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(54) Title: TETRACYCLIC BENZAMIDE DERIVATIVES AND METHODS OF USE THEREOF

(57) Abstract: The invention relates to Tetracyclic Benzamide Derivatives; compositions comprising a Tetracyclic Benzamide Derivative; and methods for treating or preventing an inflammatory disease, a reperfusion disease, an ischemic condition, renal failure, diabetes, a diabetic complication, a vascular disease, or cancer, comprising administering to a subject in need thereof an effective amount of a Tetracyclic Benzamide Derivative.

**TETRACYCLIC BENZAMIDE DERIVATIVES
AND METHODS OF USE THEREOF**

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This application claims benefit of U.S. provisional application no. 60/450,925, filed February 28, 2003, the entire disclosure of which is hereby incorporated by reference.

This invention was made with government support under grant no. R44 DK54099-03 and grant no. 1R43 CA90016-01A1, which were awarded by the National Institutes of Health. The government has certain rights in the invention.

1. FIELD OF THE INVENTION

The invention relates to Tetracyclic Benzamide Derivatives; compositions comprising an effective amount of a Tetracyclic Benzamide Derivative; and methods for treating or preventing an inflammatory disease, a reperfusion disease, an ischemic condition, renal failure, diabetes, a diabetic complication, a vascular disease, or cancer, comprising administering to a subject in need thereof an effective amount of a Tetracyclic Benzamide Derivative.

2. BACKGROUND OF THE INVENTION

Inflammatory diseases, such as arthritis, colitis, and autoimmune diabetes, typically manifest themselves as disorders distinct from those associated with reperfusion diseases, *e.g.*, stroke and heart attack, and can clinically manifest themselves as different entities. However, there can be common underlying mechanisms between these two types of disorders. In particular, inflammatory disease and reperfusion disease can induce proinflammatory cytokine and chemokine synthesis which can, in turn, result in production of cytotoxic free radicals such as nitric oxide and superoxide. NO and superoxide can react to form peroxynitrite (ONOO⁻) (Szabó *et al.*, Shock 6:79-88, 1996).

The ONOO⁻-induced cell necrosis observed in inflammatory disease and in reperfusion disease involves the activation of the nuclear enzyme poly (ADP-ribose) synthetase (PARS), also known as poly (ADP-ribose) polymerase (PARP). Activation of PARP is thought to be an important step in the cell-mediated death observed in inflammation and reperfusion disease (Szabó *et al.*, Trends Pharmacol. Sci. 19:287-98, 1998).

- A number of PARP inhibitors have been described in the art. See, e.g., Banasik *et al.*, J. Biol. Chem., 267:1569-75, 1992, and Banasik *et al.*, Mol. Cell. Biochem., 138:185-97, 1994; WO 00/39104; WO 00/39070; WO 99/59975; WO 99/59973; WO 99/11649; WO 99/11645; WO 99/11644; WO 99/11628; WO 99/11623; WO 99/11311; WO 00/42040; Zhang *et al.*, Biochem. Biophys. Res. Commun., 278:590-98, 2000; White *et al.*, J. Med. Chem., 43:4084-4097, 2000; Griffin *et al.*, J. Med. Chem., 41:5247-5256, 1998; Shinkwin *et al.*, Bioorg. Med. Chem., 7:297-308, 1999; and Soriano *et al.*, Nature Medicine, 7:108-113, 2001. Adverse effects associated with administration of PARP inhibitors have been discussed in Milan *et al.*, Science, 223:589-591, 1984.
- 10 S.P. Hiremath *et al.*, *Oriental Journal of Chemistry* 13(2):173-176 (1997) discloses isoquinoline compounds allegedly useful as antifungal, antibacterial or anthelmintic agents.
- S.P. Hiremath *et al.*, *Journal of the Indian Chemical Society* 72(10):735-738 (1995) discloses isoquinolinone compounds
- 15 S.P. Hiremath *et al.*, *Indian Journal of Heterocyclic Chemistry* 3(1):37-42 (1993) discloses isoquinolinethione compounds allegedly useful as antifungal, antibacterial, oxytocic or anthelmintic agents.
- S.P. Hiremath *et al.*, *Indian Journal of Chemistry, Section B* 24B(12):1235-1238 (1985) discloses indoloisoquinoline compounds.
- 20 U.S. Patent No. 4,623,304 to Ishizumi *et al.* discloses indoloisoquinoline compounds allegedly having anti-tumor activity.
- United Kingdom Patent No. GB 2025932 B2 by Sumitomo Chemical Co. discloses indoloisoquinoline compounds allegedly having bacteriacidal or fungicidal activity.
- 25 G. Winters *et al.*, *Farmaco. Ed. Sci.* 34(6):507-517 (1979) discloses indoloisoquinolinones allegedly having antibacterial or fungicidal activity.
- U.S. Patent No. 4,113,731 to G. Winters *et al.* discloses indoloisoquinolines.
- U.S. Patents No. 5,733,918, 5,710,162, and 6,028,079 to Okazaki *et al.* disclose indenoquinolines allegedly useful as antitumor agents.
- 30 S. Srivastava *et al.*, *Journal of the Indian Chemical Society* 66(4):276-81 (1989) discloses a synthesis of indenoisocoumarins and indenoisoquinolones.
- G. Jha *et al.*, *Indian Journal of Chemistry, Section B* 24B(4):440-444 (1985) discloses a synthesis of indenoisocoumarins and indenoisoquinolones.

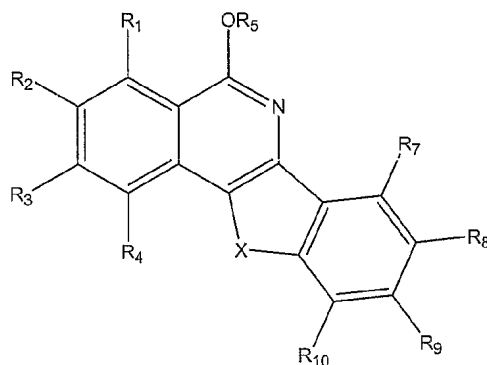
J.N. Chatterjea et al., *J. Indian Chem. Soc.* 44(11):911-919 (1967) discloses a synthesis of dihydroisocoumarins.

There remains, however, a need in the art for compounds useful for treating or preventing an inflammatory disease, a reperfusion disease, an ischemic condition, renal failure, diabetes, a diabetic complication, a vascular disease, or cancer.

Citation of any reference in Section 2 of this application is not an admission that the reference is prior art.

3. SUMMARY OF THE INVENTION

The present invention encompasses compounds having the Formula (I):



(I)

and pharmaceutically acceptable salts and hydrates thereof, wherein:

R₅ is -C₁-C₁₀ alkyl, halo-substituted-(C₁-C₅ alkyl), HO-substituted-(C₁-C₅ alkyl), carboxy-substituted-(C₁-C₅ alkyl), -C(O)-C₁-C₁₀ alkyl, -C(O)-aryl, -C(O)-(3- to 7-membered monocyclic heterocycle), -C(O)-(7- to 10-membered bicyclic heterocycle) or -glycoside;

X is -C(O)-, -CH₂-, -CH(halo)-, -(C(OH)((CH₂)_nCH₃))- , -(C(OH)(aryl))- , -O-, -NH-, -S-, -CH(NR₁₁R₁₂)- or -N(SO₂Y)-, wherein Y is -OH, -NH₂, -(C₁-C₅ alkyl)-(3- to 7-membered monocyclic heterocycle), or -(C₁-C₅ alkyl)-(7- to 10-membered bicyclic heterocycle) and n is an integer ranging from 0-5;

R₁₁ and R₁₂ are independently -hydrogen or -C₁-C₉ alkyl, or N, R₁₁ and R₁₂ are taken together to form a -(nitrogen-containing 3- to 7-membered monocyclic heterocycle), or a -(nitrogen-containing 7- to 10-membered bicyclic heterocycle);

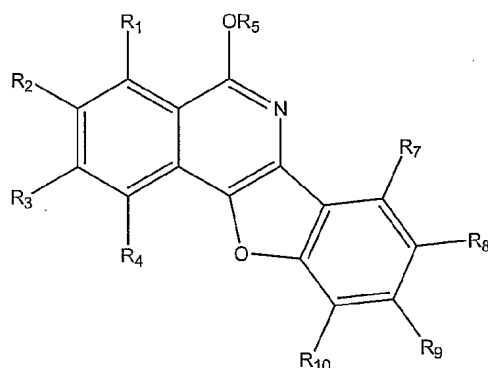
R₁, R₂, R₃, R₄, R₇, R₈, R₉ and R₁₀ are independently -hydrogen, -halo, -hydroxy, -O-(C₁-C₅ alkyl), -C₁-C₁₀ alkyl, halo-substituted-(C₁-C₅ alkyl), -C₂-C₁₀ alkenyl, -C₃-C₈-cycloalkyl, -aryl, -NH₂, amino-substituted-(C₁-C₅ alkyl), -C(O)OH, -C(O)O(C₁-C₅ alkyl), -OC(O)(C₁-C₅ alkyl), NO₂ or -A-B;

5 A is -SO₂-, -SO₂NH-, -NHCO-, -NHCONH-, -O-, -CO-, -OC(O)-, -C(O)O-, -CONH-, -CON(C₁-C₄ alkyl)-, -NH-, -CH₂-, -S- or -C(S)-;

B is -C₁-C₁₀ alkyl, -C₂-C₁₀ alkenyl, -(nitrogen-containing 3- to 7-membered monocyclic heterocycle), -(nitrogen-containing 7- to 10-membered bicyclic heterocycle), -(3- to 7-membered monocyclic heterocycle), -(7- to 10-membered bicyclic heterocycle),
 10 -C₃-C₈ cycloalkyl, -aryl, -NZ₁Z₂, -(C₁-C₅ alkylene)-NZ₁Z₂, amino-substituted-(C₁-C₅ alkyl), -N(C₁-C₅ alkyl)(C₁-C₅ alkyl), -(C₁-C₅ alkyl)-(3- to 7-membered monocyclic heterocycle), or -(C₁-C₅ alkyl)-(7- to 10-membered bicyclic heterocycle), -(H₂NC(O))-substituted aryl, -(H₂NC(O))-substituted pyridyl, -C(O)OH, -C(O)O-(C₁-C₅ alkyl), -C(O)O-phenyl or -C(NH)NH₂, each of which is unsubstituted or
 15 substituted with one or more of -O-(C₁-C₅ alkyl), -halo, halo-substituted-(C₁-C₅ alkyl), HO-substituted-(C₁-C₅ alkyl), amino-substituted-(C₁-C₅ alkyl), -hydroxy, -NO₂, -NH₂, -CN, -NH(C₁-C₅ alkyl), -N(C₁-C₅ alkyl)(C₁-C₅ alkyl), -(nitrogen-containing 3- to 7-membered monocyclic heterocycle), 7- to 10-membered bicycloheterocyclic amine, -C₁-C₁₀ alkyl, -C₂-C₁₀ alkenyl, -C₂-C₁₀ alkynyl, -aryl, -benzyl, -(C(O)NH₂)-substituted(C₁-C₅ alkyl),
 20 alkyl), carboxy-substituted-(C₁-C₅ alkyl), -C(O)OH, -C₁-C₅-alkylene-C(O)O-(C₁-C₅ alkyl) or -C₁-C₅ alkylene-OC(O)-(C₁-C₅ alkyl); and

Z₁ and Z₂ are independently -H or -C₁-C₁₀ alkyl, which is unsubstituted or substituted with one or more of -halo, -OH or -N(Z₃)(Z₄), where Z₃ and Z₄ are independently, -H or -C₁-C₅ alkyl, which is unsubstituted or substituted with one or more
 25 of -halo, -hydroxy or -NH₂; or N, Z₃ and Z₄ are taken together to form a -(nitrogen-containing 3- to 7-membered monocyclic heterocycle) or a -(nitrogen-containing 7- to 10-membered bicyclic heterocycle); or N, Z₁ and Z₂ are taken together to form a -(nitrogen-containing 3- to 7-membered monocyclic heterocycle), or a -(nitrogen-containing 7- to 10-membered bicyclic heterocycle).

The present invention also encompasses compounds of Formula (Ia):



(Ia)

and pharmaceutically acceptable salts and hydrates thereof,

5 wherein:

R₅ is -C₁-C₁₀ alkyl, halo-substituted-(C₁-C₅ alkyl), HO-substituted-(C₁-C₅ alkyl), carboxy-substituted-(C₁-C₅ alkyl), -C(O)-C₁-C₁₀ alkyl, -C(O)-aryl, -C(O)-(3- to 7-membered monocyclic heterocycle), -C(O)-(7- to 10-membered bicyclic heterocycle) or -glycoside;

10 R₁, R₂, R₃, R₄, R₇, R₈, R₉ and R₁₀ are independently -hydrogen, -halo, -hydroxy, -O-(C₁-C₅ alkyl), -C₁-C₁₀ alkyl, halo-substituted-(C₁-C₅ alkyl), -C₂-C₁₀ alkenyl, -C₃-C₈-cycloalkyl, -aryl, -NH₂, amino-substituted-(C₁-C₅ alkyl), -C(O)OH, -C(O)O(C₁-C₅ alkyl), -OC(O)(C₁-C₅ alkyl), NO₂ or -A-B;

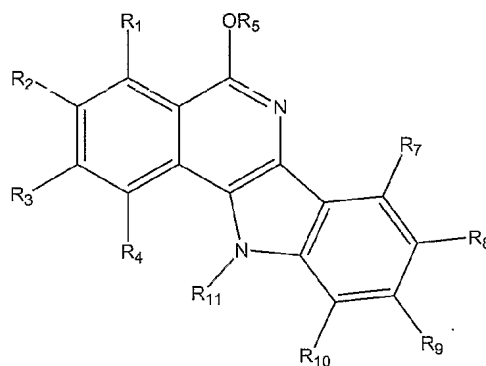
A is -SO₂-, -SO₂NH-, -NHCO-, -NHCONH-, -O-, -CO-, -OC(O)-, -C(O)O-,
15 -CONH-, -CON(C₁-C₄ alkyl)-, -NH-, -CH₂-, -S- or -C(S)-;

B is -C₁-C₁₀ alkyl, -C₂-C₁₀ alkenyl, -(nitrogen-containing 3- to 7-membered monocyclic heterocycle), -(nitrogen-containing 7- to 10-membered bicyclic heterocycle), -(3- to 7-membered monocyclic heterocycle), -(7- to 10-membered bicyclic heterocycle), -C₃-C₈ cycloalkyl, -aryl, -NZ₁Z₂, -(C₁-C₅ alkylene)-NZ₁Z₂, amino-substituted-(C₁-C₅ alkyl),
20 -N(C₁-C₅ alkyl)(C₁-C₅ alkyl), -(C₁-C₅ alkyl)-(3- to 7-membered monocyclic heterocycle), or -(C₁-C₅ alkyl)-(7- to 10-membered bicyclic heterocycle), -(H₂NC(O))-substituted aryl, -(H₂NC(O))-substituted pyridyl, -C(O)OH, -C(O)O-(C₁-C₅ alkyl), -C(O)O-phenyl or -C(NH)NH₂, each of which is unsubstituted or substituted with one or more of -O-(C₁-C₅ alkyl), -halo, halo-substituted-(C₁-C₅ alkyl),
25 HO-substituted-(C₁-C₅ alkyl), amino-substituted-(C₁-C₅ alkyl), -hydroxy, -NO₂, -NH₂, -CN, -NH(C₁-C₅ alkyl), -N(C₁-C₅ alkyl)(C₁-C₅ alkyl), -(nitrogen-containing 3- to 7-membered monocyclic heterocycle), 7- to 10-membered bicycloheterocyclic amine, -C₁-

C₁₀ alkyl, -C₂-C₁₀ alkenyl, -C₂-C₁₀ alkynyl, -aryl, -benzyl, -(H₂NC(O))-substituted(C₁-C₅ alkyl), carboxy-substituted-(C₁-C₅ alkyl), -C(O)OH, -C₁-C₅-alkylene-C(O)O-(C₁-C₅ alkyl) or -C₁-C₅ alkylene-OC(O)-(C₁-C₅ alkyl); and

- Z₁ and Z₂ are independently -H or -C₁-C₁₀ alkyl, which is unsubstituted or substituted with one or more of -halo, -OH or -N(Z₃)(Z₄), where Z₃ and Z₄ are independently, -H or -C₁-C₅ alkyl, which is unsubstituted or substituted with one or more of -halo, -hydroxy or -NH₂; or N, Z₃ and Z₄ are taken together to form a -(nitrogen-containing 3- to 7-membered monocyclic heterocycle) or a -(nitrogen-containing 7- to 10-membered bicyclic heterocycle); or N, Z₁ and Z₂ are taken together to form a -(nitrogen-containing 3- to 7-membered monocyclic heterocycle), or a -(nitrogen-containing 7- to 10-membered bicyclic heterocycle).

