ANTI-VIRAL COMPOUNDS

This application claims the benefit from and incorporates herein by references the entire content of U.S. Provisional Application No. 61/140,318, filed December 23, 2008.

FIELD

The present invention relates to compounds effective in inhibiting replication of Hepatitis C virus ("HCV"). The present invention also relates to compositions comprising these compounds and methods of using these compounds to treat HCV infection.

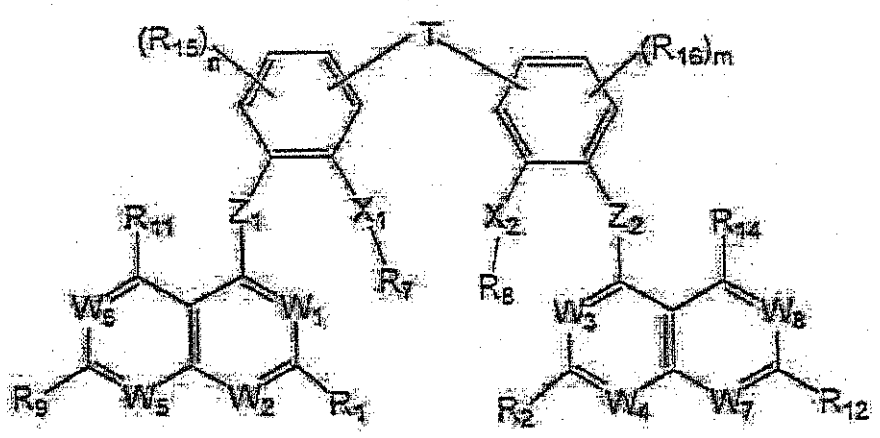
BACKGROUND

HCV is an RNA virus belonging to the Hepacivirus genus in the Flaviviridae family. HCV has enveloped virions that contain a positive stranded RNA genome encoding all known virus-specific proteins in one single, uninterrupted, open reading frame. The open reading frame comprises approximately 9500 nucleotides encoding a single large polyprotein of about 3000 amino acids. The polyprotein comprises a core protein, envelope proteins E1 and E2, a membrane bound protein p7, and the non-structural proteins NS2, NS3, NS4A, NS4B, NS5A and NS5B.

HCV infection is associated with progressive liver pathology, including cirrhosis and hepatocellular carcinoma. Chronic hepatitis C may be treated with peginterferon-alpha in combination with ribavirin. Substantial limitations to efficacy and tolerability remain as many users suffer from side effects and viral elimination from the body is often inadequate. Therefore, there is a need for new drugs to treat HCV infection.

SUMMARY

In a first aspect, there is provided a compound of Formula II, or a pharmaceutically acceptable salt thereof,



II

wherein:

X_1 and X_2 are each independently selected from a bond, $-CH_2-$, -O-, or -S-, and at least one of X_1 and X_2 is selected from $-CH_2-$, -O-, or -S-;

R_7 and R_8 are each independently selected from hydrogen or C_6aryl optionally substituted with one or more R_A, and at least one of R_7 and R_8 is selected from C_6aryl optionally substituted with one or more R_A;

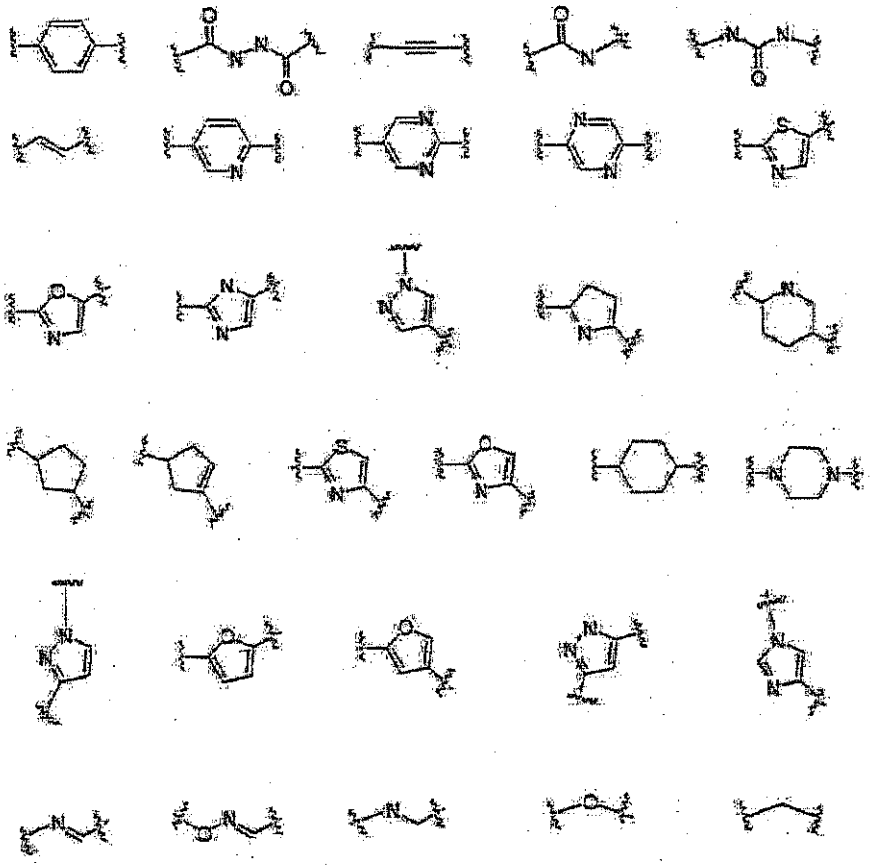
Z_1 and Z_2 are each selected from $-N(R_B)-$;

