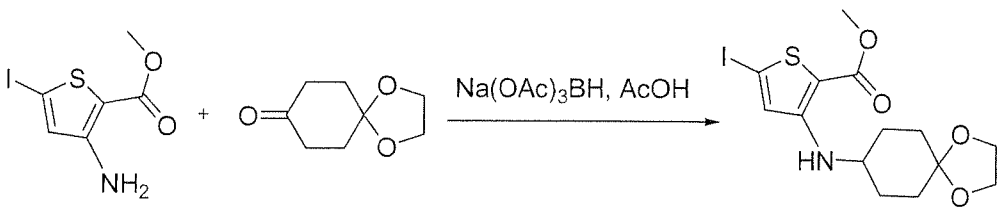
Compound 18 was synthesized in a manner analogous to **Compound 18** utilizing the (R)-tetrahydrofuran-3-ol. MS (m/z): 558.1 [M+H]+ ; HPLC retention time 4.48 min (2-98% acetonitrile: water with 0.1% trifluoroacetic acid) 6 min run.

Example 32



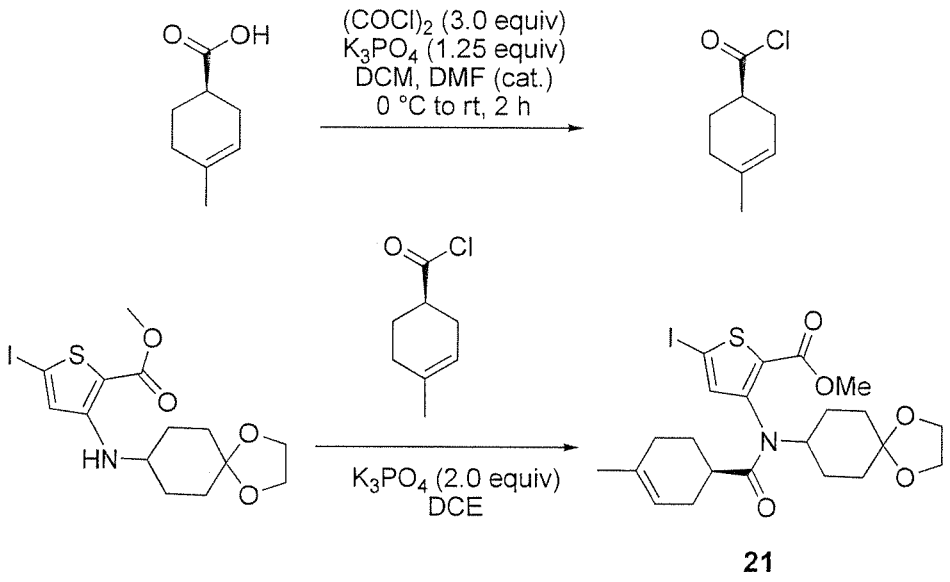
19

HATU (32.5 g, 85.5 mmol, 1.1 equiv) and N,O-dimethylhydroxylamine hydrochloride (8.3 g, 85.5 mmol, 1.1 equiv) were charged into a round-bottomed flask containing 300 mL dichloromethane. DIEA (40 mL, 233 mmol, 3.0 equiv) was added, followed by a solution of d_9-pivalic acid (8.6 g, 77.7 mmol, 1.0 equiv) in DCM (25 mL). The reaction was stirred at room temperature until complete consumption of the carboxylic acid. The solution was concentrated in vacuo to remove volatiles and the residue was partitioned between DCM (200 mL) and saturated NH_4Cl (100 mL). The aqueous phase was extracted with DCM (200 mL) and the combined organics were dried over Na_2SO_4 and then concentrated. The residue was purified by silica gel chromatography to afford **19** (5.1 g, 33 mmol, 42% yield) as colorless oil.



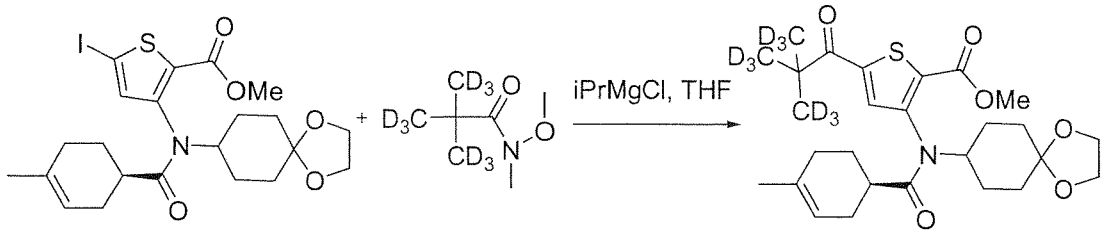
20

Methyl 3-amino-5-iodothiophene-2-carboxylate (6.24 g, 22 mmol, 1.0 equiv) and ketal (5.16 g, 33 mmol, 1.5 equiv) were dissolved in 27 mL acetic acid in a round-bottomed flask. Sodium triacetoxyborohydride (7.0 g, 33 mmmol, 1.5 equiv) was added in portions at room temperature. After the reaction was complete, water (30 mL) was added and the mixture was poured into EtOAc (200 mL). The phases were separated and the organics were washed with H_2O and brine, and then dried over Na_2SO_4. The volatiles were removed in vacuo and the residue was purified by silica gel chromatography to afford **20** (7.1 g, 17 mmol, 76% yield) as a yellow solid.



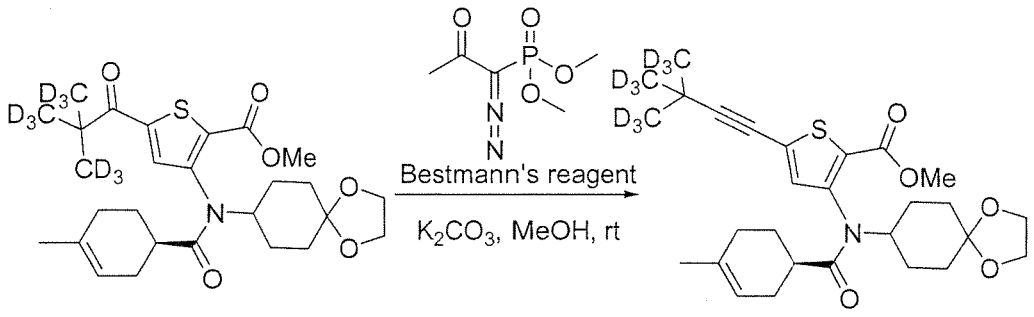
21

Compound **20** (7.1 g, 17 mmol) and freshly grounded K_3PO_4 (7.12 g, 33 mmol) were suspended in DCE (40 mL) in a 250 mL round-bottomed flask. The solution was cooled to 0 °C in an ice-water bath. (R)-4-Methylcyclohex-3-enecarbonyl chloride (7.9 g, 50 mmol) in DCE (25 mL) was added dropwise via syringe. After the addition, the reaction was stirred overnight at reflux. The reaction was diluted with DCM (200 mL), and the organics were washed with saturated NH_4Cl (2 × 100 mL). After drying over Na_2SO_4, the organic layer was concentrated to give a yellow foamy solid. The residue was purified by silica gel chromatography to afford **21** (5.5 g, 10 mmol, 60% yield) as an off-white solid.