The present invention also encompasses compounds of Formula (Ib):



(Ib)

- and pharmaceutically acceptable salts and hydrates thereof, wherein:

- R₅ is -C₁-C₁₀ alkyl, halo-substituted-(C₁-C₅ alkyl), HO-substituted-(C₁-C₅ alkyl), carboxy-substituted-(C₁-C₅ alkyl), -C(O)-C₁-C₁₀ alkyl, -C(O)-aryl, -C(O)-(3- to 7-membered monocyclic heterocycle), -C(O)-(7- to 10-membered bicyclic heterocycle) or -glycoside;

R₁₁ -H, -C₁-C₅ alkyl, -aryl, -C(O)-C₁-C₅ alkyl, or -SO₂Y, wherein Y is -OH, -NH₂ or -(C₁-C₅ alkyl)-(3- to 7-membered monocyclic heterocycle), or -(C₁-C₅ alkyl)-(7- to 10-membered bicyclic heterocycle);

- R₁, R₂, R₃, R₄, R₇, R₈, R₉ and R₁₀ are independently -hydrogen, -halo, -hydroxy, -O-(C₁-C₅ alkyl), -C₁-C₁₀ alkyl, halo-substituted-(C₁-C₅ alkyl), -C₂-C₁₀ alkenyl, -C₃-C₈-cycloalkyl, -aryl, -NH₂, amino-substituted-(C₁-C₅ alkyl), -C(O)OH, -C(O)O(C₁-C₅ alkyl),

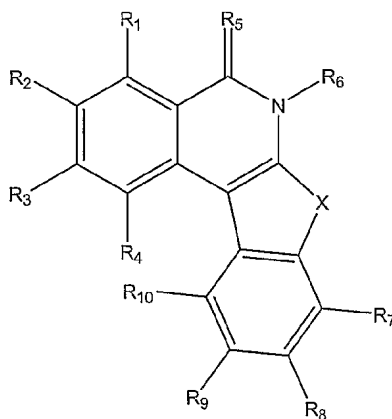
-OC(O)(C₁-C₅ alkyl), NO₂ or -A-B;

A is -SO₂-, -SO₂NH-, -NHCO-, -NHCONH-, -O-, -CO-, -OC(O)-, -C(O)O-,
-CONH-, -CON(C₁-C₄ alkyl)-, -NH-, -CH₂-, -S- or -C(S)-;

B is -C₁-C₁₀ alkyl, -C₂-C₁₀ alkenyl, -(nitrogen-containing 3- to 7-membered
5 monocyclic heterocycle), -(nitrogen-containing 7- to 10-membered bicyclic heterocycle),
-(3- to 7-membered monocyclic heterocycle), -(7- to 10-membered bicyclic heterocycle),
-C₃-C₈ cycloalkyl, -aryl, -NZ₁Z₂, -(C₁-C₅ alkylene)-NZ₁Z₂, amino-substituted-(C₁-C₅
alkyl), -N(C₁-C₅ alkyl)(C₁-C₅ alkyl), -(C₁-C₅ alkyl)-(3- to 7-membered
monocyclic heterocycle), or -(C₁-C₅ alkyl)-(7- to 10-membered bicyclic heterocycle), -
10 (H₂NC(O))-substituted aryl, -(H₂NC(O))-substituted pyridyl, -C(O)OH,
-C(O)O-(C₁-C₅ alkyl), -C(O)O-phenyl or -C(NH)NH₂, each of which is unsubstituted or
substituted with one or more of -O-(C₁-C₅ alkyl), -halo, halo-substituted-(C₁-C₅ alkyl),
HO-substituted-(C₁-C₅ alkyl), amino-substituted-(C₁-C₅ alkyl), -hydroxy, -NO₂, -NH₂,
-CN, -NH(C₁-C₅ alkyl), -N(C₁-C₅ alkyl)(C₁-C₅ alkyl), -(nitrogen-containing 3- to 7-
15 membered monocyclic heterocycle)), 7- to 10-membered bicycloheterocyclic amine, -C₁-
C₁₀ alkyl, -C₂-C₁₀ alkenyl, -C₂-C₁₀ alkynyl, -aryl, -benzyl, -(H₂NC(O))-substituted(C₁-C₅
alkyl), carboxy-substituted-(C₁-C₅ alkyl), -C(O)OH, -C₁-C₅-alkylene-C(O)O-(C₁-C₅
alkyl) or -C₁-C₅ alkylene-OC(O)-(C₁-C₅ alkyl); and

Z₁ and Z₂ are independently -H or -C₁-C₁₀ alkyl, which is unsubstituted or
20 substituted with one or more of -halo, -OH or -N(Z₃)(Z₄), where Z₃ and Z₄ are
independently, -H or -C₁-C₅ alkyl, which is unsubstituted or substituted with one or more
of -halo, -hydroxy or -NH₂; or N, Z₃ and Z₄ are taken together to form a -(nitrogen-
containing 3- to 7-membered monocyclic heterocycle) or a -(nitrogen-containing 7- to
10-membered bicyclic heterocycle); or N, Z₁ and Z₂ are taken together to form a -
25 (nitrogen-containing 3- to 7-membered monocyclic heterocycle), or a -(nitrogen-
containing 7- to 10-membered bicyclic heterocycle).

The invention also relates to compounds of Formula (II):



(II)

and pharmaceutically acceptable salts and hydrates thereof,

5 wherein:

R_5 is O, NH or S;

R_6 is -H or C_1 - C_4 alkyl;

X is -C(O)-, -CH₂-, -CH(halo)-, -(C(OH)((CH₂)_nCH₃))-, -(C(OH)(aryl))-, -O-, -NH-, -S-, -CH(NR₁₁R₁₂)- or -N(SO₂Y)-, wherein Y is -OH, -NH₂, -(C₁-C₅ alkyl)-(3- to 7-
10 membered monocyclic heterocycle), or -(C₁-C₅ alkyl)-(7- to 10-membered bicyclic heterocycle) and n is an integer ranging from 0-5;

R_{11} and R_{12} are independently -hydrogen or -C₁-C₉ alkyl, or N, R_{11} and R_{12} are taken together to form a -(nitrogen-containing 3- to 7-membered monocyclic heterocycle), or a -(nitrogen-containing 7- to 10-membered bicyclic heterocycle);

15 R_1 , R_2 , R_3 , R_4 , R_7 , R_8 , R_9 and R_{10} are independently -hydrogen, -halo, -hydroxy, -O-(C₁-C₅ alkyl), -C₁-C₁₀ alkyl, halo-substituted-(C₁-C₅ alkyl), -C₂-C₁₀ alkenyl, -C₃-C₈-cycloalkyl, -aryl, -NH₂, amino-substituted-(C₁-C₅ alkyl), -C(O)OH, -C(O)O(C₁-C₅ alkyl), -OC(O)(C₁-C₅ alkyl), NO₂ or -A-B;

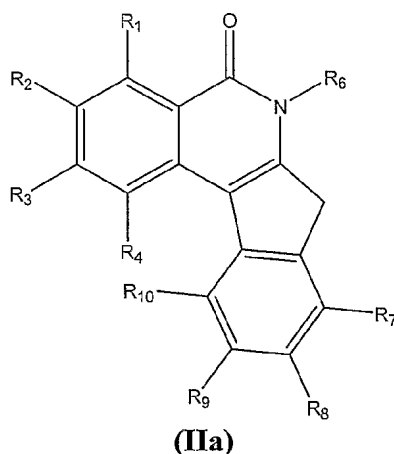
A is -SO₂-, -SO₂NH-, -NHCO-, -NHCONH-, -O-, -CO-, -OC(O)-, -C(O)O-,
20 -CONH-, -CON(C₁-C₄ alkyl)-, -NH-, -CH₂-, -S- or -C(S)-;

B is -C₁-C₁₀ alkyl, -C₂-C₁₀ alkenyl, -(nitrogen-containing 3- to 7-membered monocyclic heterocycle), -(nitrogen-containing 7- to 10-membered bicyclic heterocycle), -(3- to 7-membered monocyclic heterocycle), -(7- to 10-membered bicyclic heterocycle), -C₃-C₈ cycloalkyl, -aryl, -NZ₁Z₂, -(C₁-C₅ alkylene)-NZ₁Z₂, amino-substituted-(C₁-C₅
25 alkyl), -N(C₁-C₅ alkyl)(C₁-C₅ alkyl), -(C₁-C₅ alkyl)-(3- to 7-membered monocyclic heterocycle), or -(C₁-C₅ alkyl)-(7- to 10-membered bicyclic heterocycle), -

(H₂NC(O))-substituted aryl, -(H₂NC(O))-substituted pyridyl, -C(O)OH, -C(O)O-(C₁-C₅ alkyl), -C(O)O-phenyl or -C(NH)NH₂, each of which is unsubstituted or substituted with one or more of -O-(C₁-C₅ alkyl), -halo, halo-substituted-(C₁-C₅ alkyl), HO-substituted-(C₁-C₅ alkyl), amino-substituted-(C₁-C₅ alkyl), -hydroxy, -NO₂, -NH₂,
 5 -CN, -NH(C₁-C₅ alkyl), -N(C₁-C₅ alkyl)(C₁-C₅ alkyl), -(nitrogen-containing 3- to 7-membered monocyclic heterocycle)), 7- to 10-membered bicycloheterocyclic amine, -C₁-C₁₀ alkyl, -C₂-C₁₀ alkenyl, -C₂-C₁₀ alkynyl, -aryl, -benzyl, -(H₂NC(O))-substituted(C₁-C₅ alkyl), carboxy-substituted-(C₁-C₅ alkyl), -C(O)OH, -C₁-C₅-alkylene-C(O)O-(C₁-C₅ alkyl) or -C₁-C₅ alkylene-OC(O)-(C₁-C₅ alkyl); and

- 10 Z₁ and Z₂ are independently -H or -C₁-C₁₀ alkyl, which is unsubstituted or substituted with one or more of -halo, -OH or -N(Z₃)(Z₄), where Z₃ and Z₄ are independently, -H or -C₁-C₅ alkyl, which is unsubstituted or substituted with one or more of -halo, -hydroxy or -NH₂; or N, Z₃ and Z₄ are taken together to form a -(nitrogen-containing 3- to 7-membered monocyclic heterocycle) or a -(nitrogen-containing 7- to
 15 10-membered bicyclic heterocycle); or N, Z₁ and Z₂ are taken together to form a -(nitrogen-containing 3- to 7-membered monocyclic heterocycle), or a -(nitrogen-containing 7- to 10-membered bicyclic heterocycle).

The invention also relates to compounds of Formula (IIa):



and pharmaceutically acceptable salts and hydrates thereof,
 wherein:

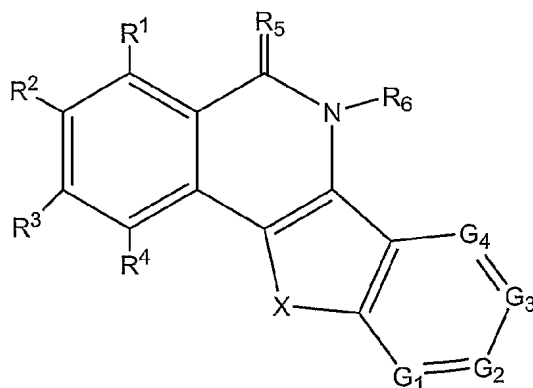
- 20 R₆ is -H or C₁-C₄ alkyl;
 25 R₁, R₂, R₃, R₄, R₇, R₈, R₉ and R₁₀ are independently -hydrogen, -halo, -hydroxy, -O-(C₁-C₅ alkyl), -C₁-C₁₀ alkyl, halo-substituted-(C₁-C₅ alkyl), -C₂-C₁₀ alkenyl, -C₃-C₈-cycloalkyl, -aryl, -NH₂, amino-substituted-(C₁-C₅ alkyl), -C(O)OH, -C(O)O(C₁-C₅ alkyl), -OC(O)(C₁-C₅ alkyl), NO₂ or -A-B;

A is $-\text{SO}_2-$, $-\text{SO}_2\text{NH}-$, $-\text{NHCO}-$, $-\text{NHCONH}-$, $-\text{O}-$, $-\text{CO}-$, $-\text{OC(O)}-$, $-\text{C(O)O}-$, $-\text{CONH}-$, $-\text{CON}(\text{C}_1\text{-C}_4 \text{ alkyl})-$, $-\text{NH}-$, $-\text{CH}_2-$, $-\text{S}-$ or $-\text{C(S)}-$;

B is $-\text{C}_1\text{-C}_{10}$ alkyl, $-\text{C}_2\text{-C}_{10}$ alkenyl, $-(\text{nitrogen-containing } 3\text{- to } 7\text{-membered monocyclic heterocycle})$, $-(\text{nitrogen-containing } 7\text{- to } 10\text{-membered bicyclic heterocycle})$,
 5 $-(3\text{- to } 7\text{-membered monocyclic heterocycle})$, $-(7\text{- to } 10\text{-membered bicyclic heterocycle})$, $-\text{C}_3\text{-C}_8$ cycloalkyl, $-\text{aryl}$, $-\text{NZ}_1\text{Z}_2$, $-(\text{C}_1\text{-C}_5 \text{ alkylene})\text{-NZ}_1\text{Z}_2$, amino-substituted- $(\text{C}_1\text{-C}_5 \text{ alkyl})$,
 $-\text{N}(\text{C}_1\text{-C}_5 \text{ alkyl})(\text{C}_1\text{-C}_5 \text{ alkyl})$, $-(\text{C}_1\text{-C}_5 \text{ alkyl})\text{-(} 3\text{- to } 7\text{-membered monocyclic heterocycle)}$, or $-(\text{C}_1\text{-C}_5 \text{ alkyl})\text{-(} 7\text{- to } 10\text{-membered bicyclic heterocycle)}$, $-(\text{H}_2\text{NC(O)})\text{-substituted aryl}$, $-(\text{H}_2\text{NC(O)})\text{-substituted pyridyl}$, $-\text{C(O)OH}$,
 10 $-\text{C(O)O}(\text{C}_1\text{-C}_5 \text{ alkyl})$, $-\text{C(O)O-phenyl}$ or $-\text{C(NH)NH}_2$, each of which is unsubstituted or substituted with one or more of $-\text{O}(\text{C}_1\text{-C}_5 \text{ alkyl})$, $-\text{halo}$, $\text{halo-substituted}(\text{C}_1\text{-C}_5 \text{ alkyl})$, $\text{HO-substituted}(\text{C}_1\text{-C}_5 \text{ alkyl})$, $\text{amino-substituted}(\text{C}_1\text{-C}_5 \text{ alkyl})$, $-\text{hydroxy}$, $-\text{NO}_2$, $-\text{NH}_2$, $-\text{CN}$, $-\text{NH}(\text{C}_1\text{-C}_5 \text{ alkyl})$, $-\text{N}(\text{C}_1\text{-C}_5 \text{ alkyl})(\text{C}_1\text{-C}_5 \text{ alkyl})$, $-(\text{nitrogen-containing } 3\text{- to } 7\text{-membered monocyclic heterocycle})$, $7\text{- to } 10\text{-membered bicycloheterocyclic amine}$, $-\text{C}_1\text{-C}_{10}$ alkyl, $-\text{C}_2\text{-C}_{10}$ alkenyl, $-\text{C}_2\text{-C}_{10}$ alkynyl, $-\text{aryl}$, $-\text{benzyl}$, $-(\text{H}_2\text{NC(O)})\text{-substituted}(\text{C}_1\text{-C}_5 \text{ alkyl})$, $\text{carboxy-substituted}(\text{C}_1\text{-C}_5 \text{ alkyl})$, $-\text{C(O)OH}$, $-\text{C}_1\text{-C}_5\text{-alkylene-C(O)O}(\text{C}_1\text{-C}_5 \text{ alkyl})$ or $-\text{C}_1\text{-C}_5 \text{ alkylene-OC(O)}(\text{C}_1\text{-C}_5 \text{ alkyl})$; and

Z_1 and Z_2 are independently $-\text{H}$ or $-\text{C}_1\text{-C}_{10}$ alkyl, which is unsubstituted or substituted with one or more of $-\text{halo}$, $-\text{OH}$ or $-\text{N}(\text{Z}_3)(\text{Z}_4)$, where Z_3 and Z_4 are
 20 independently, $-\text{H}$ or $-\text{C}_1\text{-C}_5$ alkyl, which is unsubstituted or substituted with one or more of $-\text{halo}$, $-\text{hydroxy}$ or $-\text{NH}_2$; or N , Z_3 and Z_4 are taken together to form a $-(\text{nitrogen-containing } 3\text{- to } 7\text{-membered monocyclic heterocycle})$ or a $-(\text{nitrogen-containing } 7\text{- to } 10\text{-membered bicyclic heterocycle})$; or N , Z_1 and Z_2 are taken together to form a $-(\text{nitrogen-containing } 3\text{- to } 7\text{-membered monocyclic heterocycle})$, or a $-(\text{nitrogen-containing } 7\text{- to } 10\text{-membered bicyclic heterocycle})$.
 25