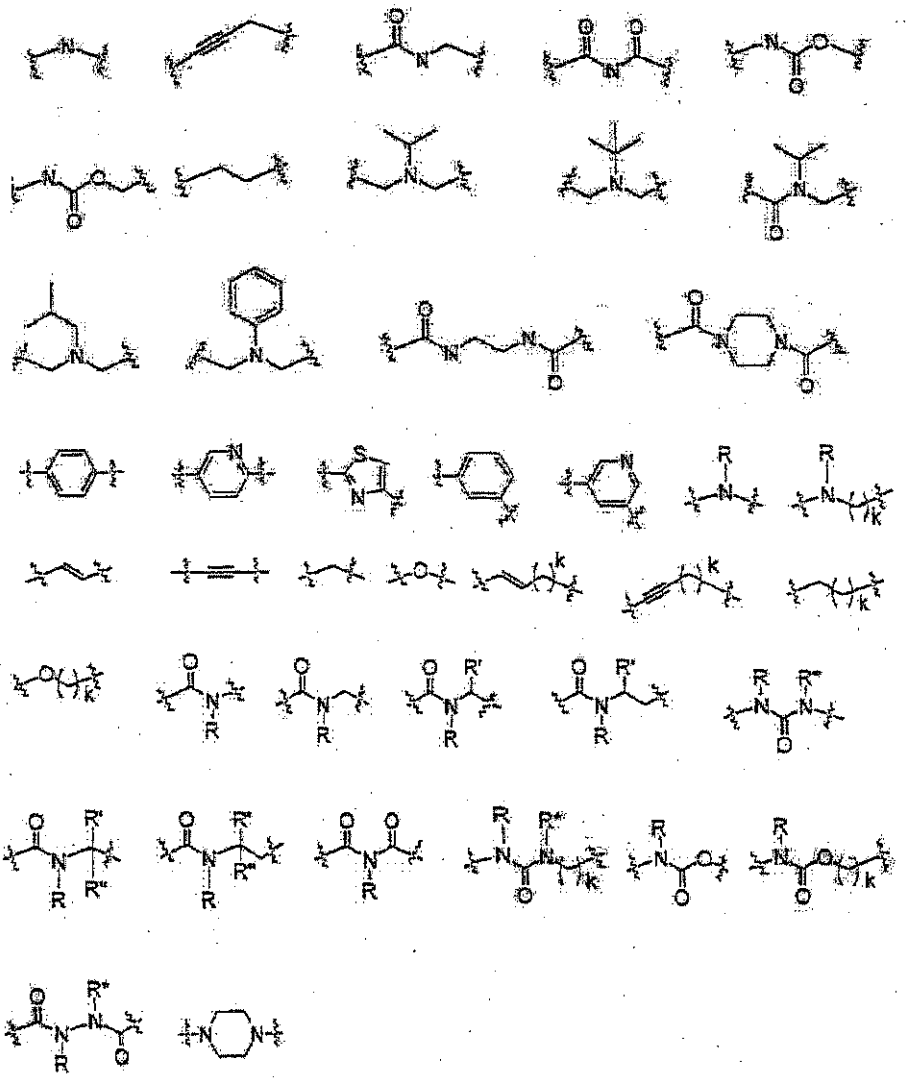
W_1, W_2, W_3, W_4, W_5, W_6, W_7, and W_8 are each independently selected from N or $C(R_D)$, wherein R_D is selected at each occurrence from hydrogen;