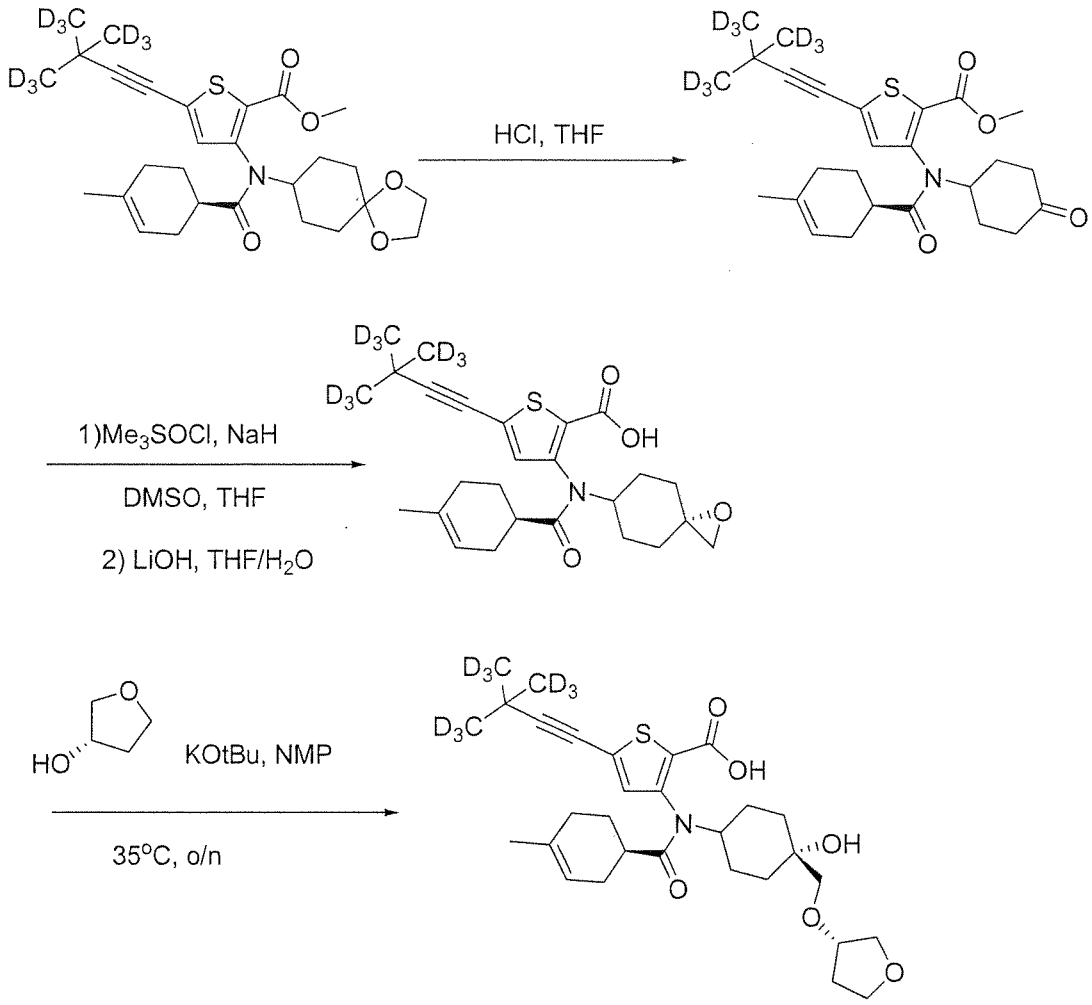
22

A solution of **21** (1.0 g, 1.9 mmol, 1.0 equiv) in THF (12.0 mL) in a round-bottomed flask was cooled to 0 °C. Isopropylmagnesium chloride (2.0 M in THF, 2.1 mmol, 1.1 equiv) was added dropwise and the mixture was stirred for 30 min. A solution of the Weinreb amide **19** (322 mg, 2.1 mmol, 1.1 equiv) in THF (1.0 mL) was added slowly and the resulting solution was gradually warmed to room temperature and stirred overnight. The reaction was poured into saturated NH_4Cl (50 mL) and extracted with DCM (2 × 100 mL). The combined organics were dried over Na_2SO_4 and then concentrated. The crude **22** was taken to the next step without purification.



23

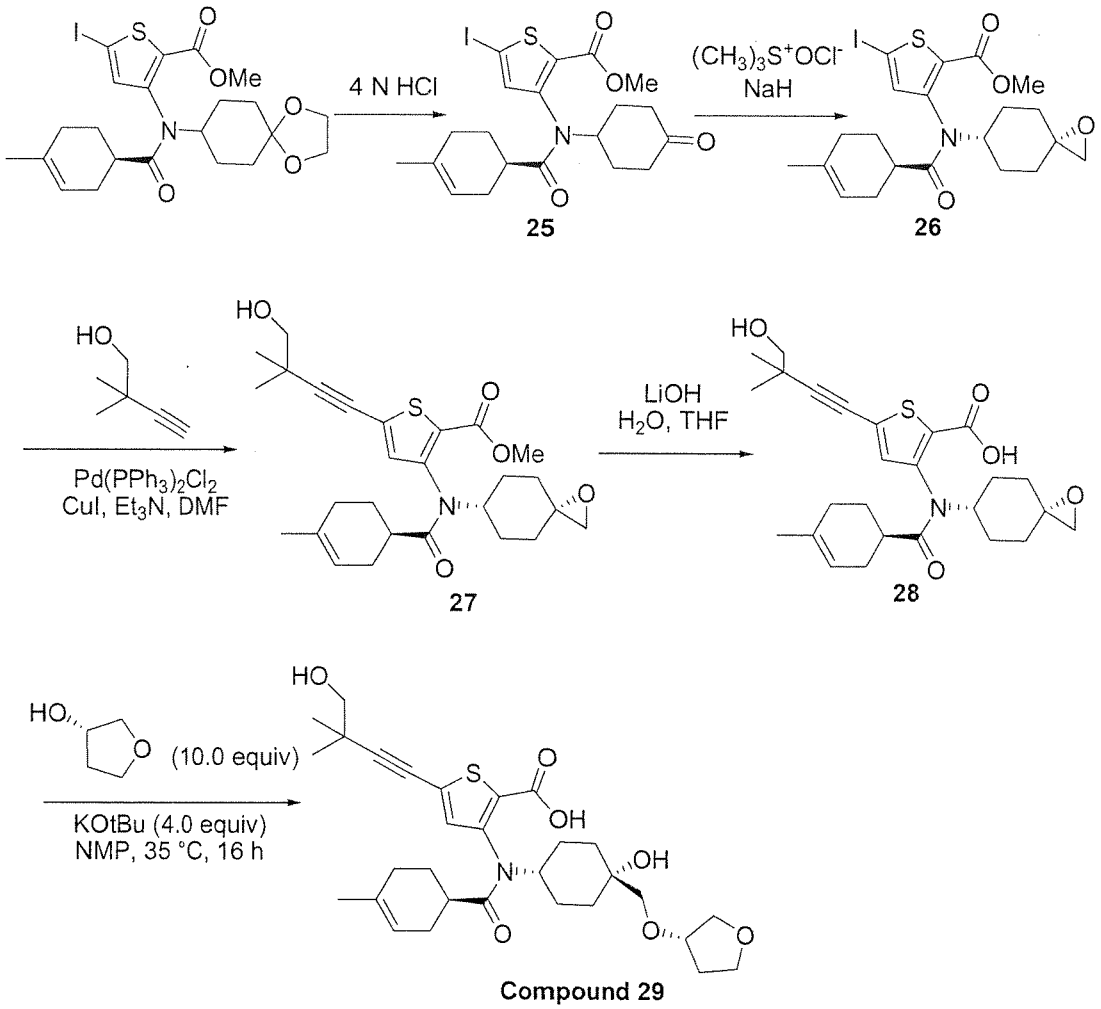
To a solution of **22** (97 mg, 0.19 mmol, 1.0 equiv) and dimethyl 1-diazo-2-oxopropylphosphonate (110 mg, 0.57 mmole, 3.0 equiv) in MeOH (3.0 mL) was added K_2CO_3 (105 mg, 0.758 mmol, 4.0 equiv). The resulting solution was stirred over night at room temperature. The reaction was then partitioned between EtOAc (50 mL) and 1 N HCl (50 mL). The organic was dried over Na_2SO_4 and then concentrated. The crude was purified by silica gel column chromatography to afford **23** (70 mg, 0.138 mmol, 73% yield) as a white solid.