The invention further relates to compounds of Formula (III):



and pharmaceutically acceptable salts and hydrates thereof,

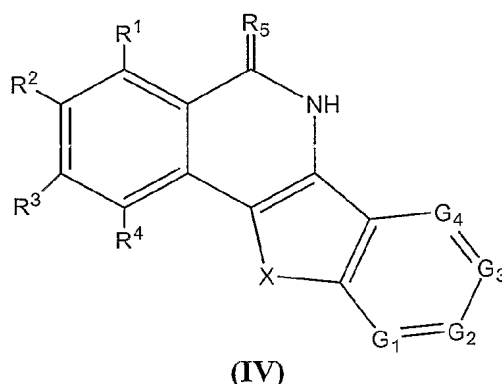
wherein:

- R₅ is O, NH or S;
- 5 R₆ is -H or -C₁-C₄ alkyl;
- X is -C(O)-, -CH₂-, -CH(halo)-, -(C(OH)((CH₂)_nCH₃))-, -(C(OH)(aryl))-, -O-, -NH-, -S-, -CH(NR₁₁R₁₂)- or -N(SO₂Y)-, wherein Y is -OH, -NH₂, -(C₁-C₅ alkyl)-(3- to 7-membered monocyclic heterocycle), or -(C₁-C₅ alkyl)-(7- to 10-membered bicyclic heterocycle) and n is an integer ranging from 0-5;
- 10 R₁₁ and R₁₂ are independently -hydrogen or -C₁-C₉ alkyl, or N, R₁₁ and R₁₂ are taken together to form a -(nitrogen-containing 3- to 7-membered monocyclic heterocycle), or a -(nitrogen-containing 7- to 10-membered bicyclic heterocycle);
- one of G₁-G₄ is C-R₇ and the remaining G₁-G₄ are independently N or C-R₇;
- R₁, R₂, R₃, and R₄ are independently -hydrogen, -halo, -hydroxy, -O-(C₁-C₅ alkyl),
- 15 -C₁-C₁₀ alkyl, halo-substituted-(C₁-C₅ alkyl), -C₂-C₁₀ alkenyl, -C₃-C₈-cycloalkyl, -aryl, -NH₂, amino-substituted-(C₁-C₅ alkyl), -C(O)OH, -C(O)O(C₁-C₅ alkyl), -OC(O)(C₁-C₅ alkyl), NO₂ or -A-B;
- A is -SO₂-, -SO₂NH-, -NHCO-, -NHCONH-, -O-, -CO-, -OC(O)-, -C(O)O-, -CONH-, -CON(C₁-C₄ alkyl)-, -NH-, -CH₂-, -S- or -C(S)-;
- 20 B is -C₁-C₁₀ alkyl, -C₂-C₁₀ alkenyl, -(nitrogen-containing 3- to 7-membered monocyclic heterocycle), -(nitrogen-containing 7- to 10-membered bicyclic heterocycle), -(3- to 7-membered monocyclic heterocycle), -(7- to 10-membered bicyclic heterocycle), -C₃-C₈ cycloalkyl, -aryl, -NZ₁Z₂, -(C₁-C₅ alkylene)-NZ₁Z₂, amino-substituted-(C₁-C₅ alkyl), -N(C₁-C₅ alkyl)(C₁-C₅ alkyl), -(C₁-C₅ alkyl)-(3- to 7-membered
- 25 monocyclic heterocycle), or -(C₁-C₅ alkyl)-(7- to 10-membered bicyclic heterocycle), -(H₂NC(O))-substituted aryl, -(H₂NC(O))-substituted pyridyl, -C(O)OH, -C(O)O-(C₁-C₅ alkyl), -C(O)O-phenyl or -C(NH)NH₂, each of which is unsubstituted or substituted with one or more of -O-(C₁-C₅ alkyl), -halo, halo-substituted-(C₁-C₅ alkyl), HO-substituted-(C₁-C₅ alkyl), amino-substituted-(C₁-C₅ alkyl), -hydroxy, -NO₂, -NH₂,
- 30 -CN, -NH(C₁-C₅ alkyl), -N(C₁-C₅ alkyl)(C₁-C₅ alkyl), -(nitrogen-containing 3- to 7-membered monocyclic heterocycle)), 7- to 10-membered bicycloheterocyclic amine, -C₁-C₁₀ alkyl, -C₂-C₁₀ alkenyl, -C₂-C₁₀ alkynyl, -aryl, -benzyl, -(H₂NC(O))-substituted(C₁-C₅ alkyl), carboxy-substituted-(C₁-C₅ alkyl), -C(O)OH, -C₁-C₅-alkylene-C(O)O-(C₁-C₅ alkyl) or -C₁-C₅ alkylene-OC(O)-(C₁-C₅ alkyl); and

Z_1 and Z_2 are independently -H or -C₁-C₁₀ alkyl, which is unsubstituted or substituted with one or more of -halo, -OH or -N(Z_3)(Z_4), where Z_3 and Z_4 are independently, -H or -C₁-C₅ alkyl, which is unsubstituted or substituted with one or more of -halo, -hydroxy or -NH₂; or N, Z_3 and Z_4 are taken together to form a –(nitrogen-
 5 containing 3- to 7-membered monocyclic heterocycle) or a –(nitrogen-containing 7- to 10-membered bicyclic heterocycle); or N, Z_1 and Z_2 are taken together to form a –(nitrogen-containing 3- to 7-membered monocyclic heterocycle), or a –(nitrogen-containing 7- to 10-membered bicyclic heterocycle);

each R_7 is independently -H, -C₁-C₆ alkyl, -O-(C₁-C₆ alkyl), -S-(C₁-C₆ alkyl),
 10 -SO₂NH(C₁-C₆ alkyl) or C(O)NH-(C₁-C₆ alkyl).

The invention further relates to compounds of Formula (IV):



15 and pharmaceutically acceptable salts and hydrates thereof,
 wherein:

R_5 is O, NH or S;

X is -C(O)-, -CH₂-, -CH(halo)-, -CH(OH)-, -(C(OH))((CH₂)_mCH₃))-, -
 (C(OH)(aryl))-, -O-, -N(Z_5)-, -S-, -CH(NR₁₁R₁₂)- or -N(SO₂Y)-, wherein Y is -OH, -
 20 NH₂, -(C₁-C₅ alkyl)-(3- to 7-membered monocyclic heterocycle), or -(C₁-C₅ alkyl)-(7- to 10-membered bicyclic heterocycle) and m is an integer ranging from 0-5;

R_{11} and R_{12} are independently -hydrogen or -C₁-C₉ alkyl, or N, R_{11} and R_{12} are taken together to form a –(nitrogen-containing 3- to 7-membered monocyclic heterocycle), or a –(nitrogen-containing 7- to 10-membered bicyclic heterocycle);

25 one of G₁-G₄ is C- R_7 and the remaining G₁-G₄ are independently N or C- R_7 ;

R_1 , R_2 , R_3 , and R_4 are independently -hydrogen, -halo, -hydroxy, -O-(C₁-C₅ alkyl), -C₁-C₁₀ alkyl, halo-substituted-(C₁-C₅ alkyl), -C₂-C₁₀ alkenyl, -C₃-C₈-cycloalkyl, -aryl, -NH₂, amino-substituted-(C₁-C₅ alkyl), -C(O)OH, -C(O)O(C₁-C₅ alkyl), -OC(O)(C₁-C₅ alkyl), NO₂ or -A-B;

A is -SO₂-, -SO₂NH-, -NHCO-, -NHCONH-, -O-, -CO-, -OC(O)-, -C(O)O-,
-CONH-, -CON(C₁-C₄ alkyl)-, -NH-, -CH₂-, -S- or -C(S)-;

B is -C₁-C₁₀ alkyl, -C₂-C₁₀ alkenyl, -(nitrogen-containing 3- to 7-membered
monocyclic heterocycle), -(nitrogen-containing 7- to 10-membered bicyclic heterocycle),
5 -(3- to 7-membered monocyclic heterocycle), -(7- to 10-membered bicyclic heterocycle),
-C₃-C₈ cycloalkyl, -aryl, -NZ₁Z₂, -(C₁-C₅ alkylene)-NZ₁Z₂, amino-substituted-(C₁-C₅
alkyl), -N(C₁-C₅ alkyl)(C₁-C₅ alkyl), -(C₁-C₅ alkyl)-(3- to 7-membered
monocyclic heterocycle), or -(C₁-C₅ alkyl)-(7- to 10-membered bicyclic heterocycle), -
(H₂NC(O))-substituted aryl, -(H₂NC(O))-substituted pyridyl, -C(O)OH,
10 -C(O)O-(C₁-C₅ alkyl), -C(O)O-phenyl or -C(NH)NH₂, each of which is unsubstituted or
substituted with one or more of -O-(C₁-C₅ alkyl), -halo, halo-substituted-(C₁-C₅ alkyl),
HO-substituted-(C₁-C₅ alkyl), amino-substituted-(C₁-C₅ alkyl), -hydroxy, -NO₂, -NH₂,
-CN, -NH(C₁-C₅ alkyl), -N(C₁-C₅ alkyl)(C₁-C₅ alkyl), -(nitrogen-containing 3- to 7-
membered monocyclic heterocycle), 7- to 10-membered bicycloheterocyclic amine, -C₁-
15 C₁₀ alkyl, -C₂-C₁₀ alkenyl, -C₂-C₁₀ alkynyl, -aryl, -benzyl, -(H₂NC(O))-substituted(C₁-C₅
alkyl), carboxy-substituted-(C₁-C₅ alkyl), -C(O)OH, -C₁-C₅-alkylene-C(O)O-(C₁-C₅
alkyl) or -C₁-C₅ alkylene-OC(O)-(C₁-C₅ alkyl);

Z₁ and Z₂ are independently -H or -C₁-C₁₀ alkyl, which is unsubstituted or
substituted with one or more of -halo, -OH or -N(Z₃)(Z₄), where Z₃ and Z₄ are
20 independently, -H or -C₁-C₅ alkyl, which is unsubstituted or substituted with one or more
of -halo, -hydroxy or -NH₂; or N, Z₃ and Z₄ are taken together to form a -(nitrogen-
containing 3- to 7-membered monocyclic heterocycle) or a -(nitrogen-containing 7- to
10-membered bicyclic heterocycle); or N, Z₁ and Z₂ are taken together to form a -
(nitrogen-containing 3- to 7-membered monocyclic heterocycle), or a -(nitrogen-
25 containing 7- to 10-membered bicyclic heterocycle);

each R₇ is independently -H, -C₁-C₆ alkyl, -O-(C₁-C₆ alkyl), -S-(C₁-C₆ alkyl),
-SO₂NH(C₁-C₆ alkyl) or C(O)NH-(C₁-C₆ alkyl);

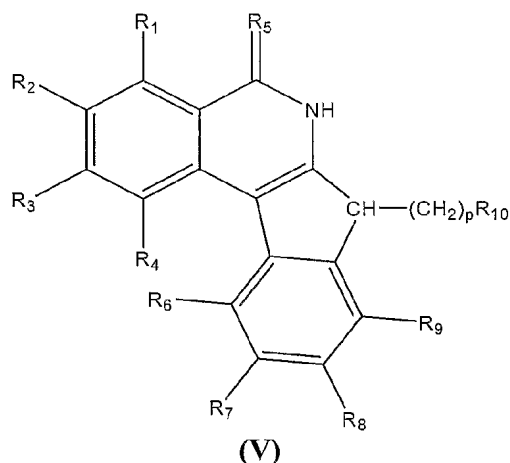
Z₅ is -H, -C₁-C₅ alkyl, -(CH₂)_n-CN, -(CH₂)_n-aryl, -(CH₂)_n-(3- to 7-membered
monocyclic heterocycle), -(CH₂)_n-(7- to 10-membered bicyclic heterocycle), -(CH₂)_n-
30 COO-(C₁-C₅ alkyl), -(CH₂)_n-COO-aryl, -(CH₂)_n-COOH, -CONH-(CH₂)_n-COOH, -
CONH-(CH₂)_n-COO-(C₁-C₅ alkyl), -CONH-(CH₂)_n-aryl, -CONHNH-(C₁-C₅ alkyl), -
CONHNH-aryl, -(CH₂)_n-CONH₂, -(CH₂)_n-CONH-(C₁-C₅ alkyl), -(CH₂)_n-CONH-aryl, -
(CH₂)_n-CONH-(CH₂)_q-aryl, -(CH₂)_n-CONH-(CH₂)_q-(3- to 7-membered monocyclic
heterocycle), -(CH₂)_n-CONH-(CH₂)_q-(3- to 7-membered monocyclic heterocycle), -

$(\text{CH}_2)_n\text{-CONH-}(\text{CH}_2)_q\text{-CONH}_2$ $(\text{CH}_2)_n\text{-CONH-}(\text{CH}_2)_q\text{-CONH-}(\text{C}_1\text{-C}_5 \text{ alkyl})$, $(\text{CH}_2)_n\text{-CONH-}(\text{CH}_2)_q\text{-CON}(\text{C}_1\text{-C}_5 \text{ alkyl})_2$, $-\text{C}(\text{O})(\text{CH}_2)_n\text{-(C}_1\text{-C}_5 \text{ alkyl)}$, $-\text{C}(\text{O})(\text{CH}_2)_n\text{-aryl}$, $-\text{C}(\text{O})(\text{CH}_2)_n\text{-COOH}$, $-\text{C}(\text{O})(\text{CH}_2)_n\text{-COO-}(\text{C}_1\text{-C}_5\text{alkyl})$, $-\text{C}(\text{O})(\text{CH}_2)_n\text{-COO-}$ (3- to 7-membered monocyclic heterocycle), $-\text{C}(\text{O})(\text{CH}_2)_n\text{-COO-}$ (7- to 10-membered bicyclic heterocycle), $-\text{C}(\text{O})(\text{CH}_2)_n\text{-phenyl}$, $-\text{C}(\text{O})(\text{CH}_2)_n\text{-(3- to 7-membered monocyclic heterocycle)}$, $-\text{C}(\text{O})(\text{CH}_2)_n\text{-phenyl}$, $-\text{C}(\text{O})(\text{CH}_2)_n\text{-(7- to 10-membered bicyclic heterocycle)}$, $-\text{C}(\text{O})\text{O}(\text{CH}_2)_n\text{-phenyl}$, $-\text{C}(\text{O})\text{O}(\text{CH}_2)_n\text{-(3- to 7-membered monocyclic heterocycle)}$, $-\text{C}(\text{O})(\text{CH}_2)_n\text{-phenyl}$, $-\text{C}(\text{O})(\text{CH}_2)_n\text{-(7- to 10-membered bicyclic heterocycle)}$, $-\text{C}(\text{O})\text{N}((\text{CH}_2)_n\text{-phenyl})_2$, $-\text{C}(\text{O})\text{N}((\text{CH}_2)_n\text{-phenyl})((\text{CH}_2)_q\text{-3- to 7-membered monocyclic heterocycle)}$, $-\text{C}(\text{O})\text{N}((\text{CH}_2)_n\text{-phenyl})((\text{CH}_2)_q\text{ 7- to 10-membered bicyclic heterocycle)}$, $-\text{C}(\text{O})\text{N}((\text{CH}_2)_n\text{-(3- to 7-membered monocyclic heterocycle)})_2$, $-\text{C}(\text{O})\text{N}((\text{CH}_2)_n\text{-7- to 10-membered bicyclic heterocycle})_2$, or $-\text{SO}_2\text{NH}_2$;

each n is an integer ranging from 0 to 10; and

q is an integer ranging from 0 to 10.

