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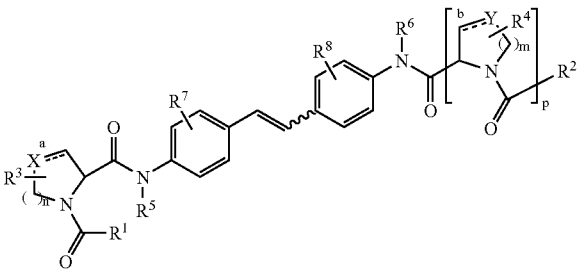
(57) **ABSTRACT**

Compounds having the structure of formula I are described.

(I)



The compounds can inhibit hepatitis C virus (HCV) replication, and in particular can inhibit the function of the HCV NS5A protein.

INHIBITORS OF HCV REPLICATION

CROSS REFERENCE TO RELATED APPLICATION

[0001] This application claims priority from U.S. Provisional Application Ser. No. 60/687,760, filed Jun. 6, 2005.

FIELD OF THE INVENTION

[0002] The present invention is generally directed to antiviral compounds, and more specifically directed to compounds which can inhibit the function of the NS5A protein encoded by Hepatitis C virus (HCV), compositions comprising such compounds, and methods for inhibiting the function of the NS5A protein.

BACKGROUND OF THE INVENTION

[0003] HCV is a major human pathogen, infecting an estimated 170 million persons worldwide—roughly five times the number infected by human immunodeficiency virus type 1. A substantial fraction of these HCV infected individuals develop serious progressive liver disease, including cirrhosis and hepatocellular carcinoma (Lauer, G. M.; Walker, B. D. *N. Engl. J. Med.* 2001, 345, 41-52).

[0004] Presently, the most effective HCV therapy employs a combination of alpha-interferon and ribavirin, leading to sustained efficacy in 40% of patients (Poynard, T. et al. *Lancet* 1998, 352, 1426-1432). Recent clinical results demonstrate that pegylated alpha-interferon is superior to unmodified alpha-interferon as monotherapy (Zeuzem, S. et al. *N. Engl. J. Med.* 2000, 343, 1666-1672). However, even with experimental therapeutic regimens involving combinations of pegylated alpha-interferon and ribavirin, a substantial fraction of patients do not have a sustained reduction in viral load. Thus, there is a clear and long-felt need to develop effective therapeutics for treatment of HCV infection.

[0005] HCV is a positive-stranded RNA virus. Based on a comparison of the deduced amino acid sequence and the extensive similarity in the 5' untranslated region, HCV has been classified as a separate genus in the Flaviviridae family. All members of the Flaviviridae family have enveloped virions that contain a positive stranded RNA genome encoding all known virus-specific proteins via translation of a single, uninterrupted, open reading frame.

[0006] Considerable heterogeneity is found within the nucleotide and encoded amino acid sequence throughout the HCV genome. At least six major genotypes have been characterized, and more than 50 subtypes have been described. The major genotypes of HCV differ in their distribution worldwide, and the clinical significance of the genetic heterogeneity of HCV remains elusive despite numerous studies of the possible effect of genotypes on pathogenesis and therapy.

[0007] The single strand HCV RNA genome is approximately 9500 nucleotides in length and has a single open reading frame (ORF) encoding a single large polyprotein of about 3000 amino acids. In infected cells, this polyprotein is cleaved at multiple sites by cellular and viral proteases to produce the structural and non-structural (NS) proteins. In the case of HCV, the generation of mature non-structural [illegible] be a metalloprotease and cleaves at the NS2-NS3 junction; the second one is a serine protease contained within the N-terminal region of NS3 (also referred to herein as NS3 protease) and mediates all the subsequent cleavages downstream of NS3, both in cis, at the NS3-NS4A cleavage site, and in trans, for the remaining NS4A-NS4B, NS4B-NS5A, NS5A-NS5B sites. The NS4A protein appears to serve multiple functions, acting as a cofactor for the NS3 protease and possibly assisting in the membrane localization of NS3 and other viral replicase components. The complex formation of the NS3 protein with NS4A seems necessary to the processing events, enhancing the proteolytic efficiency at all of the sites. The NS3 protein also exhibits nucleoside triphosphatase and RNA helicase activities. NS5B (also referred to herein as HCV polymerase) is a RNA-dependent RNA polymerase that is involved in the replication of HCV.