Compound 24

The subsequent synthetic transformations necessary for the preparation of **Compound 24** were performed in a manner similar those described in Example 27. MS (m/z): 553.1 [M+H]+; HPLC retention time 4.46min (2-98% acetonitrile: water with 0.05% trifluoroacetic acid over 6 min).

Example 33: Compound 29



Step 1: Synthesis of (R)-methyl 5-iodo-3-(4-methyl-N-(4-oxocyclohexyl)cyclohex-3-enecarboxamido)thiophene-2-carboxylate (**25**)

A mixture of **21** (2.0 g, 3.6 mmol) and HCl (40 mmol, 4 N HCl) in THF (20 mL) was heated at 45 °C for 20 min. The reaction was diluted with ethyl acetate and the organic layer was separated then washed with sodium bicarbonate (sat aq) and brine. The organic layer was dried over sodium sulfate, filtered and concentrated to afford **25**. The crude was taken to the next step without further purification.

MS (m/z): 502.2 [M+H]; HPLC retention time: 2.67 min (2-98% acetonitrile:water with 0.05% formic acid over 3.5 min).

Step 2: Synthesis of methyl 5-iodo-3-((R)-4-methyl-N-((3S,6s)-1-oxaspiro[2.5]octan-6-yl)cyclohex-3-enecarboxamido)thiophene-2-carboxylate (**26**)

Trimethylsulfoxonium chloride (592 mg, 4.6 mmol) in DMSO (10 mL) was treated with sodium hydride (162 mg, 60% oil dispersion, 4.03 mmol) and stirred at ambient temperature for 30 min. Compound **25** (residue from previous step) in THF (10 mL) was added dropwise and the reaction mixture was stirred for 30 min. The orange solution was treated with 10% citric acid until pH~4 and partitioned between water and ethyl acetate. The organic layer was separated and the aqueous was extracted again with ethyl acetate. The combined organics were washed with water and brine, and dried over sodium sulfate. After filtration and concentration, the residue was purified by flash chromatography (EtOAc:hexanes) to afford **26** (1.3 g, 2.52 mmol, 69%) as a white solid.

MS (m/z): 515.9 [M+H]; HPLC retention time: 2.76 min (2-98% acetonitrile:water with 0.05% formic acid over 3.5 min).

Step 3: Synthesis of methyl 5-(4-hydroxy-3,3-dimethylbut-1-ynyl)-3-((R)-4-methyl-N-((3S,6s)-1-oxaspiro[2.5]octan-6-yl)cyclohex-3-enecarboxamido)thiophene-2-carboxylate (**27**)

Compound **26** (260 mg, 0.5 mmol), 2,2-dimethylbut-3-yn-1-ol (150 mg, 1.5 mmol), bis(triphenylphosphine)palladium(II) dichloride (18 mg, 0.025 mmol), CuI (9.5 mg, 0.05 mmol) and triethylamine (1 mL) were dissolved in DMF (5 mL) in a sealed tube. The mixture was heated at 80 °C for 5 h. The reaction was then poured into EtOAc (200 mL) and washed with NH_4Cl (2 × 50 mL) and 5% LiCl (2 × 50 mL). The organic layer was separated and the aqueous was extracted again with ethyl acetate. The combined organics were washed with water and brine, and dried over sodium sulfate. After filtration and concentration, the residue was purified by flash chromatography (EtOAc:hexanes) to afford **27** (203 mg, 0.42 mmol, 84%) as a white solid.

MS (m/z): 486.1 [M+H]; HPLC retention time: 2.60 min (2-98% acetonitrile:water with 0.05% formic acid over 3.5 min).

Step 4: Synthesis of 5-(4-hydroxy-3,3-dimethylbut-1-ynyl)-3-((R)-4-methyl-N-((3S,6s)-1-oxaspiro[2.5]octan-6-yl)cyclohex-3-enecarboxamido)thiophene-2-carboxylic acid (**28**)

Compound **27** (203 mg, 0.42 mmol) was dissolved in THF (5 mL) and water (3 mL). $LiOH.H_2O$ (176 mg) was added. The mixture was stirred at ambient

temperature for one day and then quenched with 10% citric acid aqueous solution (5 mL). The reaction mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried and concentrated to give **28** (186 mg).