The invention also relates to compounds of Formula (V):



and pharmaceutically acceptable salts and hydrates thereof,

wherein:

R_5 is O, S, or NH;

$R_1, R_2, R_3, R_4, R_6, R_7, R_8$, and R_9 are independently -hydrogen, -halo, -hydroxy, - NH_2 , NO_2 , or -A-B;

A is $-\text{SO}_2\text{-}$, $-\text{SO}_2\text{NH-}$, $-\text{NHCO-}$, $-\text{NHCONH-}$, $-\text{O-}$, $-\text{CO-}$, $-\text{OC(O)-}$, $-\text{C(O)O-}$, $-\text{CONH-}$, $-\text{CON}(\text{C}_1\text{-C}_4 \text{ alkyl})\text{-}$, $-\text{NH-}$, $-\text{CH}_2\text{-}$, $-\text{S-}$ or $-\text{C(S)-}$;

B is $-\text{C}_1\text{-C}_{10} \text{ alkyl}$, $-\text{C}_2\text{-C}_{10} \text{ alkenyl}$, $-(\text{nitrogen-containing 3- to 7-membered monocyclic heterocycle})$, $-(\text{nitrogen-containing 7- to 10-membered bicyclic heterocycle})$, $-(3\text{- to 7-membered monocyclic heterocycle})$, $-(7\text{- to 10-membered bicyclic heterocycle})$,

-C₃-C₈ cycloalkyl, -aryl, -NZ₁Z₂, -(C₁-C₅ alkylene)-NZ₁Z₂, amino-substituted-(C₁-C₅ alkyl),
 -N(C₁-C₅ alkyl)(C₁-C₅ alkyl), -(C₁-C₅ alkyl)-(3- to 7-membered monocyclic heterocycle), or -(C₁-C₅ alkyl)-(7- to 10-membered bicyclic heterocycle), -
 (H₂NC(O))-substituted aryl, -(H₂NC(O))-substituted pyridyl, -C(O)OH,
 5 -C(O)O-(C₁-C₅ alkyl), -C(O)O-phenyl or -C(NH)NH₂, each of which is unsubstituted or substituted with one or more of -O-(C₁-C₅ alkyl), -halo, halo-substituted-(C₁-C₅ alkyl), HO-substituted-(C₁-C₅ alkyl), amino-substituted-(C₁-C₅ alkyl), -hydroxy, -NO₂, -NH₂, -CN, -NH(C₁-C₅ alkyl), -N(C₁-C₅ alkyl)(C₁-C₅ alkyl), -(nitrogen-containing 3- to 7-membered monocyclic heterocycle)), 7- to 10-membered bicycloheterocyclic amine, -C₁-
 10 C₁₀ alkyl, -C₂-C₁₀ alkenyl, -C₂-C₁₀ alkynyl, -aryl, -benzyl, -(H₂NC(O))-substituted(C₁-C₅ alkyl), carboxy-substituted-(C₁-C₅ alkyl), -C(O)OH, -C₁-C₅-alkylene-C(O)O-(C₁-C₅ alkyl) or -C₁-C₅ alkylene-OC(O)-(C₁-C₅ alkyl); and

Z₁ and Z₂ are independently -H or -C₁-C₁₀ alkyl, which is unsubstituted or substituted with one or more of -halo, -OH or -N(Z₃)(Z₄), where Z₃ and Z₄ are
 15 independently, -H or -C₁-C₅ alkyl, which is unsubstituted or substituted with one or more of -halo, -hydroxy or -NH₂; or N, Z₃ and Z₄ are taken together to form a -(nitrogen-containing 3- to 7-membered monocyclic heterocycle) or a -(nitrogen-containing 7- to 10-membered bicyclic heterocycle); or N, Z₁ and Z₂ are taken together to form a -(nitrogen-containing 3- to 7-membered monocyclic heterocycle), or a -(nitrogen-containing 7- to 10-membered bicyclic heterocycle);
 20 containing 7- to 10-membered bicyclic heterocycle);

R₁₀ is -H, -C₁-C₅ alkyl, -(CH₂)_n-CN, -(CH₂)_n-aryl, -(CH₂)_n-(3- to 7-membered monocyclic heterocycle), -(CH₂)_n-(7- to 10-membered bicyclic heterocycle), -(CH₂)_n-COO-(C₁-C₅ alkyl), -(CH₂)_n-COO-aryl, -(CH₂)_n-COOH, -CONH-(CH₂)_n-COOH, -CONH-(CH₂)_n-COO-(C₁-C₅ alkyl), -CONH-(CH₂)_n-aryl, -CONHNH-(C₁-C₅ alkyl), -CONHNH-aryl, -(CH₂)_n-CONH₂, -(CH₂)_n-CONH-(C₁-C₅ alkyl), -(CH₂)_n-CONH-aryl, -(CH₂)_n-CONH-(CH₂)_q-aryl, -(CH₂)_n-CONH-(CH₂)_q-(3- to 7-membered monocyclic heterocycle), -(CH₂)_n-CONH-(CH₂)_q-(3- to 7-membered monocyclic heterocycle), -(CH₂)_n-CONH-(CH₂)_q-CONH₂, -(CH₂)_n-CONH-(CH₂)_q-CONH-(C₁-C₅ alkyl), -(CH₂)_n-CONH-(CH₂)_q-CON(C₁-C₅ alkyl)₂, -C(O)(CH₂)_n-(C₁-C₅ alkyl), -C(O)(CH₂)_n-aryl, -C(O)(CH₂)_n-COOH, -C(O)(CH₂)_n-COO-(C₁-C₅ alkyl), -C(O)(CH₂)_n-COO-(3- to 7-membered monocyclic heterocycle), -C(O)(CH₂)_n-COO-(7- to 10-membered bicyclic heterocycle), -C(O)(CH₂)_n-phenyl, -C(O)(CH₂)_n-(3- to 7-membered monocyclic heterocycle), -C(O)(CH₂)_n-phenyl, -C(O)(CH₂)_n-(7- to 10-membered bicyclic heterocycle), -C(O)O(CH₂)_n-phenyl, -C(O)O(CH₂)_n-(3- to 7-membered monocyclic

heterocycle), $-C(O)(CH_2)_n$ -phenyl, $-C(O)(CH_2)_n$ -(7- to 10-membered bicyclic heterocycle), $-C(O)N((CH_2)_n$ -phenyl)₂, $-C(O)N((CH_2)_n$ -phenyl)((CH₂)_q-3- to 7-membered monocyclic heterocycle), $-C(O)N((CH_2)_n$ -phenyl)((CH₂)_q-7- to 10-membered bicyclic heterocycle), $-C(O)N((CH_2)_n$ -(3- to 7-membered monocyclic heterocycle)₂, -

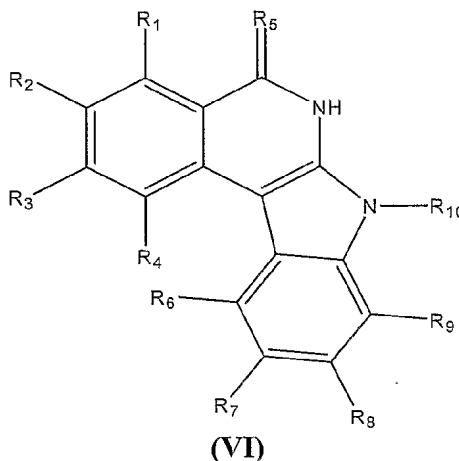
5 $C(O)N((CH_2)_n$ -7- to 10-membered bicyclic heterocycle)₂, or $-SO_2NH_2$;

each n is an integer ranging from 0 to 10;

p is an integer ranging from 0 to 5, with p being other than 0 when R₁₀ is -H; and

q is an integer ranging from 0 to 10.

The invention also relates to compounds of Formula (VI):



and pharmaceutically acceptable salts and hydrates thereof,
wherein:

15 R₅ is O, S, or NH;

R₁, R₂, R₃, R₄, R₆, R₇, R₈, and R₉ are independently -hydrogen, -halo, -hydroxy, -NH₂, -NO₂, or -A-B;

A is $-SO_2$ -, $-SO_2NH$ -, $-NHCO$ -, $-NHCONH$ -, $-O$ -, $-CO$ -, $-OC(O)$ -, $-C(O)O$ -, $-CONH$ -, $-CON(C_1-C_4 \text{ alkyl})$ -, $-NH$ -, $-CH_2$ -, $-S$ - or $-C(S)$ -;

20 B is $-C_1-C_{10}$ alkyl, $-C_2-C_{10}$ alkenyl, -(nitrogen-containing 3- to 7-membered monocyclic heterocycle), -(nitrogen-containing 7- to 10-membered bicyclic heterocycle), -(3- to 7-membered monocyclic heterocycle), -(7- to 10-membered bicyclic heterocycle), $-C_3-C_8$ cycloalkyl, -aryl, $-NZ_1Z_2$, $-(C_1-C_5 \text{ alkylene})-NZ_1Z_2$, amino-substituted- $(C_1-C_5 \text{ alkyl})$, $-N(C_1-C_5 \text{ alkyl})(C_1-C_5 \text{ alkyl})$, $-(C_1-C_5 \text{ alkyl})$ -(3- to 7-membered monocyclic heterocycle), or $-(C_1-C_5 \text{ alkyl})$ -(7- to 10-membered bicyclic heterocycle), - $(H_2NC(O))$ -substituted aryl, $-(H_2NC(O))$ -substituted pyridyl, $-C(O)OH$, $-C(O)O-(C_1-C_5 \text{ alkyl})$, $-C(O)O$ -phenyl or $-C(NH)NH_2$, each of which is unsubstituted or substituted with one or more of $-O-(C_1-C_5 \text{ alkyl})$, -halo, halo-substituted- $(C_1-C_5 \text{ alkyl})$,

HO-substituted-(C₁-C₅ alkyl), amino-substituted-(C₁-C₅ alkyl), -hydroxy, -NO₂, -NH₂,
 -CN, -NH(C₁-C₅ alkyl), -N(C₁-C₅ alkyl)(C₁-C₅ alkyl), -(nitrogen-containing 3- to 7-
 membered monocyclic heterocycle), 7- to 10-membered bicycloheterocyclic amine, -C₁-
 C₁₀ alkyl, -C₂-C₁₀ alkenyl, -C₂-C₁₀ alkynyl, -aryl, -benzyl, -(H₂NC(O))-substituted(C₁-C₅
 5 alkyl), carboxy-substituted-(C₁-C₅ alkyl), -C(O)OH, -C₁-C₅-alkylene-C(O)O-(C₁-C₅
 alkyl) or -C₁-C₅ alkylene-OC(O)-(C₁-C₅ alkyl);

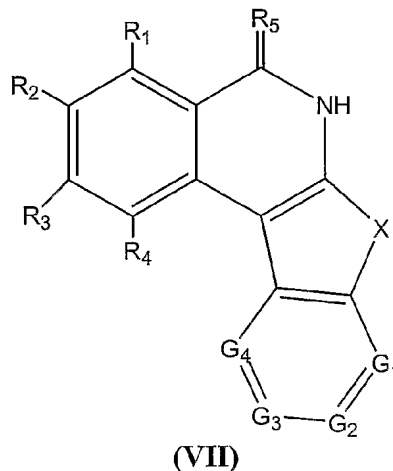
Z₁ and Z₂ are independently -H or -C₁-C₁₀ alkyl, which is unsubstituted or
 substituted with one or more of -halo, -OH or -N(Z₃)(Z₄), where Z₃ and Z₄ are
 independently, -H or -C₁-C₅ alkyl, which is unsubstituted or substituted with one or more
 10 of -halo, -hydroxy or -NH₂; or N, Z₃ and Z₄ are taken together to form a -(nitrogen-
 containing 3- to 7-membered monocyclic heterocycle) or a -(nitrogen-containing 7- to
 10-membered bicyclic heterocycle); or N, Z₁ and Z₂ are taken together to form a -
 (nitrogen-containing 3- to 7-membered monocyclic heterocycle), or a -(nitrogen-
 containing 7- to 10-membered bicyclic heterocycle);

15 R₁₀ is -H, -C₁-C₅ alkyl, -(CH₂)_n-CN, -(CH₂)_n-aryl, -(CH₂)_n-(3- to 7-membered
 monocyclic heterocycle), -(CH₂)_n-(7- to 10-membered bicyclic heterocycle), -(CH₂)_n-
 COO-(C₁-C₅ alkyl), -(CH₂)_n-COO-aryl, -(CH₂)_n-COOH, -CONH-(CH₂)_n-COOH, -
 CONH-(CH₂)_n-COO-(C₁-C₅ alkyl), -CONH-(CH₂)_n-aryl, -CONHNH-(C₁-C₅ alkyl), -
 CONHNH-aryl, -(CH₂)_n-CONH₂, -(CH₂)_n-CONH-(C₁-C₅ alkyl), -(CH₂)_n-CONH-aryl, -
 20 (CH₂)_n-CONH-(CH₂)_q-aryl, -(CH₂)_n-CONH-(CH₂)_q-(3- to 7-membered monocyclic
 heterocycle), -(CH₂)_n-CONH-(CH₂)_q-(3- to 7-membered monocyclic heterocycle), -
 (CH₂)_n-CONH-(CH₂)_q-CONH₂, -(CH₂)_n-CONH-(CH₂)_q-CONH-(C₁-C₅ alkyl), -(CH₂)_n-
 CONH-(CH₂)_q-CON(C₁-C₅ alkyl)₂, -C(O)(CH₂)_n-(C₁-C₅ alkyl), -C(O)(CH₂)_n-aryl, -
 C(O)(CH₂)_n-COOH, -C(O)(CH₂)_n-COO-(C₁-C₅alkyl), -C(O)(CH₂)_n-COO-(3- to 7-
 25 membered monocyclic heterocycle), -C(O)(CH₂)_n-COO-(7- to 10-membered bicyclic
 heterocycle), -C(O)(CH₂)_n-phenyl, -C(O)(CH₂)_n-(3- to 7-membered monocyclic
 heterocycle), -C(O)(CH₂)_n-phenyl, -C(O)(CH₂)_n-(7- to 10-membered bicyclic
 heterocycle), -C(O)O(CH₂)_n-phenyl, -C(O)O(CH₂)_n-(3- to 7-membered monocyclic
 heterocycle), -C(O)(CH₂)_n-phenyl, -C(O)(CH₂)_n-(7- to 10-membered bicyclic
 30 heterocycle), -C(O)N((CH₂)_n-phenyl)₂, -C(O)N((CH₂)_n-phenyl)((CH₂)_q-3- to 7-membered
 monocyclic heterocycle), -C(O)N((CH₂)_n-phenyl)((CH₂)_q 7- to 10-membered bicyclic
 heterocycle), -C(O)N((CH₂)_n-(3- to 7-membered monocyclic heterocycle)₂, -
 C(O)N((CH₂)_n-7- to 10-membered bicyclic heterocycle)₂, or -SO₂NH₂;

each n is an integer ranging from 0 to 10; and

q is an integer ranging from 0 to 10.

The invention also relates to compounds of Formula (VII):



5

and pharmaceutically acceptable salts and hydrates thereof,
wherein

R₅ is O, NH or S;

X is -C(O)-, -CH₂-, -CH(halo)-, -CH(OH)-, -(C(OH)((CH₂)_mCH₃))-, -
10 (C(OH)(aryl))-, -O-, -N(Z₅)-, -S-, -CH(NR₁₁R₁₂)- or -N(SO₂Y)-, wherein Y is -OH, -
NH₂, -(C₁-C₅ alkyl)-(3- to 7-membered monocyclic heterocycle), or -(C₁-C₅ alkyl)-(7- to
10-membered bicyclic heterocycle) and m is an integer ranging from 0-5;

R₁₁ and R₁₂ are independently -hydrogen or -C₁-C₉ alkyl, or N, R₁₁ and R₁₂ are
taken together to form a -(nitrogen-containing 3- to 7-membered monocyclic
15 heterocycle), or a -(nitrogen-containing 7- to 10-membered bicyclic heterocycle);

one of G₁-G₄ is C-R₇ and the remaining G₁-G₄ are independently N or C-R₇;

R₁, R₂, R₃, and R₄ are independently -hydrogen, -halo, -hydroxy, -O-(C₁-C₅ alkyl),
-C₁-C₁₀ alkyl, halo-substituted-(C₁-C₅ alkyl), -C₂-C₁₀ alkenyl, -C₃-C₈-cycloalkyl, -aryl, -
NH₂, amino-substituted-(C₁-C₅ alkyl), -C(O)OH, -C(O)O(C₁-C₅ alkyl), -OC(O)(C₁-C₅
20 alkyl), NO₂ or -A-B;

A is -SO₂-, -SO₂NH-, -NHCO-, -NHCONH-, -O-, -CO-, -OC(O)-, -C(O)O-,
-CONH-, -CON(C₁-C₄ alkyl)-, -NH-, -CH₂-, -S- or -C(S)-;

B is -C₁-C₁₀ alkyl, -C₂-C₁₀ alkenyl, -(nitrogen-containing 3- to 7-membered
monocyclic heterocycle), -(nitrogen-containing 7- to 10-membered bicyclic heterocycle),
25 -(3- to 7-membered monocyclic heterocycle), -(7- to 10-membered bicyclic heterocycle),
-C₃-C₈ cycloalkyl, -aryl, -NZ₁Z₂, -(C₁-C₅ alkylene)-NZ₁Z₂, amino-substituted-(C₁-C₅
alkyl), -N(C₁-C₅ alkyl)(C₁-C₅ alkyl), -(C₁-C₅ alkyl)-(3- to 7-membered

monocyclic heterocycle), or $-(C_1-C_5 \text{ alkyl})-(7\text{- to }10\text{-membered bicyclic heterocycle})$, $-(H_2NC(O))\text{-substituted aryl}$, $-(H_2NC(O))\text{-substituted pyridyl}$, $-C(O)OH$, $-C(O)O-(C_1-C_5 \text{ alkyl})$, $-C(O)O\text{-phenyl}$ or $-C(NH)NH_2$, each of which is unsubstituted or substituted with one or more of $-O-(C_1-C_5 \text{ alkyl})$, $-\text{halo}$, $\text{halo-substituted-}(C_1-C_5 \text{ alkyl})$, $HO\text{-substituted-}(C_1-C_5 \text{ alkyl})$, $\text{amino-substituted-}(C_1-C_5 \text{ alkyl})$, $-\text{hydroxy}$, $-\text{NO}_2$, $-\text{NH}_2$, $-\text{CN}$, $-\text{NH}(C_1-C_5 \text{ alkyl})$, $-\text{N}(C_1-C_5 \text{ alkyl})(C_1-C_5 \text{ alkyl})$, $-(\text{nitrogen-containing } 3\text{- to } 7\text{-membered monocyclic heterocycle})$, $7\text{- to } 10\text{-membered bicycloheterocyclic amine}$, $-C_1-C_{10} \text{ alkyl}$, $-C_2-C_{10} \text{ alkenyl}$, $-C_2-C_{10} \text{ alkynyl}$, $-\text{aryl}$, $-\text{benzyl}$, $-(H_2NC(O))\text{-substituted}(C_1-C_5 \text{ alkyl})$, $\text{carboxy-substituted-}(C_1-C_5 \text{ alkyl})$, $-C(O)OH$, $-C_1-C_5\text{-alkylene-}C(O)O-(C_1-C_5 \text{ alkyl})$ or $-C_1-C_5 \text{ alkylene-OC(O)-}(C_1-C_5 \text{ alkyl})$;