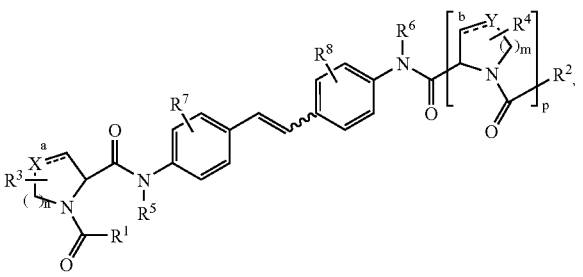
[0008] Among the compounds that have demonstrated efficacy in inhibiting HCV replication as selective HCV serine protease inhibitors are the peptide compounds disclosed in U.S. Patent No. 6,323,180. NS5B polymerase inhibitors have also demonstrated activity. However, none of these compounds have, to date, progressed beyond clinical trials (De Clercq, E. *J Clin. Virol.* 2001, 22, 73-89).

[0009] Compounds useful for treating HCV-infected patients are desired which selectively inhibit HCV viral replication. In particular, compounds which are effective to inhibit the function of the NS5A protein are desired. The HCV NS5A protein is described, for example, in Tan, S.-L., Katzel, M.G. *Virology* 2001, 284, 1-12; and in Park, K.-J.; Choi, S.-H, *J Biological Chemistry* 2003.

SUMMARY OF THE INVENTION

[0010] The present invention relates to compounds of formula (I)

(I)



or pharmaceutically acceptable salts thereof, wherein

[0011] $\overset{a}{\text{-----}}$ is a single or double bond;

[0012] $\overset{b}{\text{-----}}$ is a single or double bond;

[0013] when $\overset{a}{\text{-----}}$ is a single bond, X is selected from the group consisting of O, CH_2, and CHR^3;

[0014] when $\overset{a}{\text{-----}}$ is a double bond, X is selected from the group consisting of CH and CR^3;

[illegible]

[0016] when $\overset{b}{\cdots}$ is a double bond, Y is selected from the group consisting of CH and CR^4;

[0017] n and m are independently 0, 1, 2, or 3;

[0018] p is 0 or 1;

[0019] R^1 and R^2 are independently selected from the group consisting of alkoxy, alkoxyalkoxyalkyl, alkoxyalkyl, alkyl, alkylsulfenylalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, aryl, arylalkoxy, arylalkoxyalkyl, arylalkyl, arylcarbonyl, aryloxy, aryloxyalkyl, arylsulfenylalkyl, arylsulfinylalkyl, arylsulfonylalkyl, carboxyalkyl, cycloalkenyl, cycloalkenylalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkoxy, heterocyclylalkoxyalkyl, heterocyclylalkyl, heterocyclylcarbonyl, heterocyclyloxy, heterocyclyloxyalkyl, —NR^aR^b, and (NR^aR^b)alkyl;

[0020] R^3 and R^4 are independently selected from the group consisting of hydrogen, alkenyl, alkoxy, alkoxycarbonyloxy, alkyl, alkylsulfonyl, alkylsulfonyloxy, aryl, arylalkyl, azido, hydroxy, —NR^aR^b, (NR^aR^b)alkyl, and (NR^aR^b)carbonyloxy; wherein the alkenyl and the alkyl can optionally form a saturated or unsaturated cyclic structure, respectively, with an adjacent carbon atom;

[0021] R^5 and R^6 are independently selected from the group consisting of hydrogen, alkenyl, alkoxycarbonyl, alkyl, alkylcarbonyl, aryl, arylalkyl, heterocyclylalkylcarbonyl, and heterocyclylcarbonyl;

[0022] R^7 and R^8 are independently selected from the group consisting of hydrogen, alkenyl, alkoxy, alkyl, halo, and haloalkyl; and

[0023] R^a and R^b are independently selected from the group consisting of hydrogen, alkenyl, alkyl, alkylcarbonyl, aryl, arylalkyl, arylalkylcarbonyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl.