R_1, R_2, R_9, R_{11}, R_{12}, R_{14}, R_{15}, and R_{16} are each independently selected at each occurrence from hydrogen or RA;

m and n are each 0;

T is selected from a bond, $-L_S-$, $-L_S-M-L_S-$, or from the following moieties:





in which k is 1 or 2, R and R* are independently hydrogen or C_1-C_6alkyl, and R' and R'' are independently C_1-C_6alkyl or C_6-C_{10}aryl; wherein M and M' are each independently selected from a -N(R_B)-, -C(O)N(R_B)-, -N(R_B)C(O)-, -N(R_B)C(O)N($R_{B'}$)-, C_6aryl, or 6-membered heterocycle containing an N heteroatom, and wherein T is optionally substituted with one or more R_A;

R_A is independently selected at each occurrence from halogen, hydroxy, amino, -L_A, or -L_S-R_E;

R_B and $R_{B'}$ are each independently selected at each occurrence from hydrogen; or C_1-C_6alkyl, C_6aryl, or C_6arylC_1-C_6alkyl;

R_C and $R_{C'}$ are each independently selected at each occurrence from hydrogen; halogen; hydroxy; mercapto; amino; carboxy; nitro; phosphate; oxo;

thioxo; formyl; cyano; or C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, or C_3-C_6carbocyclyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, phosphate, oxo, thioxo, formyl or cyano;

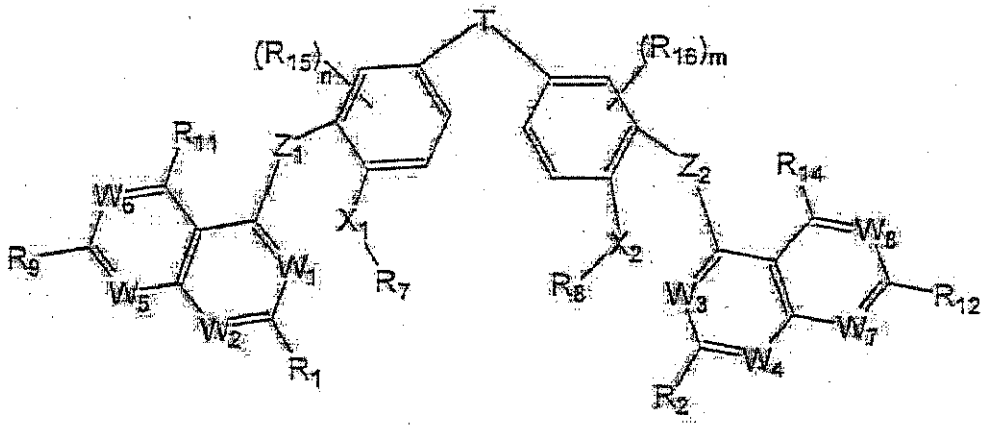
L_A is selected at each occurrence from C_1-C_6alkyl;

L_S, $L_{S'}$ and $L_{S''}$ are each independently selected at each occurrence from a bond; or C_1-C_6alkylene, or C_2-C_6alkynylene;

R_E is independently selected at each occurrence from -O-R_S or-N($R_SR_{S'}$); and

R_S and $R_{S'}$ are each independently selected at each occurrence from hydrogen; or C_1-C_6alkyl, or C_6arylC_1-C_6alkyl.

In a second aspect, there is provided a compound of Formula III, or a pharmaceutically acceptable salt thereof,



III

wherein:

X_1 and X_2 are each independently selected from a bond, -CH_2-, -O-, or -S-, and at least one of X_1 and X_2 is selected from -CH_2-, -O-, or -S-;

R_7 and R_8 are each independently selected from hydrogen or C_6aryl optionally substituted with one or more R_A, and at least one of R_7 and R_8 is selected from C_6aryl optionally substituted with one or more R_A;