Step 5: Synthesis of 5-(4-hydroxy-3,3-dimethylbut-1-ynyl)-3-((R)-N-((1R,4S)-4-hydroxy-4-(((S)-tetrahydrofuran-3-yloxy)methyl)cyclohexyl)-4-methylcyclohex-3-enecarboxamido)thiophene-2-carboxylic acid (**29**)

(*S*)-Tetrahydro-furan-3-ol (187 mg, 2.1 mmol) in 1-methyl-pyrrolidin-2-one (4.0 mL) was treated with potassium *tert*-butoxide (95 mg, 0.848 mmol) and stirred at ambient temperature for 20 minutes. To this mixture was added **28** (100 mg, 0.21 mmol). The reaction mixture was heated at 35 °C for 16 h under an inert atmosphere. After cooling the mixture was treated with 10% citric acid aqueous solution until pH~3, partitioned between ethyl acetate and water and separated. The aqueous layer was extracted again with ethyl acetate and the combined organics were washed with water, brine and dried over sodium sulfate. After filtration and concentration the residue was purified by HPLC with CH_3CN (0.1% TFA)/H_2O(0.1% TFA) to afford **Compound 29** (10 mg, 0.018 mmol, 9%).
MS (m/z): 560.1 [M+H]+

Biological Examples

Antiviral Activity

Another aspect of the invention relates to methods of inhibiting viral infections, comprising the step of treating a sample or subject suspected of needing such inhibition with a composition of the invention.

Within the context of the invention samples suspected of containing a virus include natural or man-made materials such as living organisms; tissue or cell cultures; biological samples such as biological material samples (blood, serum, urine, cerebrospinal fluid, tears, sputum, saliva, tissue samples, and the like); laboratory samples; food, water, or air samples; bioproduct samples such as extracts of cells, particularly recombinant cells synthesizing a desired glycoprotein; and the like. Typically the sample will be suspected of containing an organism which induces a viral infection, frequently a pathogenic organism such as a tumor virus. Samples can

be contained in any medium including water and organic solvent\water mixtures. Samples include living organisms such as humans, and man made materials such as cell cultures.

If desired, the anti-virus activity of a compound of the invention after application of the composition can be observed by any method including direct and indirect methods of detecting such activity. Quantitative, qualitative, and semiquantitative methods of determining such activity are all contemplated. Typically one of the screening methods described above are applied, however, any other method such as observation of the physiological properties of a living organism are also applicable.

The antiviral activity of a compound of the invention can be measured using standard screening protocols that are known. For example, the antiviral activity of a compound can be measured using the following general protocols.

Cell-based Flavivirus Immunodetection assay

BHK21 or A549 cells are trypsinized, counted and diluted to $2x10^5$ cells/mL in Hams F-12 media (A549 cells) or RPMI-1640 media (BHK21 cells) supplemented with 2% fetal bovine serum (FBS) and 1% penicillin/streptomycin. $2x10^4$ cells are dispensed in a clear 96-well tissue culture plates per well and palced at 37° C, 5% CO_2 overnight. On the next day, the cells are infected with viruses at multiplicity of infection (MOI) of 0.3 in the presence of varied concentrations of test compounds for 1 hour at 37° C and 5% CO_2 for another 48 hours. The cells are washed once with PBS and fixed with cold methanol for 10 min. After washing twice with PBS, the fixed cells are blocked with PBS containing 1% FBS and 0.05% Tween-20 for 1 hour at room temperature. The primary antibody solution (4G2) is then added at a concentration of 1:20 to 1:100 in PBS containing 1% FBS and 0.05% Tween-20 for 3 hours. The cells are then washed three times with PBS followed by one hour incubation with horseradish peroxidase(HRP)-conjugated anti-mouse IgG (Sigma, 1:2000 dilution). After washing three times with PBS, 50 microliters of 3,3',5,5'-tetramethylbenzidine (TMB) substrate solution (Sigma) is added to each well for two minutes. The reaction is stopped by addition of 0.5 M sulfuric acid. The plates are read at 450 nm abosorbance for viral load quantification. After measurement, the

cells are washed three times with PBS followed by incubation with propidium iodide for 5 min. The plate is read in a Tecan Safire™ reader (excitation 537 nm, emission 617 nm) for cell number quantification. Dose response curves are plotted from the mean absorbance versus the log of the concentration of test compounds. The EC_{50} is calculated by non-linear regression analysis. A positive control such as N-nonyl-deoxynojirimycin may be used.

Cell-based Flavivirus cytopathic effect assay

For testing against West Nile virus or Japanese encephalitis virus, BHK21 cells are trypsinized and diluted to a concentration of 4 x 10^5 cells/mL in RPMI-1640 media supplemented with 2% FBS and 1% penicillin/streptomycin. For testing against dengue virus, Huh7 cells are trypsinized and diluted to a concentration of 4 x 10^5 cells/mL in DMEM media supplemented with 5% FBS and 1% penicillin/streptomycin. A 50 microliter of cell suspension (2 x 10^4 cells) is dispensed per well in a 96-well optical bottom PIT polymer-based plates (Nunc). Cells are grown overnight in culture medium at 37° C, 5% CO_2, and then infected with West Nile virus (e.g. B956 strain) or Japanese encephalitis virus (e.g. Nakayama strain) at MOI = 0.3, or with dengue virus (e.g. DEN-2 NGC strain) at MOI = 1, in the presence of different concentrations of test compounds. The plates containing the virus and the compounds are further incubated at 37°C, 5% CO_2 for 72 hours. At the end of incubation, 100 microliters of CellTiter-Glo™ reagent is added into each well. Contents are mixed for 2 minutes on an orbital shaker to induce cell lysis. The plates are incubated at room temperature for 10 minutes to stabilize luminescent signal. Lumnescence reading is recorded using a plate reader. A positive control such as N-nonyl-deoxynojirimycin may be used.

Antiviral Activity in a Mouse Model of Dengue Infection.

Compounds are tested *in vivo* in a mouse model of dengue virus infection (Schul *et al.* J. Infectious Dis. 2007; 195:665-74). Six to ten week old AG129 mice (B&K Universal Ltd, Hll, UK) are housed in individually ventilated cages. Mice are injected intraperitoneally with 0.4 mL TSV01 dengue virus 2 suspension. Blood samples are taken by retro orbital puncture under isoflurane anaesthesia. Blood samples are collected in tubes containing sodium citrate to a final concentration of 0.4%, and immediately centrifuged for 3 minutes at 6000g to obtain plasma. Plasma

(20 microliters) is diluted in 780 microliters RPMI-1640 medium and snap frozen in liquid nitrogen for plaque assay analysis. The remaining plasma is reserved for cytokine and NS1 protein level determination. Mice develop dengue viremia rising over several days, peaking on day 3 post-infection.

For testing of antiviral activity, a compound of the invention is dissolved in vehicle fluid, e.g. 10% ethanol, 30% PEG 300 and 60% D5W (5% dextrose in water; or 6N HCl (1.5 eq):1N NaOH (pH adjusted to 3.5): 100 mM citrate buffer pH 3.5 (0.9% v/v:2.5% v/v: 96.6% v/v). Thirty six 6-10 week old AG129 mice are divided into six groups of six mice each. All mice are infected with dengue virus as described above (day 0). Group 1 is dosed by oral gavage of 200 mL/mouse with 0.2 mg/kg of a compound of the invention twice a day (once early in the morning and once late in the afternoon) for three consecutive days starting on day 0 (first dose just before dengue infection). Groups 2, 3 and 4 are dosed the same way with 1 mg/kg, 5 mg/kg and 25 mg/kg of the compound, respectively. A positive control may be used, such as (2R,3R,4R,5R)-2-(2-amino-6-hydroxy-purin-9-yl)-5-hydroxymethyl-3-methyl-tetrahydro-furan-3,4-diol, dosed by oral gavage of 200 microliters/mouse the same way as the previous groups. A further group is treated with only vehicle fluid.