[0024] The present invention also provides compositions comprising the compounds of the invention or pharmaceutically acceptable enantiomers, diastereomers, salts, or solvates thereof and a pharmaceutically acceptable carrier. In particular, the present invention provides pharmaceutical compositions useful for inhibiting the function of the HCV NS5A protein comprising a compound of the present invention, or a pharmaceutically acceptable enantiomer, diastereomer, salt, or solvate thereof, and a pharmaceutically acceptable carrier.

[0025] The present invention fuirther provides methods for treating patients infected with HCV comprising administering to the patient a therapeutically effective amount of a compound of the present invention, or a pharmaceutically acceptable enantiomer, diastereomer, salt, or solvate thereof. Additionally, the present invention provides methods of inhibiting the function of HCV NS5A protein by contacting the HCV NS5A protein with a compound of the present invention.

[0026] By virtue of the present invention, it is now possible to provide improved drugs comprising the compounds of the invention which can be effective in the treatment of patients infected with HCV. Specifically, the present invention provides compounds that can inhibit the function of the NS5A protein. Further, a compound in accordance with the present invention, which is effective to inhibit the HCV NS5A protein, can be administered with another compound having anti-HCV activity, e.g., a compound which is effective to inhibit the function of a target selected from the group consisting of HCV metalloprotease, HCV serine protease, HCV polymerase, HCV helicase, HCV NS4B protein, HCV entry, HCV assembly, HCV egress, HCV NS5B protein, IMPDH, and a nucleoside analog for the treatment of an HCV infection.

DETAILED DESCRIPTION OF THE INVENTION

[0027] As used in the present specification the following terms have the meanings indicated:

[0028] The term "alkenyl," as used herein, refers to a straight or branched chain group of two to six carbon atoms containing at least one carbon-carbon double bond. Examples of alkenyl groups include, but are not limited to, ethenyl, 2-propenyl, and isobutenyl.

[0029] The term "alkoxy," as used herein, refers to an alkyl group attached to the parent molecular moiety through an oxygen atom.

[0030] The term "alkoxyalkoxy," as used herein, refers to an alkoxyalkyl group attached to the parent molecular moiety through an oxygen atom.

[0031] The term "alkoxyalkoxyalkyl," as used herein, refers to an alkyl group substituted with one, two, or three alkoxyalkoxy groups.

[0032] The term "alkoxyalkyl," as used herein, refers to an alkyl group substituted with one, two, or three alkoxy groups.

[0033] The term "alkoxycarbonyl," as used herein, refers to an alkoxy group attached to the parent molecular moiety through a carbonyl group.

[0034] The term "alkoxycarbonyloxy," as used herein, refers to an alkoxycarbonyl group attached to the parent molecular moiety through an oxygen atom.

[0035] The term "alkyl," as used herein, refers to a group derived from a straight or branched chain saturated hydrocarbon containing from one to six carbon atoms. Examples of alkyl groups include, but are not limited to, methyl, ethyl, isopropyl, and tert-butyl.

[0036] The term "alkylcarbonyl," as used herein, refers to an alkyl group attached to the parent molecular moiety through a carbonyl group.

[0037] The term "alkylsulfenyl," as used herein, refers to an alkyl group attached to the parent molecular moiety through a sulfur atom.

[0038] The term "alkylsulfenylalkyl," as used herein, refers to an alkyl group substituted with one, two, or three alkylsulfenyl groups.

[0039] The term "alkylsulfinyl," as used herein, refers to an alkyl group attached to the parent molecular moiety through a sulfinyl group.

[0040] The term "alkylsulfinylalkyl," as used herein,

[0041] The term "alkylsulfonyl," as used herein, refers to an alkyl group attached to the parent molecular moiety through a sulfonyl group.

[0042] The term "alkylsulfonylalkyl," as used herein, refers to an alkyl group substituted with one, two, or three alkylsulfonyl groups.

[0043] The term "alkylsulfonyloxy," as used herein, refers to an alkylsulfonyl group attached to the parent molecular moiety through an oxygen atom.

[0044] The term "alkynyl," as used herein, refers to a straight or branched chain hydrocarbon of two to six carbon atoms containing at least one carbon-carbon triple bond. Examples of alkynyl groups include, but are not limited to, ethynyl, propynyl, and 4-methyl-1-pentynyl.