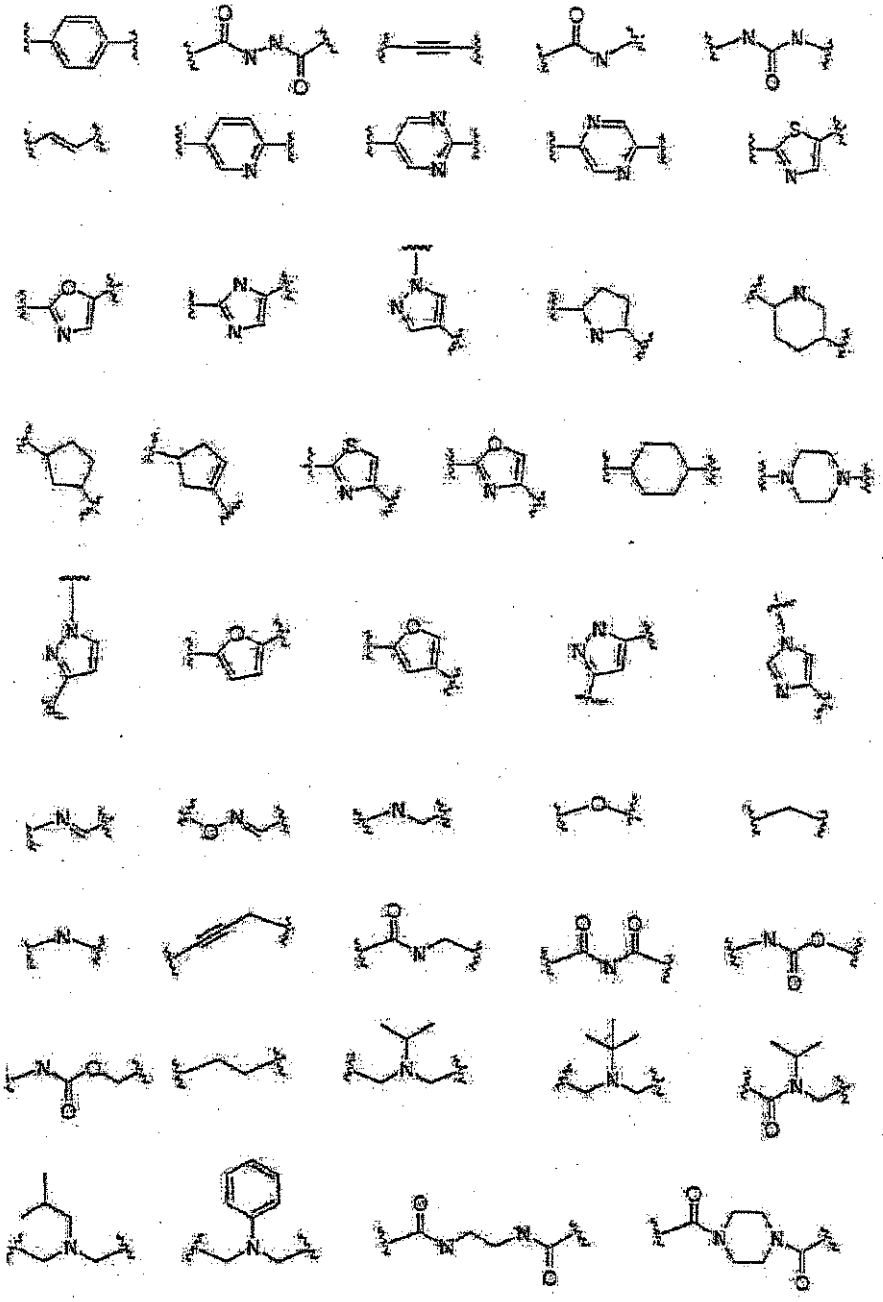
Z_1 and Z_2 are each selected from -N(R_B)-;