On day 3 post-infection approximately 100 microliter blood samples (anti-coagulated with sodium citrate) are taken from the mice by retro-orbital puncture under isoflurane anaesthesia. Plasma is obtained from each blood sample by centrifugation and snap frozen in liquid nitrogen for plague assay analysis. The collected plasma samples are analyzed by plague assay as described in Schul *et al.* Cytokines are also analysed as as described by Schul. NS1 protein levels are analysed using a Platelia™ kit (BioRad Laboratories). An anti-viral effect is indicated by a reduction in cytokine levels and/or NS1 protein levels.

Typically, reductions in viremia of about 5-100 fold, more typically 10-60 fold, most typically 20-30 fold, are obtained with 5-50 mg/kg bid dosages of the compounds of the invention.

HCV Assay Protocol

The anti-HCV activity of the compounds of this invention was tested in a human hepatoma Huh-7 cell line harboring a HCV replicon. The assay comprised the following steps:

Step 1: compound preparation and serial dilution.

Serial dilution was performed in 100% DMSO in a 384-well plate. A solution containing a compound at 225-fold concentration of the starting final serial dilution concentration was prepared in 100% DMSO and 15 uL added to the pre-specified wells in column 3 or 13 of a polypropylene 384-well plate. The rest of the 384-well plate was filled with 10 uL 100% DMSO except for columns 23 and 24, where 10 uL of 500 uM a HCV protease inhibitor (ITMN-191) in 100% DMSO was added. The HCV protease inhibitor was used a control of 100% inhibition of HCV replication. The plate was then placed on a Biomek FX Workstation to start the serial dilution. The serial dilution was performed for ten cycles of 3-fold dilution from column 3 to 12 or from column 13 to 22.

Step 2: cell culture plate preparation and compound addition

To each well of a black polypropylene 384-well plate, 90 µL of cell media containing 1600 suspended Huh-7 HCV replicon cells was added with a Biotek uFlow Workstation. A volume of 0.4 µL of the compound solution was transferred from the serial dilution plate to the cell culture plate on a Biomek FX Workstation. The DMSO concentration in the final assay condition was 0.44%. The plates were incubated for 3 days at 37 °C with 5% CO2 and 85% humidity.

Step 3: detection of cytotoxicity and inhibition of viral replication

a) Assessment of cytotoxicity: The media in the 384-well cell culture plate was aspirated with a Biotek EL405 plate-washer. A volume of 50 µL of a solution containing 400 nM Calcein AM in 100% PBS was added to each well of the plate with a Biotek uFlow Workstation. The plate was incubated for 30 minutes at room temperature before the fluorescence signal (emission 490 nm, exitation 520 nm) was measured with a Perkin Elmer Envision Plate Reader.

b) Assessment of inhibition of viral replication: The calcein-PBS solution in the 384-well cell culture plate was aspirated with a Biotek EL405 plate-washer. A volume of 20 µL of Dual-Glo luciferase buffer (Promega, Dual-Glo Luciferase Assay Reagent, cat. #E298B) was added to each well of the plate with a Biotek uFlow Workstation. The plate was incubated for 10 minutes at room temperature. A volume of 20 µL of a solution containing 1:100 mixture of Dual-Glo Stop & Glo substrate(Promega, Dual-

Glo Luciferase Assay Reagent, cat. #E313B) and Dual-Glo Stop & Glo buffer (Promega, Dual-Glo Luciferase Assay Reagent, cat. #E314B) was then added to each well of the plate with a Biotek uFlow Workstation. The plate was incubated at room temperature for 10 minutes before the luminescence signal was measured with a Perkin Elmer Envision Plate Reader.

Step 4: calculation

The percent cytotoxicity was determined by calcein AM conversion to fluorescent product. The average fluorescent signal from the DMSO control wells were defined as 100% nontoxic. The individual fluorescent signal from testing compound treated well was divided by the average signal from DMSO control wells and then multiplied by 100% to get the percent viability. The percent anti-HCV replication activity was determined by the luminescence signal from the testing well compared to DMSO controls wells. The background signal was determined by the average luminescence signal from the HCV protease inhibitor treated wells and was subtracted from the signal from the testing wells as well as the DMSO control wells. Following 3-fold serial dilutions, the EC_{50} and CC_{50} values were calculated by fitting % inhibition at each concentration to the following equation:

$$\% \text{ inhibition} = 100\%/[(EC_{50}/[I])^b + 1]$$

Where b is Hill's coefficient. See, for reference, Hill, A. V., *The Possible Effects of the Aggregation of the Molecules of Hæmoglobin on its Dissociation Curves*, J. Physiol. **40**: iv-vii. (1910).

% inhibition values at a specific concentration, for example 2μM, can also be derived from the formula above.

When tested, certain compounds of this invention were found to inhibit viral replication as listed in Table 1:

Table 1

Compound	% inhibition at 2μM
1	99.9
2	99.98
3	99.97
4	99.64
5A	99.97
5B	99.95

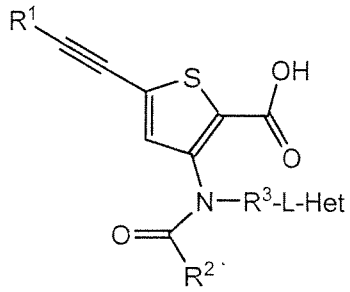
6	99.88
7	99.98
8	99.94
9	100
10	100
16	99.99
17	78.85
18	100
24	100
29	100

The specific pharmacological responses observed may vary according to and depending on the particular active compound selected or whether there are present pharmaceutical carriers, as well as the type of formulation and mode of administration employed, and such expected variations or differences in the results are contemplated in accordance with practice of the present invention.

Although specific embodiments of the present invention are herein illustrated and described in detail, the invention is not limited thereto. The above detailed descriptions are provided as exemplary of the present invention and should not be construed as constituting any limitation of the invention. Modifications will be obvious to those skilled in the art, and all modifications that do not depart from the spirit of the invention are intended to be included within the scope of the appended claims.