[0045] The term "aryl," as used herein, refers to a phenyl group, or a bicyclic or tricyclic fused ring system wherein one or more of the rings is a phenyl group. Bicyclic fused ring systems consist of a phenyl group fused to a monocyclic cycloalkenyl group, a monocyclic cycloalkyl group, or another phenyl group. Tricyclic fused ring systems consist of a bicyclic fused ring system fused to a monocyclic cycloalkenyl group, a monocyclic cycloalkyl group, or another phenyl group. The aryl groups of the present invention can be attached to the parent molecular moiety through any substitutable carbon atom in the group. Representative examples of aryl groups include, but are not limited to, anthracenyl, azulenyl, bicyclooctatrienyl, fluorenyl, indanyl, indenyl, naphthyl, phenyl, and tetrahydronaphthyl. Preferred aryl groups of the present invention are bicyclooctatrienyl, fluorenyl, naphthyl, and phenyl. The aryl groups of the present invention can be optionally substituted with one, two, three, four, or five substituents independently selected from the group consisting of alkenyl, alkoxy, alkoxycarbonyl, alkyl, alkylcarbonyl, alkylsulfenyl, alkylsulfonyl, alkynyl, a second aryl group, arylalkoxy, arylalkyl, arylcarbonyl, aryloxy, arylsulfenyl, arylsulfonyl, azido, cyano, cycloalkenyl, cycloalkenylalkyl, cycloalkyl, cycloalkylalkyl, halo, haloalkoxy, haloalkyl, heterocyclyl, heterocyclylalkoxy, heterocyclylalkyl, heterocyclylcarbonyl, heterocyclyloxy, —NR^cR^d, (NR^cR^d)alkyl, (NR^cR^d)carbonyl, and oxo; wherein the aryloxy, the arylsulfenyl, and the arylsulfonyl, the cycloalkenyl, the cycloalkenyl part of the cycloalkenylalkyl, the cycloalkyl, the cycloalkyl part of the cycloalkylalkyl, the heterocyclyl, and the heterocyclyl part of the heterocyclylalkoxy, the heterocyclylalkyl, the heterocyclylcarbonyl, and the heterocyclyloxy can be fuirther heterocyclylalkyl, the heterocyclylcarbonyl, and the heterocyclyloxy can be further selected from the group consisting of alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and oxo; and wherein Rc and Rd are each independently selected from the haloalkyl, and oxo; and wherein R^c and R^d are each independently selected from the unsubstituted aryl, unsubstituted arylalkyl, unsubstituted cycloalkyl, unsubstituted cycloalkylalkyl, unsubstituted heterocyclyl, and unsubstituted heterocyclylalkyl.

[0046] The term "arylalkoxy," as used herein, refers to an aryl group attached to the parent molecular moiety through an alkoxy group.

[0047] The term "arylalkoxyalkyl," as used herein, refers

[0048] The term "arylalkyl," as used herein, refers to an alkyl group substituted with one, two, or three aryl groups. The alkyl part of the arylalkyl can be optionally substituted with one or two additional groups selected from the group consisting of alkenyl, alkoxy, alkynyl, arylalkoxy, aryloxy, heterocyclyl, heterocyclylalkoxy, heterocyclyloxy, hydroxy, and —NR^cR^d; wherein R^c and R^d are independently selected from the group consisting of hydrogen, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, unsubstituted aryl, unsubstituted arylalkyl, unsubstituted cycloalkyl, unsubstituted cycloalkylalkyl, unsubstituted heterocyclyl, and unsubstituted heterocyclylalkyl.

[0049] The term "arylalkylcarbonyl," as used herein, refers to an arylalkyl group attached to the parent molecular moiety through a carbonyl group.

[0050] The term "arylcarbonyl," as used herein, refers to an aryl group attached to the parent molecular moiety through a carbonyl group.

[0051] The term "aryloxy," as used herein, refers to an aryl group attached to the parent molecular moiety through an oxygen atom.

[0052] The term "aryloxyalkyl," as used herein, refers to an alkyl group substituted with one, two, or three aryloxy groups.

[0053] The term "arylsulfenyl," as used herein, refers to an aryl group attached to the parent molecular moiety through a sulfur atom.