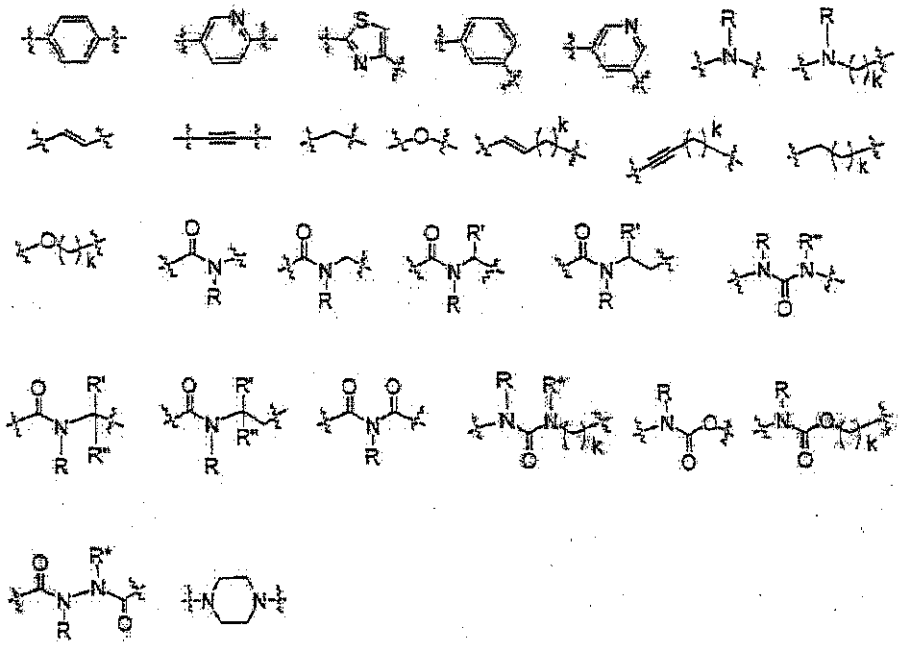
W_1, W_2, W_3, W_4, W_5, W_6, W_7, and W_8 are each independently selected from N or C(R_D), wherein R_D is selected at each occurrence from hydrogen;

R_1, R_2, R_9, R_{11}, R_{12}, R_{14}, R_{15}, and R_{16} are each independently selected at each occurrence from hydrogen or R_A;

m and n are each 0;

T is selected from a bond, -L_S-, -L_S-M-L_S-, or from the following moieties:





in which k is 1 or 2, R and R* are independently hydrogen or C_1-C_6alkyl, and R' and R'' are independently C_1-C_6alkyl or C_6-C_{10}aryl; wherein M and M' are each independently selected from a -N(R_B)-, -C(O)N(R_B)-, -N(R_B)C(O)-, -N(R_B)C(O)N($R_{B'}$)-, C_6aryl, or 6-membered heterocycle containing an N heteroatom, and wherein T is optionally substituted with one or more R_A;

R_A is independently selected at each occurrence from halogen, hydroxy, amino, -L_A, or -L_S-R_E;

R_B and $R_{B'}$ are each independently selected at each occurrence from hydrogen; or C_1-C_6alkyl, C_6aryl, or C_6arylC_1-C_6alkyl;

R_C and $R_{C'}$ are each independently selected at each occurrence from hydrogen; halogen; hydroxy; mercapto; amino; carboxy; nitro; phosphate; oxo; thioxo; formyl; cyano; or C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, or C_3-C_6carbocyclyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen,

hydroxy, mercapto, amino, carboxy, nitro, phosphate, oxo, thioxo, formyl or cyano;

L_A is selected at each occurrence from C_1-C_6alkyl;

L_S, $L_{S'}$ and $L_{S''}$ are each independently selected at each occurrence from a bond; or C_1-C_6alkylene, or C_2-C_6alkynylene;

R_E is independently selected at each occurrence from -O-R_S or -N(R_S $R_{S'}$); and

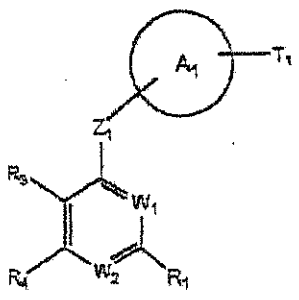
R_S and $R_{S'}$ are each independently selected at each occurrence from hydrogen; or C_1-C_6alkyl, or C_6arylC_1-C_6alkyl.

In a third aspect, there is provided a pharmaceutical composition comprising a compound or salt as defined herein.

In a fourth aspect, there is provided the use of a compound or salt as defined herein for inhibiting HCV replication in a patient, in the manufacture of a medicament for treating HCV infection.

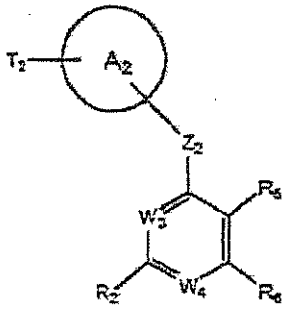
In a fifth aspect, there is provided a process of making a compound as defined herein, comprising the step of:

coupling a compound of Formula IV



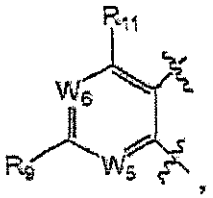
IV

to a compound of Formula V

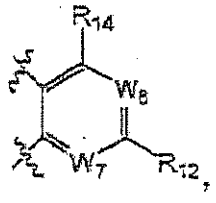


V

wherein T_1 is a carboxylic acid, an activated derivative, or an activated ester, T_2 is an amine or a substituted amine, A_1 is phenyl substituted with $-X_1$-R_7 and optionally substituted with one or more R_A, A_2 is phenyl substituted with $-X_2$-R_8 and optionally substituted with one or more R_A, R_3 and R_4, taken together with the carbon atoms to which they are attached, form



R_5 and R_6, taken together with the carbon atoms to which they are attached, form



, and

X_1, X_2, Z_1, Z_2, W_1, W_2, W_3, W_4, W_5, W_6, W_7, W_8, R_1, R_2, R_7, R_8, R_9, R_{11}, R_{12}, R_{14}, and R_A are as defined herein.