Z_1 and Z_2 are independently $-H$ or $-C_1-C_{10} \text{ alkyl}$, which is unsubstituted or substituted with one or more of $-\text{halo}$, $-\text{OH}$ or $-\text{N}(Z_3)(Z_4)$, where Z_3 and Z_4 are independently, $-H$ or $-C_1-C_5 \text{ alkyl}$, which is unsubstituted or substituted with one or more of $-\text{halo}$, $-\text{hydroxy}$ or $-\text{NH}_2$; or N , Z_3 and Z_4 are taken together to form a $-(\text{nitrogen-containing } 3\text{- to } 7\text{-membered monocyclic heterocycle})$ or a $-(\text{nitrogen-containing } 7\text{- to } 10\text{-membered bicyclic heterocycle})$; or N , Z_1 and Z_2 are taken together to form a $-(\text{nitrogen-containing } 3\text{- to } 7\text{-membered monocyclic heterocycle})$, or a $-(\text{nitrogen-containing } 7\text{- to } 10\text{-membered bicyclic heterocycle})$;

each R_7 is independently $-H$, $-C_1-C_6 \text{ alkyl}$, $-O-(C_1-C_6 \text{ alkyl})$, $-S-(C_1-C_6 \text{ alkyl})$, $-\text{SO}_2\text{NH}(C_1-C_6 \text{ alkyl})$ or $\text{C(O)NH-}(C_1-C_6 \text{ alkyl})$;

Z_5 is $-H$, $-C_1-C_5 \text{ alkyl}$, $-(CH_2)_n\text{-CN}$, $-(CH_2)_n\text{-aryl}$, $-(CH_2)_n\text{-(}3\text{- to }7\text{-membered monocyclic heterocycle)}$, $-(CH_2)_n\text{-(}7\text{- to }10\text{-membered bicyclic heterocycle)}$, $-(CH_2)_n\text{-COO-}(C_1-C_5 \text{ alkyl})$, $-(CH_2)_n\text{-COO-aryl}$, $-(CH_2)_n\text{-COOH}$, $-\text{CONH-}(CH_2)_n\text{-COOH}$, $-\text{CONH-}(CH_2)_n\text{-COO-}(C_1-C_5 \text{ alkyl})$, $-\text{CONH-}(CH_2)_n\text{-aryl}$, $-\text{CONHNH-}(C_1-C_5 \text{ alkyl})$, $-\text{CONHNH-aryl}$, $-(CH_2)_n\text{-CONH}_2$, $-(CH_2)_n\text{-CONH-}(C_1-C_5 \text{ alkyl})$, $-(CH_2)_n\text{-CONH-aryl}$, $-(CH_2)_n\text{-CONH-}(CH_2)_q\text{-aryl}$, $-(CH_2)_n\text{-CONH-}(CH_2)_q\text{-(}3\text{- to }7\text{-membered monocyclic heterocycle)}$, $-(CH_2)_n\text{-CONH-}(CH_2)_q\text{-(}3\text{- to }7\text{-membered monocyclic heterocycle)}$, $-(CH_2)_n\text{-CONH-}(CH_2)_q\text{-CONH}_2$, $-(CH_2)_n\text{-CONH-}(CH_2)_q\text{-CONH-}(C_1-C_5 \text{ alkyl})$, $-(CH_2)_n\text{-CONH-}(CH_2)_q\text{-CON-}(C_1-C_5 \text{ alkyl})_2$, $\text{C(O)}(CH_2)_n\text{-(}C_1-C_5 \text{ alkyl)}$, $\text{C(O)}(CH_2)_n\text{-aryl}$, $\text{C(O)}(CH_2)_n\text{-COOH}$, $\text{C(O)}(CH_2)_n\text{-COO-}(C_1-C_5 \text{ alkyl})$, $\text{C(O)}(CH_2)_n\text{-COO-}(3\text{- to }7\text{-membered monocyclic heterocycle})$, $\text{C(O)}(CH_2)_n\text{-COO-}(7\text{- to }10\text{-membered bicyclic heterocycle})$, $\text{C(O)}(CH_2)_n\text{-phenyl}$, $\text{C(O)}(CH_2)_n\text{-(}3\text{- to }7\text{-membered monocyclic heterocycle)}$, $\text{C(O)}(CH_2)_n\text{-phenyl}$, $\text{C(O)}(CH_2)_n\text{-(}7\text{- to }10\text{-membered bicyclic heterocycle)}$, $\text{C(O)O}(CH_2)_n\text{-phenyl}$, $\text{C(O)O}(CH_2)_n\text{-(}3\text{- to }7\text{-membered monocyclic}$

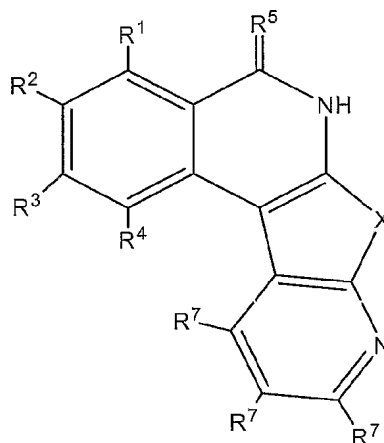
heterocycle), $-\text{C}(\text{O})(\text{CH}_2)_n\text{-phenyl}$, $-\text{C}(\text{O})(\text{CH}_2)_n\text{-(7- to 10-membered bicyclic heterocycle)}$, $-\text{C}(\text{O})\text{N}((\text{CH}_2)_n\text{-phenyl})_2$, $-\text{C}(\text{O})\text{N}((\text{CH}_2)_n\text{-phenyl})((\text{CH}_2)_q\text{-3- to 7-membered monocyclic heterocycle})$, $-\text{C}(\text{O})\text{N}((\text{CH}_2)_n\text{-phenyl})((\text{CH}_2)_q\text{ 7- to 10-membered bicyclic heterocycle})$, $-\text{C}(\text{O})\text{N}((\text{CH}_2)_n\text{-(3- to 7-membered monocyclic heterocycle)})_2$, -

5 $\text{C}(\text{O})\text{N}((\text{CH}_2)_n\text{-7- to 10-membered bicyclic heterocycle})_2$, or $-\text{SO}_2\text{NH}_2$;

each n is an integer ranging from 0 to 10; and

q is an integer ranging from 0 to 10.

The invention also relates to compounds of Formula (VIIa):



(VIIa)

and pharmaceutically acceptable salts and hydrates thereof,

wherein

15 R_5 is O, NH or S;

X is $-\text{C}(\text{O})-$, $-\text{CH}_2-$, $-\text{CH}(\text{halo})-$, $-\text{CH}(\text{OH})-$, $-(\text{C}(\text{OH})((\text{CH}_2)_m\text{CH}_3))-$, $-(\text{C}(\text{OH})(\text{aryl}))-$, $-\text{O}-$, $-\text{N}(\text{Z}_5)-$, $-\text{S}-$, $-\text{CH}(\text{NR}_{11}\text{R}_{12})-$ or $-\text{N}(\text{SO}_2\text{Y})-$, wherein Y is $-\text{OH}$, $-\text{NH}_2$, $-(\text{C}_1\text{-C}_5\text{ alkyl})\text{-(3- to 7-membered monocyclic heterocycle)}$, or $-(\text{C}_1\text{-C}_5\text{ alkyl})\text{-(7- to 10-membered bicyclic heterocycle)}$ and m is an integer ranging from 0-5;

20 R_{11} and R_{12} are independently $-\text{hydrogen}$ or $-\text{C}_1\text{-C}_9\text{ alkyl}$, or N , R_{11} and R_{12} are taken together to form a $-(\text{nitrogen-containing 3- to 7-membered monocyclic heterocycle})$, or a $-(\text{nitrogen-containing 7- to 10-membered bicyclic heterocycle})$;

R_1 , R_2 , R_3 , and R_4 are independently $-\text{hydrogen}$, $-\text{halo}$, $-\text{hydroxy}$, $-\text{O}-(\text{C}_1\text{-C}_5\text{ alkyl})$, $-\text{C}_1\text{-C}_{10}\text{ alkyl}$, $\text{halo-substituted}-(\text{C}_1\text{-C}_5\text{ alkyl})$, $-\text{C}_2\text{-C}_{10}\text{ alkenyl}$, $-\text{C}_3\text{-C}_8\text{-cycloalkyl}$, $-\text{aryl}$, $-\text{NH}_2$, amino-substituted- $(\text{C}_1\text{-C}_5\text{ alkyl})$, $-\text{C}(\text{O})\text{OH}$, $-\text{C}(\text{O})\text{O}(\text{C}_1\text{-C}_5\text{ alkyl})$, $-\text{OC}(\text{O})(\text{C}_1\text{-C}_5\text{ alkyl})$, NO_2 or $-\text{A-B}$;

A is $-\text{SO}_2-$, $-\text{SO}_2\text{NH}-$, $-\text{NHCO}-$, $-\text{NHCONH}-$, $-\text{O}-$, $-\text{CO}-$, $-\text{OC}(\text{O})-$, $-\text{C}(\text{O})\text{O}-$, $-\text{CONH}-$, $-\text{CON}(\text{C}_1\text{-C}_4\text{ alkyl})-$, $-\text{NH}-$, $-\text{CH}_2-$, $-\text{S}-$ or $-\text{C}(\text{S})-$;

B is -C₁-C₁₀ alkyl, -C₂-C₁₀ alkenyl, -(nitrogen-containing 3- to 7-membered monocyclic heterocycle), -(nitrogen-containing 7- to 10-membered bicyclic heterocycle), -(3- to 7-membered monocyclic heterocycle), -(7- to 10-membered bicyclic heterocycle), -C₃-C₈ cycloalkyl, -aryl, -NZ₁Z₂, -(C₁-C₅ alkylene)-NZ₁Z₂, amino-substituted-(C₁-C₅ alkyl),
 5 -N(C₁-C₅ alkyl)(C₁-C₅ alkyl), -(C₁-C₅ alkyl)-(3- to 7-membered monocyclic heterocycle), or -(C₁-C₅ alkyl)-(7- to 10-membered bicyclic heterocycle), -(H₂NC(O))-substituted aryl, -(H₂NC(O))-substituted pyridyl, -C(O)OH, -C(O)O-(C₁-C₅ alkyl), -C(O)O-phenyl or -C(NH)NH₂, each of which is unsubstituted or substituted with one or more of -O-(C₁-C₅ alkyl), -halo, halo-substituted-(C₁-C₅ alkyl),
 10 HO-substituted-(C₁-C₅ alkyl), amino-substituted-(C₁-C₅ alkyl), -hydroxy, -NO₂, -NH₂, -CN, -NH(C₁-C₅ alkyl), -N(C₁-C₅ alkyl)(C₁-C₅ alkyl), -(nitrogen-containing 3- to 7-membered monocyclic heterocycle), 7- to 10-membered bicycloheterocyclic amine, -C₁-C₁₀ alkyl, -C₂-C₁₀ alkenyl, -C₂-C₁₀ alkynyl, -aryl, -benzyl, -(H₂NC(O))-substituted-(C₁-C₅ alkyl), carboxy-substituted-(C₁-C₅ alkyl), -C(O)OH, -C₁-C₅-alkylene-C(O)O-(C₁-C₅ alkyl) or -C₁-C₅ alkylene-OC(O)-(C₁-C₅ alkyl); and

Z₁ and Z₂ are independently -H or -C₁-C₁₀ alkyl, which is unsubstituted or substituted with one or more of -halo, -OH or -N(Z₃)(Z₄), where Z₃ and Z₄ are independently, -H or -C₁-C₅ alkyl, which is unsubstituted or substituted with one or more of -halo, -hydroxy or -NH₂; or N, Z₃ and Z₄ are taken together to form a -(nitrogen-containing 3- to 7-membered monocyclic heterocycle) or a -(nitrogen-containing 7- to 10-membered bicyclic heterocycle); or N, Z₁ and Z₂ are taken together to form a -(nitrogen-containing 3- to 7-membered monocyclic heterocycle), or a -(nitrogen-containing 7- to 10-membered bicyclic heterocycle);

each R₇ is independently -H, -C₁-C₆ alkyl, -O-(C₁-C₆ alkyl), -S-(C₁-C₆ alkyl),
 25 -SO₂NH(C₁-C₆ alkyl) or C(O)NH-(C₁-C₆ alkyl);

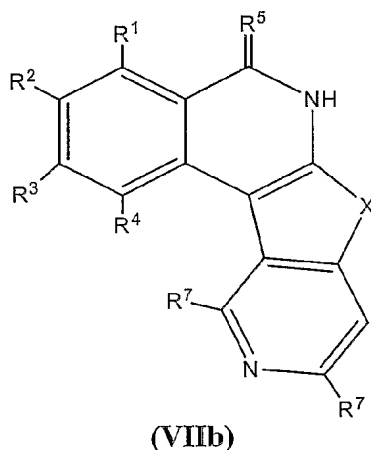
Z₅ is -H, -C₁-C₅ alkyl, -(CH₂)_n-CN, -(CH₂)_n-aryl, -(CH₂)_n-(3- to 7-membered monocyclic heterocycle), -(CH₂)_n-(7- to 10-membered bicyclic heterocycle), -(CH₂)_n-COO-(C₁-C₅ alkyl), -(CH₂)_n-COO-aryl, -(CH₂)_n-COOH, -CONH-(CH₂)_n-COOH, -CONH-(CH₂)_n-COO-(C₁-C₅ alkyl), -CONH-(CH₂)_n-aryl, -CONHNH-(C₁-C₅ alkyl), -CONHNH-aryl, -(CH₂)_n-CONH₂, -(CH₂)_n-CONH-(C₁-C₅ alkyl), -(CH₂)_n-CONH-aryl, -(CH₂)_n-CONH-(CH₂)_q-aryl, -(CH₂)_n-CONH-(CH₂)_q-(3- to 7-membered monocyclic heterocycle), -(CH₂)_n-CONH-(CH₂)_q-(3- to 7-membered monocyclic heterocycle), -(CH₂)_n-CONH-(CH₂)_q-CONH₂, -(CH₂)_n-CONH-(CH₂)_q-CONH-(C₁-C₅ alkyl), -(CH₂)_n-CONH-(CH₂)_q-CON(C₁-C₅ alkyl)₂, -C(O)(CH₂)_n-(C₁-C₅ alkyl), -C(O)(CH₂)_n-aryl, -

- $C(O)(CH_2)_n-COOH$, $-C(O)(CH_2)_n-COO-(C_1-C_5\text{alkyl})$, $-C(O)(CH_2)_n-COO-(3\text{- to }7\text{-membered monocyclic heterocycle})$, $-C(O)(CH_2)_n-COO-(7\text{- to }10\text{-membered bicyclic heterocycle})$, $-C(O)(CH_2)_n\text{-phenyl}$, $-C(O)(CH_2)_n-(3\text{- to }7\text{-membered monocyclic heterocycle})$, $-C(O)(CH_2)_n\text{-phenyl}$, $-C(O)(CH_2)_n-(7\text{- to }10\text{-membered bicyclic heterocycle})$, $-C(O)O(CH_2)_n\text{-phenyl}$, $-C(O)O(CH_2)_n-(3\text{- to }7\text{-membered monocyclic heterocycle})$, $-C(O)(CH_2)_n\text{-phenyl}$, $-C(O)(CH_2)_n-(7\text{- to }10\text{-membered bicyclic heterocycle})$, $-C(O)N((CH_2)_n\text{-phenyl})_2$, $-C(O)N((CH_2)_n\text{-phenyl})((CH_2)_q\text{-}3\text{- to }7\text{-membered monocyclic heterocycle})$, $-C(O)N((CH_2)_n\text{-phenyl})((CH_2)_q\text{-}7\text{- to }10\text{-membered bicyclic heterocycle})$, $-C(O)N((CH_2)_n-(3\text{- to }7\text{-membered monocyclic heterocycle}))_2$, -
 5 $C(O)N((CH_2)_n\text{-}7\text{- to }10\text{-membered bicyclic heterocycle})_2$, or $-SO_2NH_2$;

each n is an integer ranging from 0 to 10; and

q is an integer ranging from 0 to 10.