[0054] The term "arylsulfenylalkyl," as used herein, refers to an alkyl group substituted with one, two, or three arylsulfenyl groups.

[0055] The term "arylsulfinyl," as used herein, refers to an aryl group attached to the parent molecular moiety through a sulfinyl group.

[0056] The term "arylsulfinylalkyl," as used herein, refers to an alkyl group substituted with one, two, or three arylsulfinyl groups.

[0057] The term "arylsulfonyl," as used herein, refers to an aryl group attached to the parent molecular moiety through a sulfonyl group.

[0058] The term "arylsulfonylalkyl," as used herein, refers to an alkyl group substituted with one, two, or three arylsulfonyl groups.

[0059] The term "azido," as used herein, refers to —N_3.

[0060] The term "carbonyl," as used herein, refers to —C(O)—.

[0061] The term "carboxy," as used herein, refers to —CO_2H.

[0062] The term "carboxyalkyl," as used herein, refers to an alkyl group substituted with one, two, or three carboxy groups.

[0063] The term "cyano," as used herein, refers to —CN.

[0064] The term "cycloalkenyl," as used herein, refers to a non-aromatic, partially unsaturated monocyclic, bicyclic, or tricyclic ring system having three to fourteen carbon

hexenyl, octahydronaphthalenyl, and norbornylenyl. A preferred cycloalkenyl of the present invention is cyclopentenyl. The cycloalkenyl groups of the present invention can be optionally substituted with one, two, three, four, or five substituents independently selected from the group consisting of alkenyl, alkoxy, alkoxycarbonyl, alkyl, alkylcarbonyl, cyano, halo, haloalkoxy, haloalkyl, —NR^cR^d, (NR^cR^d)alkyl, (NR^cR^d)carbonyl, and oxo; wherein R^c and R^d are each independently selected from the group consisting of hydrogen, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, unsubstituted aryl, unsubstituted arylalkyl, unsubstituted cycloalkyl, unsubstituted cycloalkylalkyl, unsubstituted heterocyclyl, and unsubstituted heterocyclylalkyl.

[0065] The term "cycloalkenylalkyl," as used herein, refers to an alkyl group substituted with one, two, or three cycloalkenyl groups.

[0066] The term "cycloalkyl," as used herein, refers to a saturated monocyclic, bicyclic, or tricyclic hydrocarbon ring system having three to fourteen carbon atoms and zero heteroatoms. Representative examples of cycloalkyl groups include, but are not limited to, adamantyl, bicyclo[3.1.1]heptyl, cyclobutyl, cyclopentyl, and cyclopropyl. Preferred cycloalkyl groups of the present invention are cyclobutyl, cyclopentyl, and cyclopropyl. The cycloalkyl groups of the present invention can be optionally substituted with one, two, three, four, or five substituents independently selected from the group consisting of alkenyl, alkoxy, alkoxycarbonyl, alkyl, alkylcarbonyl, cyano, halo, haloalkoxy, haloalkyl, —NR^cR^d, (NR^cR^d)alkyl, (NR^cR^d)carbonyl, and oxo; wherein R^c and R^d are each independently selected from the group consisting of hydrogen, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, unsubstituted aryl, unsubstituted arylalkyl, unsubstituted cycloalkyl, unsubstituted cycloalkylalkyl, unsubstituted heterocyclyl, and unsubstituted heterocyclylalkyl.

[0067] The term "cycloalkylalkyl," as used herein, refers to an alkyl group substituted with one, two, or three cycloalkyl groups.

[0068] The terms "halo," and "halogen," as used herein, refer to Br, Cl, F, or I.

[0069] The term "haloalkoxy," as used herein, refers to a haloalkyl group attached to the parent molecular moiety through an oxygen atom.

[0070] The term "haloalkyl," as used herein, refers to an alkyl group substituted with one, two, three, or four halogen atoms.