WHAT IS CLAIMED IS:

1. A compound 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, 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, $-NO_2$, $-N(=O)$, $-SR^{10}$, $-S(O)R^{10}$, $-S(O)_2R^{10}$, $-S(O)_2 NR^{10}R^{11}$, $-NR^{10}C(O)R^{11}$, $-NR^{10}C(O)NR^{11}R^{12}$, $-NR^{10}S(O)R^{11}$, $-NR^{10}S(O)_2R^{11}$, $-OP(O)R^{11}R^{12}$, $-P(O)R^{11}R^{12}$, $-P(O)OR^{11}R^{12}$, $-P(O)(OR^{11})OR^{12}$, $-C(O)NR^{11}R^{12}$, 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, -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 $-OC(O)NR^{11}R^{12}$;

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 $-S(O)_2R^{14}$;

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;

$\mathbf{R^2}$ 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, independently, is selected from the group consisting of halogen, oxo, oxide, $-NO_2$, $-N(=O)$, $-SR^{20}$, $-S(O)R^{20}$, $-S(O)_2R^{20}$, $-S(O)_2\ NR^{20}R^{21}$, $-NR^{20}C(O)R^{21}$, $-NR^{20}C(O)NR^{21}R^{22}$, $-NR^{20}S(O)R^{21}$, $-NR^{20}S(O)_2R^{21}$, $-OP(O)R^{21}R^{22}$, $-P(O)R^{21}R^{22}$, $-P(O)OR^{21}R^{22}$, $-P(O)(OR^{21})OR^{22}$, $-C(O)NR^{21}R^{22}$, 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, -OH, $-NR^{21}R^{22}$, $-C(O)OR^{20}$, -CN, $-N_3$, $-C(=NR^{23})NR^{21}R^{22}$, $-C(=NR^{23})OR^{20}$, $-NR^{20}C(=NR^{23})N\ R^{21}R^{22}$, $-NR^{21}C(O)OR^{20}$, 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 C_{4-12} cycloalkylalkylene or substituted C_{4-12} cycloalkylalkylene;

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), $-SR^{30}$, $-S(O)R^{30}$, $-S(O)_2R^{30}$, $-S(O)_2\ NR^{30}R^{31}$, $-NR^{30}C(O)R^{31}$, $-NR^{30}C(O)NR^{31}R^{32}$, $-NR^{30}S(O)R^{31}$, $-NR^{30}S(O)_2R^{31}$, $-OP(O)R^{31}R^{32}$, $-P(O)R^{31}R^{32}$, $-P(O)OR^{31}R^{32}$, $-P(O)(OR^{31})OR^{32}$, $-C(O)NR^{31}R^{32}$, 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, -OH, $-NR^{31}R^{32}$, $-C(O)OR^{30}$, -CN, $-N_3$, $-C(=NR^{33})NR^{31}R^{32}$, $-C(=NR^{33})OR^{30}$, $-NR^{30}C(=NR^{33})N\ R^{31}R^{32}$, $-NR^{31}C(O)OR^{30}$, 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;

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 membered heteroaryl;

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), $-SR^{40}$, $-S(O)R^{40}$, $-S(O)_2R^{40}$, $-S(O)_2NR^{40}R^{41}$, $-NR^{40}C(O)R^{41}$, $-NR^{40}C(O)NR^{41}R^{42}$, $-NR^{40}S(O)R^{41}$, $-NR^{40}S(O)_2R^{41}$, $-OP(O)R^{41}R^{42}$, $-P(O)R^{41}R^{42}$, $-P(O)OR^{41}R^{42}$, $-P(O)(OR^{41})OR^{42}$, $-C(O)NR^{41}R^{42}$, 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, $-NR^{41}R^{42}$, $-C(O)OR^{40}$, -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 $-OC(O)NR^{41}R^{42}$;

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, optionally substituted 3-12 membered heterocyclyl, optionally substituted 3-18 membered heteroarylalkyl, and optionally substituted C_{6-18} arylalkyl;

or R^{41} and R^{42} taken together with the atoms to which they are attached form a 3 to 10 membered heterocyclyl;

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}, 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, $-NR^{51}R^{52}$, $-C(O)OR^{50}$, -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 $-OC(O)NR^{51}R^{52}$;

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, $-C(O)R^{54}$, -CHO and $-S(O)_2R^{54}$;

each R^{54}, independently, is optionally substituted C_{1-12} alkyl;

wherein, each substituted Q^5, substituted R^{50}, substituted R^{51}, substituted R^{52}, substituted R^{53}, or substituted R^{54} 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), $-SR^{60}$, $-S(O)R^{60}$, $-S(O)_2R^{60}$, $-S(O)_2 NR^{60} R^{61}$, $-NR^{60}C(O)R^{61}$, $-NR^{60}C(O)NR^{61}R^{62}$, $-NR^{60}S(O)R^{61}$,$-NR^{60}S(O)_2R^{61}$, $-OP(O)R^{61}R^{62}$, $-P(O)R^{61}R^{62}$, $-P(O)OR^{61}R^{62}$, $-P(O)(OR^{61})OR^{62}$, $-C(O)NR^{61}R^{62}$, 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, $-NR^{61}R^{62}$, $-C(O)OR^{60}$, -CN, $-N_3$, $-C(=NR^{63})NR^{61}R^{62}$, $-C(=NR^{63})OR^{60}$, $-NR^{60}C(=NR^{63})N R^{61}R^{62}$, $-NR^{61}C(O)OR^{60}$, and $-OC(O)NR^{61}R^{62}$;

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, optionally substituted C_{2-12} alkenyl, optionally substituted C_{2-12} alkynyl, or optionally substituted C_{3-12} cycloalkyl.

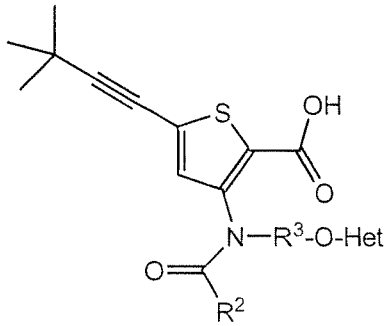
3. The compound of claim 1 or 2, wherein R^1 is optionally substituted C_3-C_7 secondary or tertiary alkyl.

4. The compound of any one of claims 1-3 wherein R^2 is optionally substituted C_{3-12} cycloalkyl.

5. The compound of any one of claims 1-4 wherein L is –O-.

6. The compound of anyone of claims 1-5 wherein R^3 is optionally substituted cycloalkylmethylene or optionally substituted cycloalkylethylene.