In a sixth aspect, there is provided a method of inhibiting HCV virus replication in vitro, comprising contacting cells infected with HCV virus with a compound or salt as defined herein.

The present ~~invention~~disclosure features compounds of Formulae I, II and III, and pharmaceutically acceptable salts thereof. These compounds and salts are capable of inhibiting the replication of HCV.

The present ~~invention~~disclosure also features compositions comprising the compounds or salts of the present ~~invention~~disclosure. The compositions can also include other therapeutic agents, such as HCV helicase inhibitors, HCV polymerase inhibitors, HCV protease inhibitors, NS5A inhibitors, CD81 inhibitors, cyclophilin inhibitors, or internal ribosome entry site (IRES) inhibitors.

The present ~~invention~~disclosure further features methods of using the compounds or salts of the present ~~invention~~disclosure to inhibit HCV replication. The methods comprise contacting cells infected with HCV virus with a compound or salt of the present ~~invention~~disclosure, thereby inhibiting the replication of HCV virus in the cells.

In addition, the present ~~invention~~disclosure features methods of using the compounds or salts of the present ~~invention~~disclosure, or compositions comprising the same, to treat HCV infection. The methods

comprise administering a compound or salt of the present ~~invention~~disclosure, or a pharmaceutical composition comprising the same, to a patient in need thereof, thereby reducing the blood or tissue level of HCV virus in the patient.

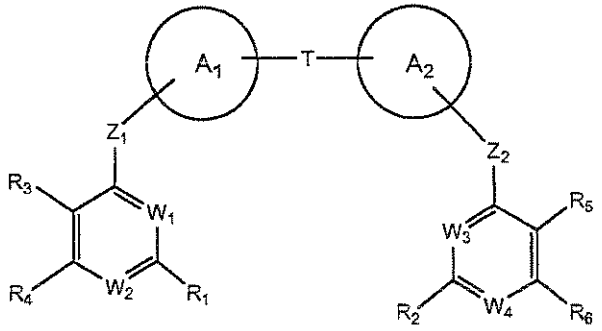
The present ~~invention~~disclosure also features use of the compounds or salts of the present ~~invention~~disclosure for the manufacture of medicaments for the treatment of HCV infection.

Furthermore, the present ~~invention~~disclosure features processes of making the compounds or salts of the ~~invention~~disclosure.

Other features, objects, and advantages of the present ~~invention~~disclosure are apparent in the detailed description that follows. It should be understood, however, that the detailed description, while indicating preferred embodiments of the ~~invention~~disclosure, are given by way of illustration only, not limitation. Various changes and modifications within the scope of the ~~invention~~disclosure will become apparent to those skilled in the art from the detailed description.

DETAILED DESCRIPTION

The present invention features compounds having Formula I, and pharmaceutically acceptable salts thereof,



I

wherein:

A_1 is C_5-C_{10}carbocyclyl or 5- to 10-membered heterocyclyl, and is substituted with $-X_1$-R_7, wherein said C_5-C_{10}carbocyclyl and 5- to 10-membered heterocyclyl are optionally substituted with one or more R_A;

A_2 is C_5-C_{10}carbocyclyl or 5- to 10-membered heterocyclyl, and is substituted with $-X_2$-R_8, wherein said C_5-C_{10}carbocyclyl and 5- to 10-membered heterocyclyl are optionally substituted with one or more R_A;

X_1 and X_2 are each independently selected from a bond, $-L_S-$, $-O-$, $-S-$, or $-N(R_B)-$;

R_7 and R_8 are each independently selected from hydrogen, $-L_A$, C_5-C_{10}carbocyclyl, or 5- to 10-membered heterocyclyl, wherein at each occurrence said C_5-C_{10}carbocyclyl and 5- to 10-membered heterocyclyl are each independently optionally substituted with one or more R_A;