[0071] The term "heterocyclyl," as used herein, refers to a three-, four-, five-, six-, or seven-membered ring containing one, two, or three heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur. The three- and four-membered rings have zero or one double bond. The five-membered ring has zero to two double bonds and the six- and seven-membered rings have zero to three double bonds. The term "heterocyclyl" also includes bicyclic groups in which the heterocyclyl ring is fused to a phenyl group, a monocyclic cycloalkenyl group, a monocyclic cycloalkyl group, or another monocyclic heterocyclyl group; and tricyclic groups in which a bicyclic system is fused to a phenyl group, a monocyclic cycloalkenyl group, invention can be attached to the parent molecular moiety through a carbon atom or a nitrogen atom in the group. Examples of heterocyclyl groups include, but are not limited to, azetidinyl, benzimidazolyl, benzothienyl, diazirenyl, furyl, hexahydrothienoimidazolyl, imidazolyl, imidazopyridinyl, imidazothiazolyl, indolinyl, indolyl, isothiazolyl, isoxazolyl, morpholinyl, oxazolyl, piperazinyl, piperidinyl, pyrazinyl, pyrazolyl, pyridinyl, pyrrolidinyl, pyrrolopyridinyl, pyrrolyl, tetrahydrofuryl, thiadiazolyl, thiazolyl, thienyl, and thiomorpholinyl. Preferred heterocyclyl groups of the present invention are azetidinyl, benzimidazolyl, diazirenyl, furyl, hexahydrothienoimidazolyl, imidazolyl, imidazopyridinyl, imidazothiazolyl, indolinyl, indolyl, isoxazolyl, morpholinyl, oxazolyl, piperidinyl, pyrazinyl, pyrazolyl, pyridinyl, tetrahydrofliryl, thiadiazolyl, and thienyl. The heterocyclyl groups of the present invention can be optionally substituted with one, two, three, four, or five substituents independently selected from the group consisting of alkenyl, alkoxy, alkoxycarbonyl, alkyl, alkylcarbonyl, alkylsulfenyl, alkylsulfonyl, alkynyl, aryl, arylalkoxy, arylalkyl, arylcarbonyl, aryloxy, arylsulfenyl, arylsulfonyl, azido, cyano, cycloalkenyl, cycloalkenylalkyl, cycloalkyl, cycloalkylalkyl, halo, haloalkoxy, haloalkyl, a second heterocyclyl group, heterocyclylalkoxy, heterocyclylalkyl, heterocyclylcarbonyl, heterocyclyloxy, —NR^cR^d, (NR^cR^d)alkyl, (NR^cR^d)carbonyl, and oxo, wherein the aryl, the aryl part of the arylalkoxy, the arylalkyl, the arylcarbonyl, the aryloxy, the arylsulfenyl, and the arylsulfonyl, the cycloalkenyl, the cycloalkenyl part of the cycloalkenylalkyl, the cycloalkyl, the cycloalkyl part of the cycloalkylalkyl, the second heterocyclyl group, and the heterocyclyl part of the heterocyclylalkoxy, the heterocyclylalkyl, the heterocyclylcarbonyl, and the heterocyclyloxy can be further optionally substituted with one, two, three, four, or five substituents independently selected from the group consisting of alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and oxo; and wherein R^c and R^d are each independently selected from the group consisting of hydrogen, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, unsubstituted aryl, unsubstituted arylalkyl, unsubstituted cycloalkyl, unsubstituted cycloalkylalkyl, unsubstituted heterocyclyl, and unsubstituted heterocyclylalkyl.

[0072] The term "heterocyclylalkoxy," as used herein, refers to a heterocyclyl group attached to the parent molecular moiety through an alkoxy group.

[0073] The term "heterocyclylalkoxyalkyl," as used herein, refers to an alkyl group substituted with one, two, or three heterocyclylalkoxy groups.

[0074] The term "heterocyclylalkyl," as used herein, refers to an alkyl group substituted with one, two, or three heterocyclyl groups. The alkyl part of the heterocyclylalkyl can be optionally substituted with one or two additional groups selected from the group consisting of alkenyl, alkoxy, alkynyl, arylalkoxy, aryloxy, heterocyclylalkoxy, heterocyclyloxy, hydroxy, and —NR^cR^d; wherein R^c and R^d are independently selected from the group consisting of hydrogen, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, unsubstituted aryl, unsubstituted arylalkyl, unsubstituted cycloalkyl, unsubstituted cycloalkylalkyl, unsubstituted heterocyclyl, and unsubstituted heterocyclylalkyl.

[0075] The term "heterocyclylalkylcarbonyl," as used

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