The invention also relates to compounds of Formula (VIIb):



15

and pharmaceutically acceptable salts and hydrates thereof,
 wherein

R_5 is O, NH or S;

- 20 X is $-C(O)-$, $-CH_2-$, $-CH(\text{halo})-$, $-CH(OH)-$, $-(C(OH)((CH_2)_mCH_3))-$, $-(C(OH)(\text{aryl}))-$, $-O-$, $-N(Z_5)-$, $-S-$, $-CH(NR_{11}R_{12})-$ or $-N(SO_2Y)-$, wherein Y is $-OH$, $-NH_2$, $-(C_1-C_5\text{ alkyl})-(3\text{- to }7\text{-membered monocyclic heterocycle})$, or $-(C_1-C_5\text{ alkyl})-(7\text{- to }10\text{-membered bicyclic heterocycle})$ and m is an integer ranging from 0-5;

- 25 R_{11} and R_{12} are independently $-hydrogen$ or $-C_1-C_9\text{ alkyl}$, or N, R_{11} and R_{12} are taken together to form a $-(\text{nitrogen-containing }3\text{- to }7\text{-membered monocyclic heterocycle})$, or a $-(\text{nitrogen-containing }7\text{- to }10\text{-membered bicyclic heterocycle})$;

R_1 , R_2 , R_3 , and R_4 are independently $-hydrogen$, $-halo$, $-hydroxy$, $-O-(C_1-C_5\text{ alkyl})$, $-C_1-C_{10}\text{ alkyl}$, $\text{halo-substituted-}(C_1-C_5\text{ alkyl})$, $-C_2-C_{10}\text{ alkenyl}$, $-C_3-C_8\text{-cycloalkyl}$, $-aryl$, -

NH₂, amino-substituted-(C₁-C₅ alkyl), -C(O)OH, -C(O)O(C₁-C₅ alkyl), -OC(O)(C₁-C₅ alkyl), NO₂ or -A-B;

A is -SO₂-, -SO₂NH-, -NHCO-, -NHCONH-, -O-, -CO-, -OC(O)-, -C(O)O-, -CONH-, -CON(C₁-C₄ alkyl)-, -NH-, -CH₂-, -S- or -C(S)-;

- 5 B is -C₁-C₁₀ alkyl, -C₂-C₁₀ alkenyl, -(nitrogen-containing 3- to 7-membered monocyclic heterocycle), -(nitrogen-containing 7- to 10-membered bicyclic heterocycle), -(3- to 7-membered monocyclic heterocycle), -(7- to 10-membered bicyclic heterocycle), -C₃-C₈ cycloalkyl, -aryl, -NZ₁Z₂, -(C₁-C₅ alkylene)-NZ₁Z₂, amino-substituted-(C₁-C₅ alkyl), -N(C₁-C₅ alkyl)(C₁-C₅ alkyl), -(C₁-C₅ alkyl)-(3- to 7-membered
- 10 monocyclic heterocycle), or -(C₁-C₅ alkyl)-(7- to 10-membered bicyclic heterocycle), -(H₂NC(O))-substituted aryl, -(H₂NC(O))-substituted pyridyl, -C(O)OH, -C(O)O-(C₁-C₅ alkyl), -C(O)O-phenyl or -C(NH)NH₂, each of which is unsubstituted or substituted with one or more of -O-(C₁-C₅ alkyl), -halo, halo-substituted-(C₁-C₅ alkyl), HO-substituted-(C₁-C₅ alkyl), amino-substituted-(C₁-C₅ alkyl), -hydroxy, -NO₂, -NH₂,
- 15 -CN, -NH(C₁-C₅ alkyl), -N(C₁-C₅ alkyl)(C₁-C₅ alkyl), -(nitrogen-containing 3- to 7-membered monocyclic heterocycle), 7- to 10-membered bicycloheterocyclic amine, -C₁-C₁₀ alkyl, -C₂-C₁₀ alkenyl, -C₂-C₁₀ alkynyl, -aryl, -benzyl, -(H₂NC(O))-substituted(C₁-C₅ alkyl), carboxy-substituted-(C₁-C₅ alkyl), -C(O)OH, -C₁-C₅-alkylene-C(O)O-(C₁-C₅ alkyl) or -C₁-C₅ alkylene-OC(O)-(C₁-C₅ alkyl); and

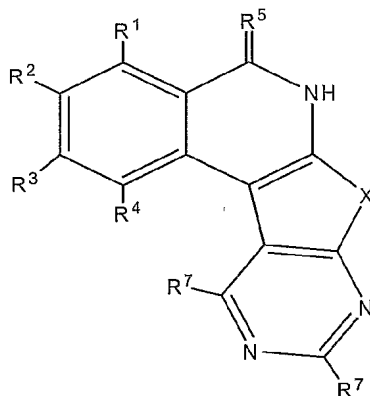
- 20 Z₁ and Z₂ are independently -H or -C₁-C₁₀ alkyl, which is unsubstituted or substituted with one or more of -halo, -OH or -N(Z₃)(Z₄), where Z₃ and Z₄ are independently, -H or -C₁-C₅ alkyl, which is unsubstituted or substituted with one or more of -halo, -hydroxy or -NH₂; or N, Z₃ and Z₄ are taken together to form a -(nitrogen-containing 3- to 7-membered monocyclic heterocycle) or a -(nitrogen-containing 7- to
- 25 10-membered bicyclic heterocycle); or N, Z₁ and Z₂ are taken together to form a -(nitrogen-containing 3- to 7-membered monocyclic heterocycle), or a -(nitrogen-containing 7- to 10-membered bicyclic heterocycle);

each R₇ is independently -H, -C₁-C₆ alkyl, -O-(C₁-C₆ alkyl), -S-(C₁-C₆ alkyl), -SO₂NH(C₁-C₆ alkyl) or C(O)NH-(C₁-C₆ alkyl);

- 30 Z₅ is -H, -C₁-C₅ alkyl, -(CH₂)_n-CN, -(CH₂)_n-aryl, -(CH₂)_n-(3- to 7-membered monocyclic heterocycle), -(CH₂)_n-(7- to 10-membered bicyclic heterocycle), -(CH₂)_n-COO-(C₁-C₅ alkyl), -(CH₂)_n-COO-aryl, -(CH₂)_n-COOH, -CONH-(CH₂)_n-COOH, -CONH-(CH₂)_n-COO-(C₁-C₅ alkyl), -CONH-(CH₂)_n-aryl, -CONHNH-(C₁-C₅ alkyl), -CONHNH-aryl, -(CH₂)_n-CONH₂, -(CH₂)_n-CONH-(C₁-C₅ alkyl), -(CH₂)_n-CONH-aryl, -

- (CH₂)_n-CONH-(CH₂)_q-aryl, -(CH₂)_n-CONH-(CH₂)_q-(3- to 7-membered monocyclic heterocycle), -(CH₂)_n-CONH-(CH₂)_q-(3- to 7-membered monocyclic heterocycle), -
 (CH₂)_n-CONH-(CH₂)_q-CONH₂ -(CH₂)_n-CONH-(CH₂)_q-CONH-(C₁-C₅ alkyl), -(CH₂)_n-
 CONH-(CH₂)_q-CON(C₁-C₅ alkyl)₂, -C(O)(CH₂)_n-(C₁-C₅ alkyl), -C(O)(CH₂)_n-aryl, -
 5 C(O)(CH₂)_n-COOH, -C(O)(CH₂)_n-COO-(C₁-C₅alkyl), -C(O)(CH₂)_n-COO-(3- to 7-
 membered monocyclic heterocycle), -C(O)(CH₂)_n-COO-(7- to 10-membered bicyclic
 heterocycle), -C(O)(CH₂)_n-phenyl, -C(O)(CH₂)_n-(3- to 7-membered monocyclic
 heterocycle), -C(O)(CH₂)_n-phenyl, -C(O)(CH₂)_n-(7- to 10-membered bicyclic
 heterocycle), -C(O)O(CH₂)_n-phenyl, -C(O)O(CH₂)_n-(3- to 7-membered monocyclic
 10 heterocycle), -C(O)(CH₂)_n-phenyl, -C(O)(CH₂)_n-(7- to 10-membered bicyclic
 heterocycle), -C(O)N((CH₂)_n-phenyl)₂, -C(O)N((CH₂)_n-phenyl)((CH₂)_q-3- to 7-membered
 monocyclic heterocycle), -C(O)N((CH₂)_n-phenyl)((CH₂)_q 7- to 10-membered bicyclic
 heterocycle), -C(O)N((CH₂)_n-(3- to 7-membered monocyclic heterocycle)₂, -
 .C(O)N((CH₂)_n-7- to 10-membered bicyclic heterocycle)₂, or -SO₂NH₂;
 15 each n is an integer ranging from 0 to 10; and
 q is an integer ranging from 0 to 10.

The invention also relates to compounds of Formula (VIIc):



(VIIc)

20

and pharmaceutically acceptable salts and hydrates thereof,
 wherein

- R₅ is O, NH or S;
 X is -C(O)-, -CH₂-, -CH(halo)-, -CH(OH)-, -(C(OH)((CH₂)_mCH₃))-, -
 25 (C(OH)(aryl))-, -O-, -N(Z₅)-, -S-, -CH(NR₁₁R₁₂)- or -N(SO₂Y)-, wherein Y is -OH, -
 NH₂, -(C₁-C₅ alkyl)-(3- to 7-membered monocyclic heterocycle), or -(C₁-C₅ alkyl)-(7- to
 10-membered bicyclic heterocycle) and m is an integer ranging from 0-5;

R₁₁ and R₁₂ are independently -hydrogen or -C₁-C₉ alkyl, or N, R₁₁ and R₁₂ are taken together to form a -(nitrogen-containing 3- to 7-membered monocyclic heterocycle), or a -(nitrogen-containing 7- to 10-membered bicyclic heterocycle);

R₁, R₂, R₃, and R₄ are independently -hydrogen, -halo, -hydroxy, -O-(C₁-C₅ alkyl),
 5 -C₁-C₁₀ alkyl, halo-substituted-(C₁-C₅ alkyl), -C₂-C₁₀ alkenyl, -C₃-C₈-cycloalkyl, -aryl, -NH₂, amino-substituted-(C₁-C₅ alkyl), -C(O)OH, -C(O)O(C₁-C₅ alkyl), -OC(O)(C₁-C₅ alkyl), NO₂ or -A-B;

A is -SO₂-, -SO₂NH-, -NHCO-, -NHCONH-, -O-, -CO-, -OC(O)-, -C(O)O-,
 -CONH-, -CON(C₁-C₄ alkyl)-, -NH-, -CH₂-, -S- or -C(S)-;

10 B is -C₁-C₁₀ alkyl, -C₂-C₁₀ alkenyl, -(nitrogen-containing 3- to 7-membered monocyclic heterocycle), -(nitrogen-containing 7- to 10-membered bicyclic heterocycle), -(3- to 7-membered monocyclic heterocycle), -(7- to 10-membered bicyclic heterocycle), -C₃-C₈ cycloalkyl, -aryl, -NZ₁Z₂, -(C₁-C₅ alkylene)-NZ₁Z₂, amino-substituted-(C₁-C₅ alkyl),
 -N(C₁-C₅ alkyl)(C₁-C₅ alkyl), -(C₁-C₅ alkyl)-(3- to 7-membered
 15 monocyclic heterocycle), or -(C₁-C₅ alkyl)-(7- to 10-membered bicyclic heterocycle), -(H₂NC(O))-substituted aryl, -(H₂NC(O))-substituted pyridyl, -C(O)OH, -C(O)O-(C₁-C₅ alkyl), -C(O)O-phenyl or -C(NH)NH₂, each of which is unsubstituted or substituted with one or more of -O-(C₁-C₅ alkyl), -halo, halo-substituted-(C₁-C₅ alkyl), HO-substituted-(C₁-C₅ alkyl), amino-substituted-(C₁-C₅ alkyl), -hydroxy, -NO₂, -NH₂,
 20 -CN, -NH(C₁-C₅ alkyl), -N(C₁-C₅ alkyl)(C₁-C₅ alkyl), -(nitrogen-containing 3- to 7-membered monocyclic heterocycle), 7- to 10-membered bicycloheterocyclic amine, -C₁-C₁₀ alkyl, -C₂-C₁₀ alkenyl, -C₂-C₁₀ alkynyl, -aryl, -benzyl, -(H₂NC(O))-substituted(C₁-C₅ alkyl), carboxy-substituted-(C₁-C₅ alkyl), -C(O)OH, -C₁-C₅-alkylene-C(O)O-(C₁-C₅ alkyl) or -C₁-C₅ alkylene-OC(O)-(C₁-C₅ alkyl); and

25 Z₁ and Z₂ are independently -H or -C₁-C₁₀ alkyl, which is unsubstituted or substituted with one or more of -halo, -OH or -N(Z₃)(Z₄), where Z₃ and Z₄ are independently, -H or -C₁-C₅ alkyl, which is unsubstituted or substituted with one or more of -halo, -hydroxy or -NH₂; or N, Z₃ and Z₄ are taken together to form a -(nitrogen-containing 3- to 7-membered monocyclic heterocycle) or a -(nitrogen-containing 7- to
 30 10-membered bicyclic heterocycle); or N, Z₁ and Z₂ are taken together to form a -(nitrogen-containing 3- to 7-membered monocyclic heterocycle), or a -(nitrogen-containing 7- to 10-membered bicyclic heterocycle);

each R₇ is independently -H, -C₁-C₆ alkyl, -O-(C₁-C₆ alkyl), -S-(C₁-C₆ alkyl), -SO₂NH(C₁-C₆ alkyl) or C(O)NH-(C₁-C₆ alkyl);

- Z_5 is $-H$, $-C_1-C_5$ alkyl, $-(CH_2)_n-CN$, $-(CH_2)_n-aryl$, $-(CH_2)_n-(3- \text{ to } 7\text{-membered monocyclic heterocycle})$, $-(CH_2)_n-(7- \text{ to } 10\text{-membered bicyclic heterocycle})$, $-(CH_2)_n-COO-(C_1-C_5 \text{ alkyl})$, $-(CH_2)_n-COO-aryl$, $-(CH_2)_n-COOH$, $-CONH-(CH_2)_n-COOH$, $-CONH-(CH_2)_n-COO-(C_1-C_5 \text{ alkyl})$, $-CONH-(CH_2)_n-aryl$, $-CONHNH-(C_1-C_5 \text{ alkyl})$, $-CONHNH-aryl$, $-(CH_2)_n-CONH_2$, $-(CH_2)_n-CONH-(C_1-C_5 \text{ alkyl})$, $-(CH_2)_n-CONH-aryl$, $-(CH_2)_n-CONH-(CH_2)_q-aryl$, $-(CH_2)_n-CONH-(CH_2)_q-(3- \text{ to } 7\text{-membered monocyclic heterocycle})$, $-(CH_2)_n-CONH-(CH_2)_q-(3- \text{ to } 7\text{-membered monocyclic heterocycle})$, $-(CH_2)_n-CONH-(CH_2)_q-CONH_2$, $-(CH_2)_n-CONH-(CH_2)_q-CONH-(C_1-C_5 \text{ alkyl})$, $-(CH_2)_n-CONH-(CH_2)_q-CON(C_1-C_5 \text{ alkyl})_2$, $-C(O)(CH_2)_n-(C_1-C_5 \text{ alkyl})$, $-C(O)(CH_2)_n-aryl$, $-C(O)(CH_2)_n-COOH$, $-C(O)(CH_2)_n-COO-(C_1-C_5 \text{ alkyl})$, $-C(O)(CH_2)_n-COO-(3- \text{ to } 7\text{-membered monocyclic heterocycle})$, $-C(O)(CH_2)_n-COO-(7- \text{ to } 10\text{-membered bicyclic heterocycle})$, $-C(O)(CH_2)_n-phenyl$, $-C(O)(CH_2)_n-(3- \text{ to } 7\text{-membered monocyclic heterocycle})$, $-C(O)(CH_2)_n-phenyl$, $-C(O)(CH_2)_n-(7- \text{ to } 10\text{-membered bicyclic heterocycle})$, $-C(O)O(CH_2)_n-phenyl$, $-C(O)O(CH_2)_n-(3- \text{ to } 7\text{-membered monocyclic heterocycle})$, $-C(O)(CH_2)_n-phenyl$, $-C(O)(CH_2)_n-(7- \text{ to } 10\text{-membered bicyclic heterocycle})$, $-C(O)N((CH_2)_n-phenyl)_2$, $-C(O)N((CH_2)_n-phenyl)((CH_2)_q-3- \text{ to } 7\text{-membered monocyclic heterocycle})$, $-C(O)N((CH_2)_n-phenyl)((CH_2)_q-7- \text{ to } 10\text{-membered bicyclic heterocycle})$, $-C(O)N((CH_2)_n-(3- \text{ to } 7\text{-membered monocyclic heterocycle}))_2$, $-C(O)N((CH_2)_n-7- \text{ to } 10\text{-membered bicyclic heterocycle})_2$, or $-SO_2NH_2$;
- each n is an integer ranging from 0 to 10; and
- q is an integer ranging from 0 to 10.