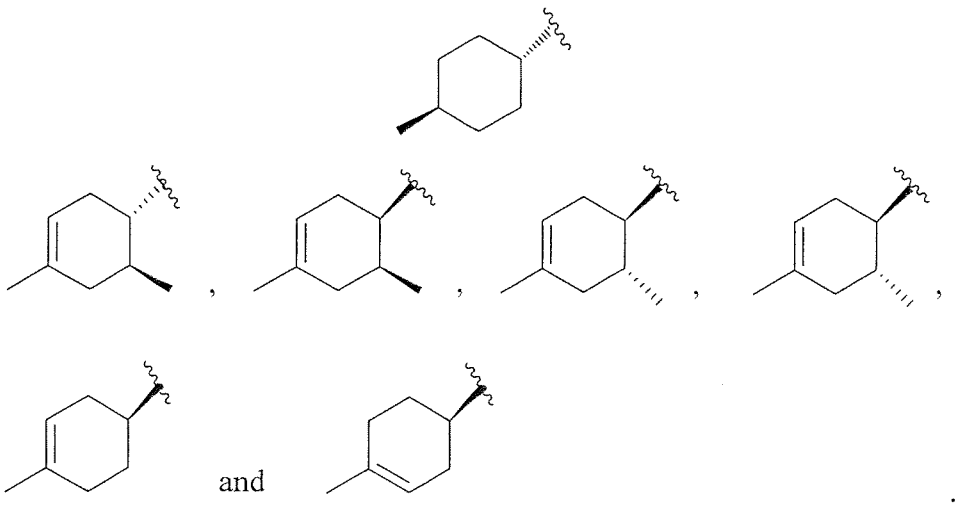
7. The compound of claim 1 represented by Formula II:



Formula II

or a pharmaceutically acceptable salt or ester thereof, wherein
R^2 is optionally substituted 4-methylcyclohexyl or optionally substituted 4-methylcyclohexenyl.

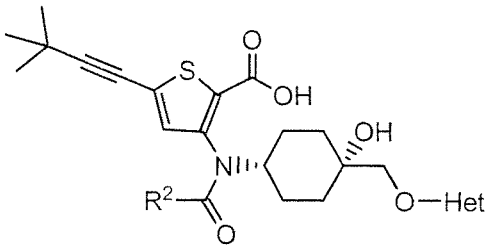
8. The compound of any one of claims 1-7 wherein R^2 is selected from the group consisting of



9. The compound of any one of claims 1-8 wherein R^3 is optionally substituted cyclohexylmethylene.

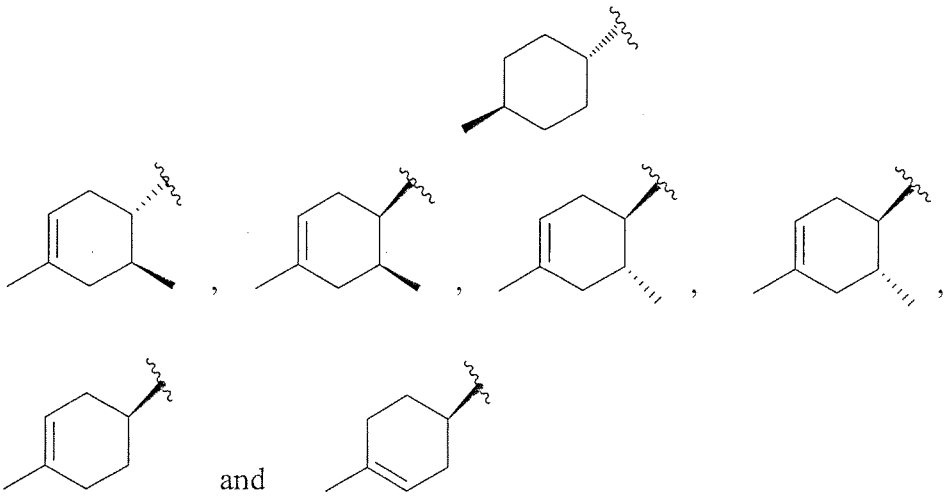
10. The compound of any one of claims 1-9, wherein Het is an optionally substituted 3-12 membered heterocyclyl comprising one or two heteroatoms selected from O, S, or N.

11. The compound of claim 1 represented by Formula III:



Formula III

wherein R^2 is selected from the group consisting of



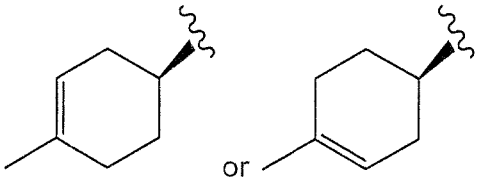
and

; or a pharmaceutically acceptable salt or ester thereof.

12. The compound of any one of claims 1-11 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 azetidinyl, optionally substituted tetrahydrofuranyl, optionally substituted tetrahydro-2*H*-furo[2,3-b]furanyl, optionally substituted thiazoyl, optionally substituted

1*H*-imidazolyl, optionally substituted 1*H*-pyrazolyl, optionally substituted quinolinyl, optionally substituted thiophenyl, optionally substituted pyrimidinyl.

13. The compound of any one of claims 1-12 wherein R^2 is

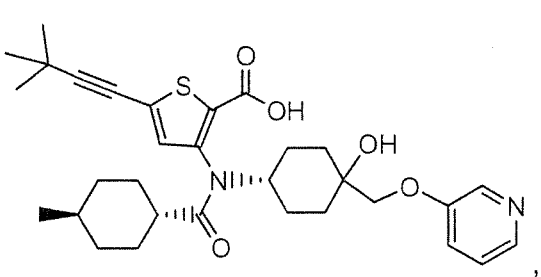


or

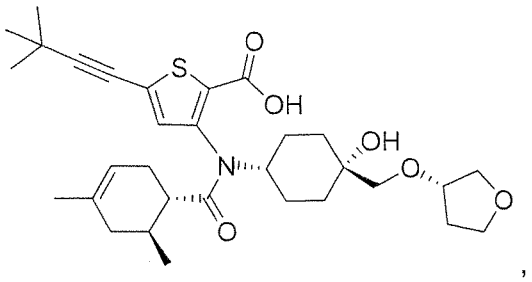
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14. The compound of any one of claims 1-13 wherein Het is optionally substituted tetrahydrofuran-3-yl.

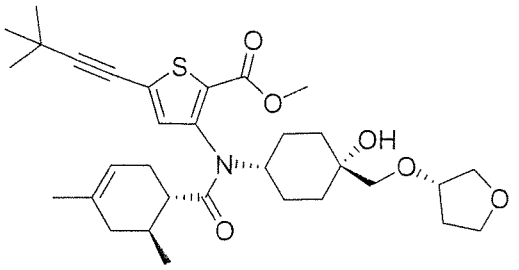
15. The compound of claim 1 selected from