- A compound of Formula (I), (Ia), (Ib), (II) (IIa), (III), (IV), (V), (VI), (VII), (VIIa), (VIIb) or (VIIc) or a pharmaceutically acceptable salt or hydrate thereof (a "Tetracyclic Benzamide Derivative") is useful for treating or preventing an inflammatory disease, a reperfusion disease, an ischemic condition, renal failure, diabetes, a diabetic complication, a vascular disease, or cancer (each being a "Condition") in an subject.

- The invention also relates to compositions comprising an amount of a Tetracyclic Benzamide Derivative that is effective to treat or prevent a Condition, and a pharmaceutically acceptable carrier or vehicle. The compositions are useful for treating or preventing a Condition in a subject.

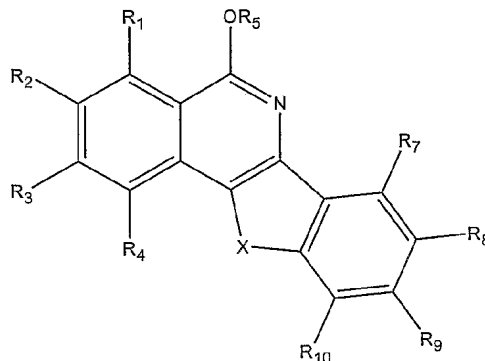
The invention further relates to methods for treating or preventing a Condition, comprising administering to a subject in need thereof an amount of a Tetracyclic Benzamide Derivative that is effective to treat or prevent the Condition.

The present invention may be understood more fully by reference to the following detailed description and illustrative examples, which are intended to exemplify non-limiting embodiments of the invention.

4. Detailed Description of the Invention

4.1 Tetracyclic Benzamide Derivatives of Formula (I)

As stated above, the present invention encompasses compounds of Formula (I)



(I)

and pharmaceutically acceptable salts and hydrates thereof, where R_1 , R_2 , R_3 , R_4 , R_5 , R_7 , R_8 , R_9 , R_{10} , and X are defined above for the Tetracyclic Benzamide Derivatives of Formula (I).

10 In one embodiment X is O .

In one embodiment R_1 - R_4 , R_7 and R_{10} are hydrogen.

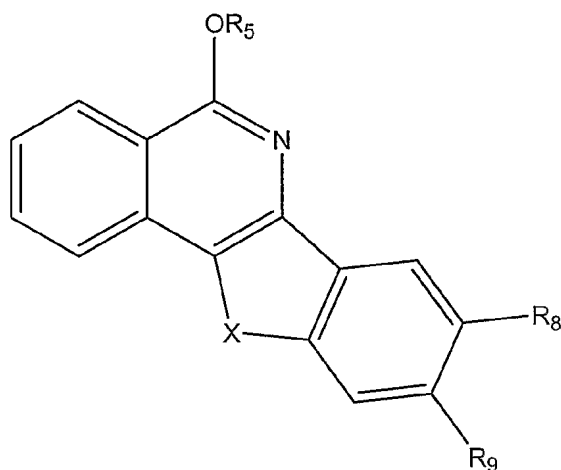
In another embodiment, at least one of R_1 , R_2 , R_3 , R_4 , R_7 , R_8 , R_9 and R_{10} is other than hydrogen.

In one embodiment R_5 is $-C_2$ - C_{10} alkyl.

15 In another embodiment R_5 is $-C_4$ - C_{10} alkyl.

In another embodiment R_5 is $-C_6$ - C_{10} alkyl.

In another embodiment the compounds of Formula (I) have the structure of Formula (I'):



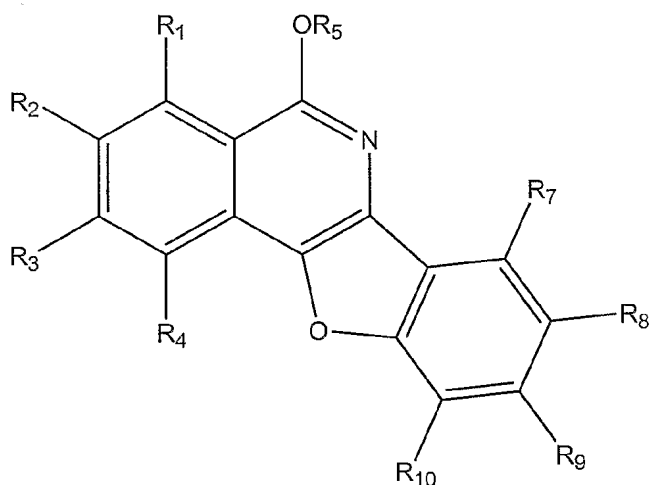
(I')

wherein X, R₅, R₈ and R₉ are defined above for the Tetracyclic Benzamide Derivatives of Formula (I).

5

4.2 Tetracyclic Benzamide Derivatives of Formula (Ia)

As stated above, the invention further encompasses compounds of Formula (Ia):



(Ia)

and pharmaceutically acceptable salts and hydrates thereof, where R₁, R₂, R₃, R₄, R₅, R₇,
 10 R₈, R₉, and R₁₀, are defined above for the Tetracyclic Benzamide Derivatives of Formula (Ia).

In one embodiment R₁-R₄, R₇ and R₁₀ are hydrogen.

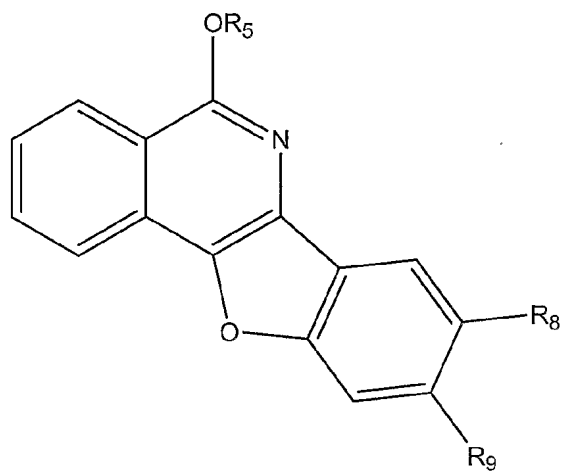
In another embodiment, at least one of R₁, R₂, R₃, R₄, R₇, R₈, R₉ or R₁₀ is other than hydrogen.

15 In one embodiment R₅ is -C₂-C₁₀ alkyl.

In another embodiment R₅ is -C₄-C₁₀ alkyl.

In another embodiment R_5 is $-C_6-C_{10}$ alkyl.

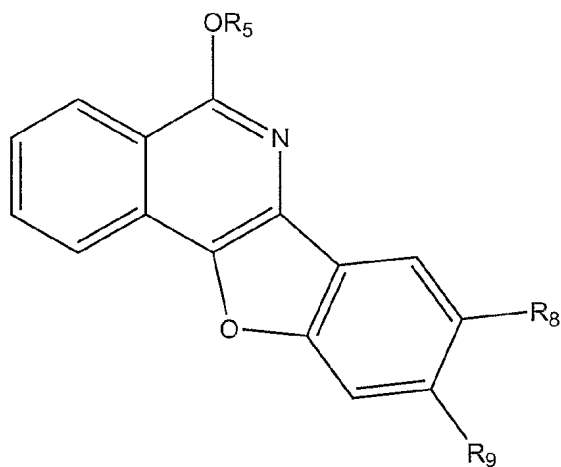
In another embodiment compounds of Formula (Ia) have the structure of Formula (Ia'):



(Ia')

wherein R_5 , R_8 , and R_9 are defined above for compounds of Formula (Ia).

Illustrative compounds of Formula (Ia') are set forth below:



(Ia')

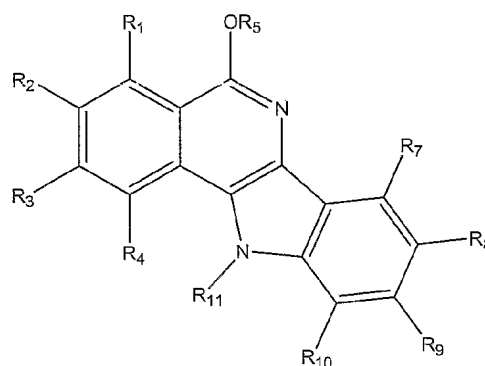
Compound No.	R_5	R_8	R_9
16a	$-CH_2COOH$	$-OCH_2COOH$	$-H$
16b	$-(CH_2)_3OH$	$-O(CH_2)_3OH$	$-H$
16c	$-(CH_2)_5OH$	$-O(CH_2)_5OH$	$-H$
16d	$-(CH_2)_6OH$	$-O(CH_2)_6OH$	$-H$
16e	$-(CH_2)_4COOH$	$-O(CH_2)_4COOH$	$-H$

16f	-CH ₃	-H	-H
16g	-C(O)CH ₃	-H	-H
16h	-glucuronide	-H	-H
16i	-CH ₃	-H	-OCH ₃
16j	-(CH ₂) ₃ OH	-H	-O(CH ₂) ₃ OH
16k	-(CH ₂) ₆ OH	-H	-O(CH ₂) ₆ OH

and pharmaceutically acceptable salts and hydrates thereof.

4.3 Tetracyclic Benzamide Derivatives of Formula (Ib)

The invention also relates to compounds of Formula (Ib):



(Ib)

and pharmaceutically acceptable salts and hydrates thereof, where R₁, R₂, R₃, R₄, R₅, R₇, R₈, R₉, R₁₀, and R₁₁ are defined above for the Tetracyclic Benzamide Derivatives of Formula (Ib).

10 In one embodiment, R₁-R₄, R₇ and R₁₀ are hydrogen.

In another embodiment, at least one of R₁, R₂, R₃, R₄, R₇, R₈, R₉ and R₁₀ is other than hydrogen.

In one embodiment R₅ is -C₂-C₁₀ alkyl.

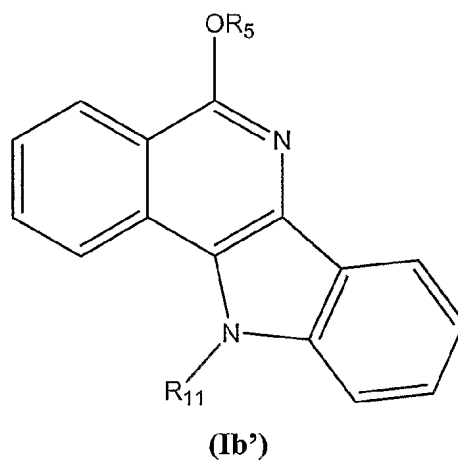
In another embodiment R₅ is -C₄-C₁₀ alkyl.

15 In another embodiment R₅ is -C₆-C₁₀ alkyl.

In a further embodiment R₅ is -C(O)(C₁-C₅ alkyl).

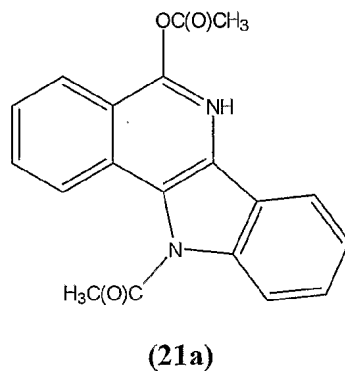
In yet another embodiment R₁₁ is -C(O)(C₁-C₅ alkyl).

In another embodiment the compounds of Formula (Ib) have the structure of Formula (Ib'):



wherein R_5 and R_{11} are defined above for Formula (Ib).

An illustrative compound of Formula (Ib') is compound **21a**, set forth below:

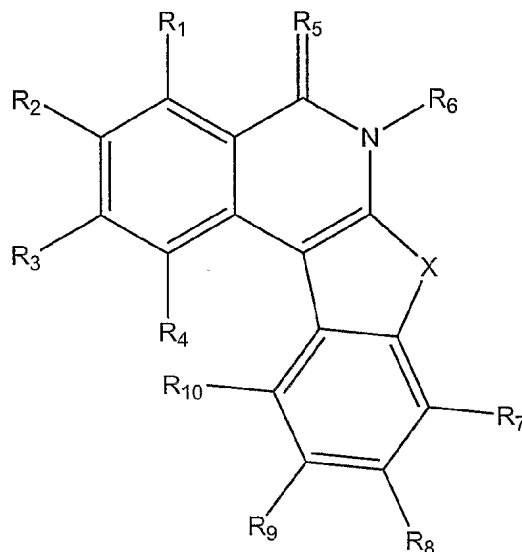


5

and pharmaceutically acceptable salts and hydrates thereof.

4.4 Tetracyclic Benzamide Derivatives of Formula (II)

As stated above, the present invention encompasses compounds of Formula (II):



(II)

- 5 and pharmaceutically acceptable salts and hydrates thereof, where R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 , R_9 , R_{10} , and X are defined above for the Tetracyclic Benzamide Derivatives of Formula (II).

In one embodiment, R_1 - R_4 , R_7 and R_{10} are hydrogen.

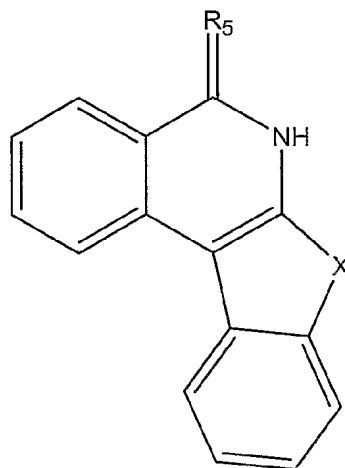
- In another embodiment, at least one of R_1 , R_2 , R_3 , R_4 , R_7 , R_8 , R_9 and R_{10} is other
10 than hydrogen.

In another embodiment R_7 - R_{10} are hydrogen.

In still another embodiment, R_6 is hydrogen.

In one embodiment R_1 - R_4 and R_7 - R_{10} is other than $-O-(C_1-C_5 \text{ alkyl})$, and $-A-B$ is other than $-O-(C_1-C_{10} \text{ alkyl})$.

In another embodiment compounds of Formula (II) have the structure of Formula (II'):



(II')

5 wherein X and R₅ are defined above for Formula (II).

In other illustrative embodiments R₅ and X of Formula (II') are as set forth below:

<u>R₅</u>	<u>X</u>
NH	-C(O)-
NH	-S-
NH	-NH-
NH	-CH ₂ -
NH	-N(SO ₂ Y)-

<u>R₅</u>	<u>X</u>
S	-C(O)-
S	-S-
S	-NH-
S	-CH ₂ -
S	-N(SO ₂ Y)-

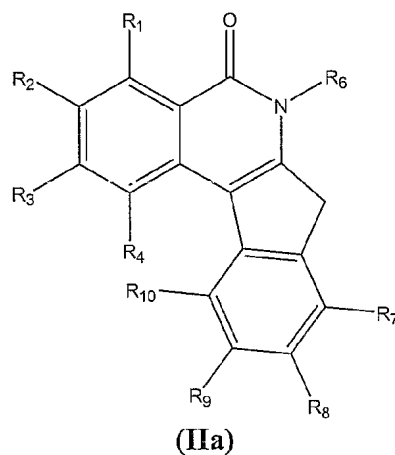
<u>R₅</u>	<u>X</u>
O	-C(O)-

O	-S-
O	-NH-
O	-CH ₂ -
O	-N(SO ₂ Y)-

and pharmaceutically acceptable salts and hydrates thereof.

4.5 Tetracyclic Benzamide Derivatives of Formula (IIa)

5 As stated above, the present invention encompasses compounds of Formula (IIa):



and pharmaceutically acceptable salts and hydrates thereof, where R₁, R₂, R₃, R₄, R₅, R₆,
 10 R₇, R₈, R₉, and R₁₀ are defined above for the Tetracyclic Benzamide Derivatives of
 Formula (IIa).

In one embodiment, R₁-R₄ are hydrogen.

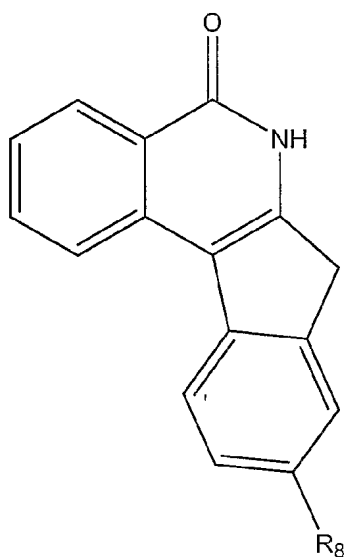
In one embodiment, R₁-R₄, R₇, R₉, and R₁₀ are hydrogen.

In another embodiment, at least one of R₁, R₂, R₃, R₄, R₇, R₈, R₉ and R₁₀ is other
 15 than hydrogen.

In still another embodiment, R₆ is hydrogen.

In one embodiment R₁-R₄ and R₇-R₁₀ is other than -O-(C₁-C₅ alkyl), and -A-B is
 other than -O-(C₁-C₁₀ alkyl).