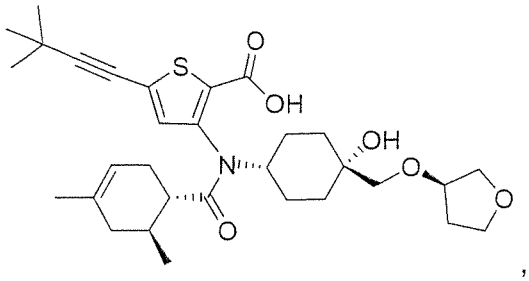
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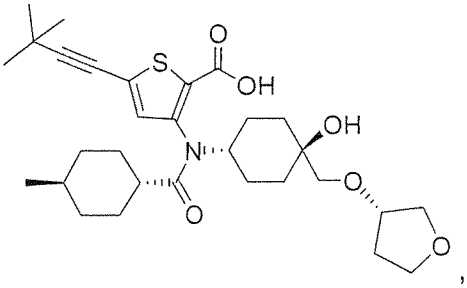
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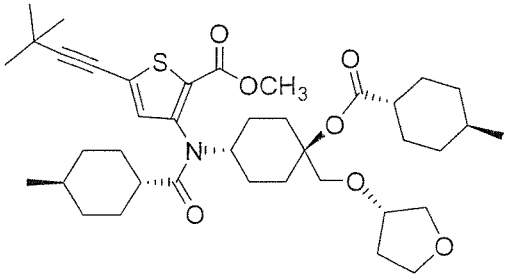
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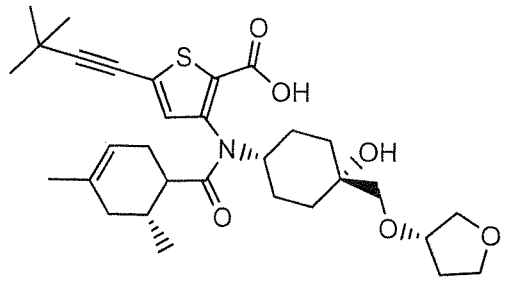
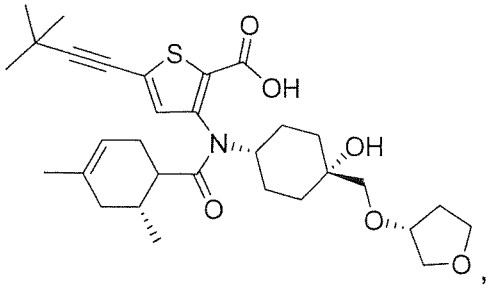
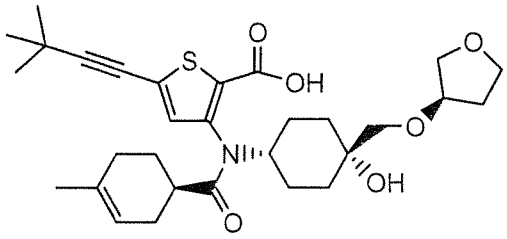
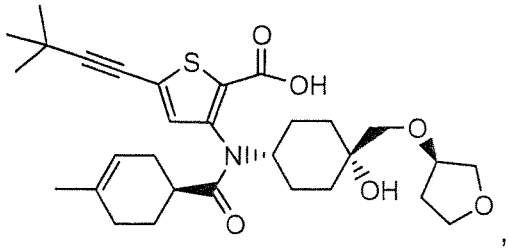
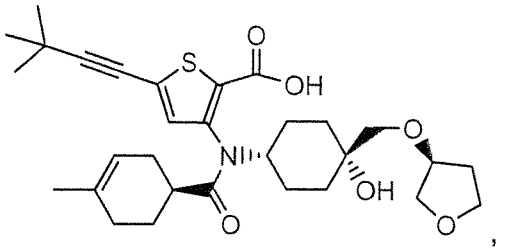
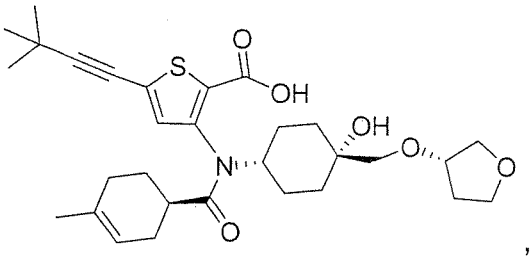
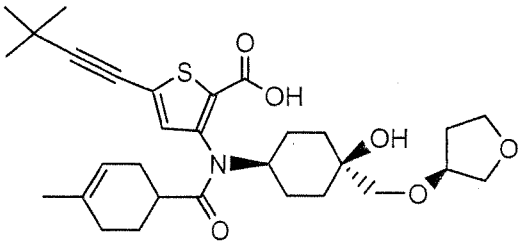
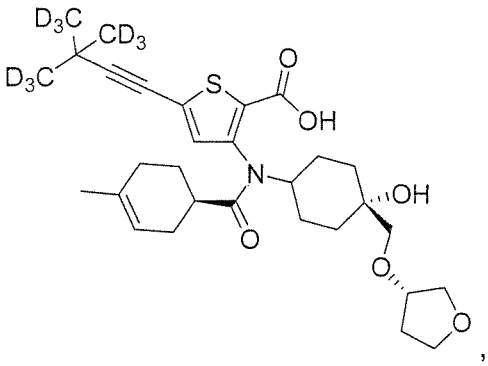
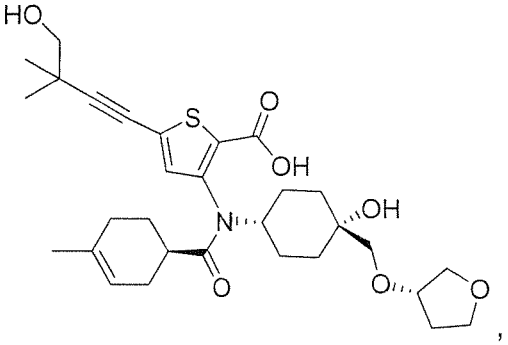
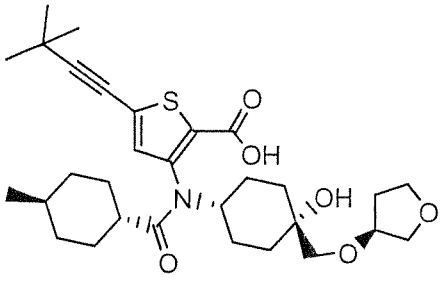
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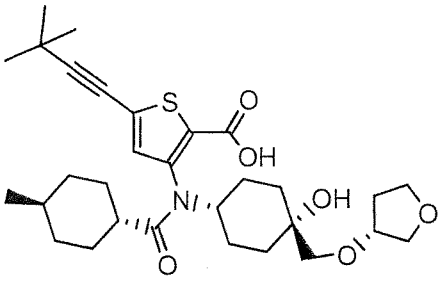


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or



; or a pharmaceutically acceptable salt or ester thereof.

16. A pharmaceutical composition comprising a therapeutically effective amount of a compound of any one of claims 1-15 and a pharmaceutically acceptable carrier or excipient.

17. The pharmaceutical composition of claim 16 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, 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. A method of treating a viral infection 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, Kunjin virus, Murray Valley encephalitis virus, St. Louis encephalitis virus, Omsk hemorrhagic fever virus, bovine viral diarrhea virus, Zika virus and Hepatitis C virus comprising administering to a mammal in need thereof a therapeutically effective amount of a compound or pharmaceutical composition of any one of claims 1-15.

19. The method of claim 18 wherein the viral infection is caused by Hepatitis C virus.

20. The method of claim 19 further comprising administering 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, 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.

21. Use of a compound according to any one of claims 1-15 for the manufacture of a medicament for the treatment of a *Flaviviridae* viral infection.

22. A compound according to any one of claims 1-15, for use in treating a *Flaviviridae* viral infection.