In another embodiment compounds of Formula (IIa) have the structure of Formula
 20 (IIa'):

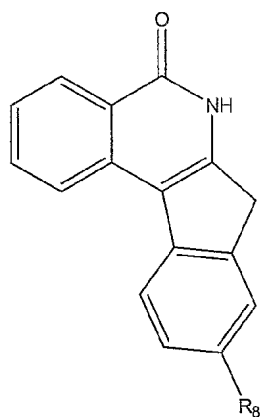


(IIa')

wherein R_8 is defined above for Formula (IIa).

In one embodiment R_8 is -A-B, where -A- is $-\text{SO}_2-$ and -B is $-\text{NZ}_1\text{Z}_2$ or $-(\text{C}_1\text{-C}_5\text{alkylene})\text{-NZ}_1\text{Z}_2$.

Illustrative compounds of Formula (IIa') are set forth below:



(IIa')

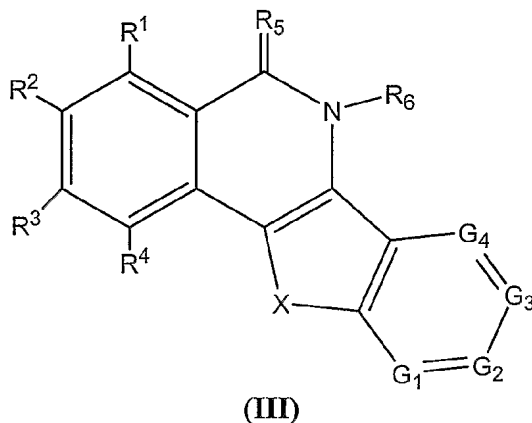
Compound No.	R_8
9a	-H
11a	$-\text{SO}_2\text{NH}_2(\text{CH}_2)_3\text{-(N-morpholinyl)}$

10

and pharmaceutically acceptable salts and hydrates thereof.

4.6 Tetracyclic Benzamide Derivatives of Formula (III)

As stated above, the present invention encompasses compounds of Formula (III):



5

and pharmaceutically acceptable salts and hydrates thereof, where R₁, R₂, R₃, R₄, R₅, R₆, G₁, G₂, G₃, G₄, and X are defined above for the Tetracyclic Benzamide Derivatives of Formula (III).

In one embodiment R₁-R₄ are hydrogen.

10

In another embodiment, at least one of R₁, R₂, R₃, R₄ and R₇ is other than hydrogen.

In yet another embodiment R₅ is oxygen.

In still another embodiment, one of G₁-G₄ is N.

In another embodiment G₁ is N; and G₂-G₄ are C-R₇.

15

In another embodiment G₂ is N; and G₁, G₃ and G₄ are C-R₇.

In another embodiment G₃ is N; and G₁, G₂ and G₄ are C-R₇.

In another embodiment G₄ is N; and G₁, G₂, and G₃ are C-R₇.

In another embodiment G₁ and G₂ are N and G₃ and G₄ are C-R₇.

In another embodiment G₁ and G₃ are N and G₂ and G₄ are C-R₇.

20

In another embodiment G₁ and G₄ are N and G₂ and G₃ are C-R₇.

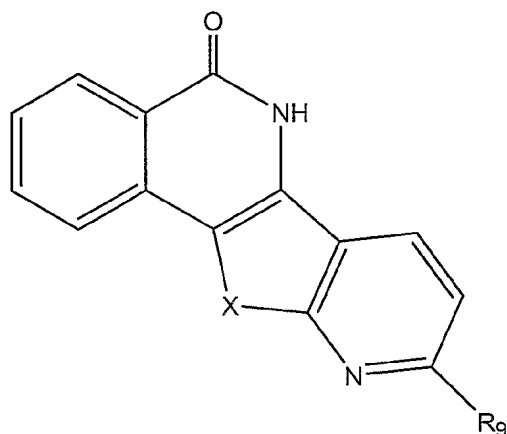
In another embodiment G₂ and G₃ are N and G₁ and G₄ are C-R₇.

In another embodiment G₂ and G₄ are N and G₁ and G₃ are C-R₇.

In another embodiment G₃ and G₄ are N and G₁ and G₂ are C-R₇.

In another embodiment compounds of Formula (III) have the structure of Formula

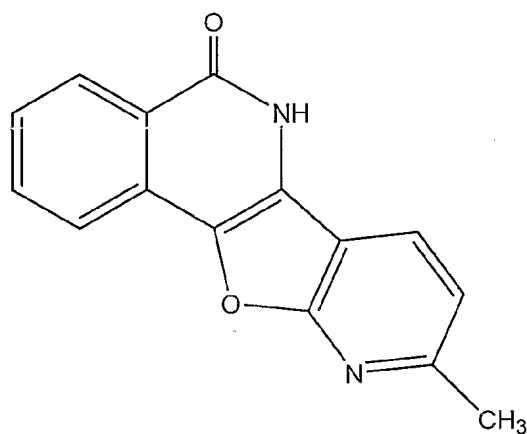
25 (III'):



(III')

wherein X, and R₉ are defined above for Formula (III).

An illustrative example of a compound of Formula (III') is set forth below:

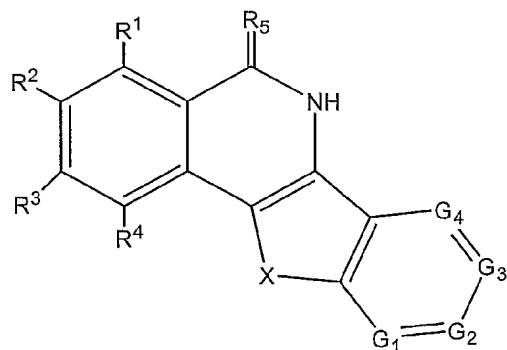


(26a)

and pharmaceutically acceptable salts and hydrates thereof.

4.7 Tetracyclic Benzamide Derivatives of Formula (IV)

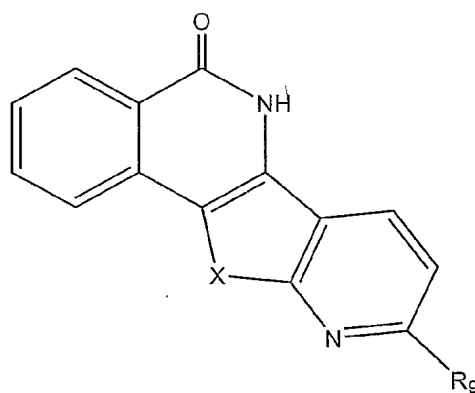
As stated above, the present invention encompasses compounds of Formula (IV):



(IV)

and pharmaceutically acceptable salts and hydrates thereof, where R_1 , R_2 , R_3 , R_4 , R_5 , G_1 , G_2 , G_3 , G_4 , and X are defined above for the Tetracyclic Benzamide Derivatives of Formula (IV).

- In one embodiment R_1 - R_4 are hydrogen.
- 5 In another embodiment, at least one of R_1 , R_2 , R_3 , R_4 or R_7 is other than hydrogen.
- In yet another embodiment R_5 is oxygen.
- In still another embodiment, R_6 is hydrogen.
- In still another embodiment, one of G_1 - G_4 is N.
- In another embodiment G_1 is N; and G_2 - G_4 are C- R_7 .
- 10 In another embodiment G_2 is N, G_1 , G_3 , G_4 are C- R_7 .
- In another embodiment G_3 is N, G_1 , G_2 , G_4 are C- R_7 .
- In another embodiment G_4 is N, G_1 , G_2 , and G_3 are C- R_7 .
- In another embodiment G_1 and G_2 are N and G_3 and G_4 are C- R_7 .
- In another embodiment G_1 and G_3 are N and G_2 and G_4 are C- R_7 .
- 15 In another embodiment G_1 and G_4 are N and G_2 and G_3 are C- R_7 .
- In another embodiment G_2 and G_3 are N and G_1 and G_4 are C- R_7 .
- In another embodiment G_2 and G_4 are N and G_1 and G_3 are C- R_7 .
- In another embodiment G_3 and G_4 are N and G_1 and G_2 are C- R_7 .
- In another embodiment compounds of Formula (IV) have the structure of Formula
- 20 (IV'):

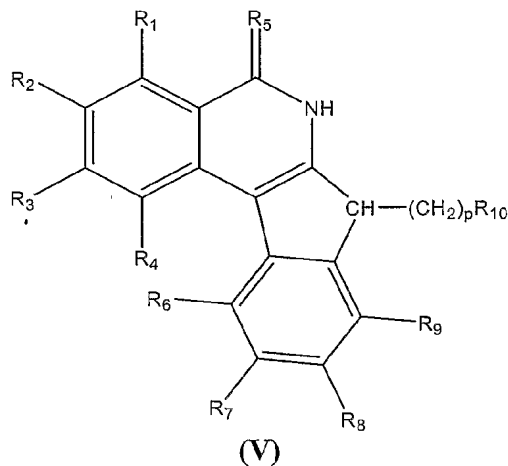


(IV')

wherein X , R_9 and R_{10} are defined above for Formula (IV).

4.8 Tetracyclic Benzamide Derivatives of Formula (V)

As stated above, the present invention encompasses compounds of Formula (V):

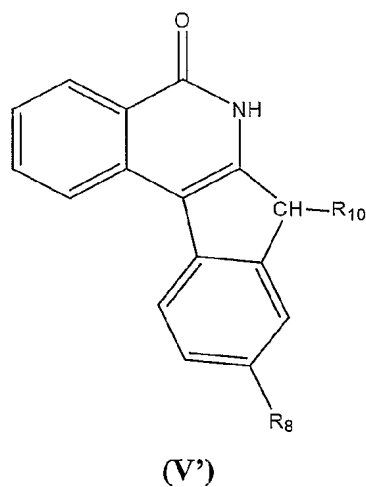


5

and pharmaceutically acceptable salts and hydrates thereof, where R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 , R_9 , R_{10} and p are defined above for the Tetracyclic Benzamide Derivatives of Formula (V).

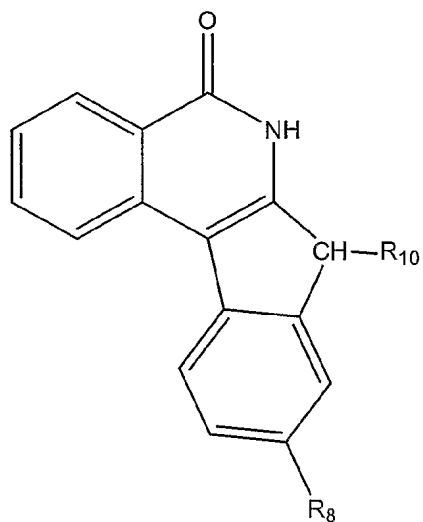
In one embodiment, R_1 - R_4 are hydrogen. In another embodiment, at least one of R_1 , R_2 , R_3 , R_4 , R_6 , R_7 , R_8 , and R_9 is other than hydrogen. In still another embodiment R_1 - R_4 and R_6 - R_9 is other than $-O-(C_1-C_5 \text{ alkyl})$, and $-A-B$ is other than $-O-(C_1-C_{10} \text{ alkyl})$. In one embodiment R_5 is O. In another embodiment R_5 is NH. In a further embodiment R_5 is S.

In another embodiment compounds of Formula (V) have the structure of Formula (V'):



wherein R_8 and R_{10} are defined above for Formula (V).

Illustrative compounds of Formula (V') are set forth below:



(V')

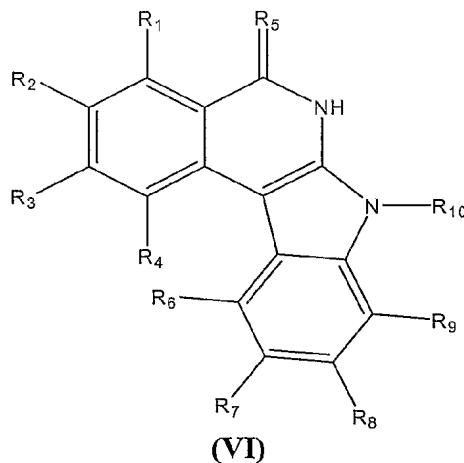
Compound	R ₈	R ₁₀
V'1	-H	-CH ₃
V'2	-H	-CH ₂ CH ₃
V'3	-H	-CH ₂ Ph
V'4	-H	-COOCH ₃
V'5	-H	-COCH ₂ COOMe
V'6	-H	-COCH ₂ COOH
V'7	-H	-COCH ₃
V'8	-H	-CONH(CH ₂) ₂ N(CH ₃) ₂
V'9	-H	-CONH(CH ₂) ₂ -(N-morpholinyl)
V'10	-H	-CONH(CH ₂) ₃ -(N-morpholinyl)
V'11	-H	-CONH(CH ₂) ₂ COOCH ₂ CH ₃
V'12	-H	-CONH(CH ₂) ₂ COOH
V'13	-H	-CONH(CH ₂) ₂ CONHCH ₃
V'14	-H	-CONH-piperidine-1-yl
V'15	-H	-CONH-(N-morpholinyl)
V'16	-H	-CO(CH ₂) ₂ -tetrazole-5-yl
V'17	-NHCOCH ₂ N(CH ₃) ₂	-COOCH ₂ CH ₃

Compound	R ₈	R ₁₀
V'18	-SO ₂ NH(CH ₂) ₃ -(<i>N</i> -morpholinyl)	-COOCH ₂ CH ₃
V'19	-NHCOCH ₂ N(CH ₃) ₂	-COOH
V'20	-SO ₂ NH(CH ₂) ₃ -(<i>N</i> -morpholinyl)	-COOH
V'21	-NHCOCH ₂ N(CH ₃) ₂	-CONHCH ₃
V'22	-SO ₂ NH(CH ₂) ₃ -(<i>N</i> -morpholinyl)	-CONHCH ₃
V'23	-NHCOCH ₂ N(CH ₃) ₂	-CONH(CH ₂) ₂ -(<i>N</i> -morpholinyl)
V'24	-SO ₂ NH(CH ₂) ₃ -(<i>N</i> -morpholinyl)	-CONH(CH ₂) ₂ N(CH ₃) ₂
V'25	-NHCOCH ₂ N(CH ₃) ₂	-CONH(CH ₂) ₂ -(<i>N</i> -morpholinyl)
V'26	-SO ₂ NH(CH ₂) ₃ -(<i>N</i> -morpholinyl)	-CONH(CH ₂) ₂ N(CH ₃) ₂

and pharmaceutically acceptable salts and hydrates thereof.

4.9 Tetracyclic Benzamide Derivatives of Formula (VI)

As stated above, the present invention encompasses compounds of Formula (VI):



5

and pharmaceutically acceptable salts and hydrates thereof, where R₁, R₂, R₃, R₄, R₅, R₆, R₇, R₈, R₉, and R₁₀ are defined above for the Tetracyclic Benzamide Derivatives of Formula (VI).

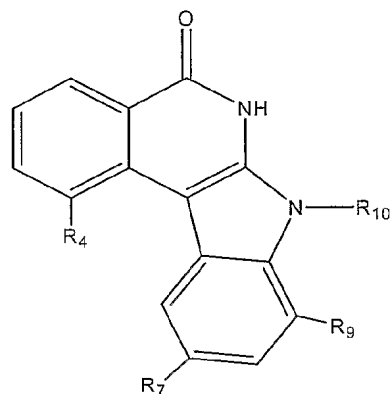
10

In one embodiment, R₁-R₄ are hydrogen. In another embodiment R₆, R₇, and R₉ are hydrogen. In another embodiment R₆-R₉ are hydrogen.

In another embodiment, at least one of R₁, R₂, R₃, R₄, R₆, R₇, R₈, and R₉ is other than hydrogen.

In one embodiment R_1 - R_4 and R_6 - R_9 is other than $-O-(C_1-C_5 \text{ alkyl})$, and $-A-B$ is other than $-O-(C_1-C_{10} \text{ alkyl})$.

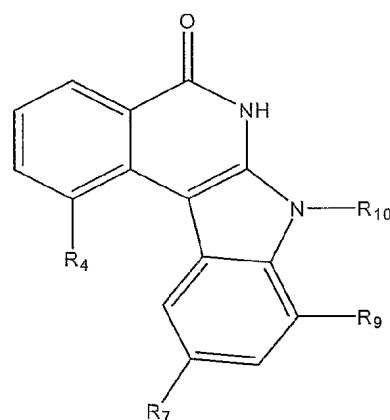
In another embodiment compounds of Formula (VI) have the structure of Formula (VI'):



(VI')

wherein R_4 , R_7 , R_9 , and R_{10} are defined above for Formula (VI).

Illustrative compounds of Formula (VI') are set forth below:



(VI')

Compound	R_4	R_7	R_9	R_{10}
VI'-1	-H	-H	-H	-H
VI'-2	-H	-H	-H	$-\text{CH}_3$
VI'-3	-H	-H	-H	$-\text{CH}_2\text{CH}_3$
VI'-4	-H	-H	-H	$-\text{CH}_2\text{COO CH}_2\text{CH}_3$
VI'-5	-H	-H	-H	$-\text{CH}_2\text{COOH}$
VI'-6	-H	-H	-H	$-\text{CH}_2\text{CONHCH}_3$
VI'-7	-H	-H	-H	$-\text{CH}_2\text{Ph}$

Compound	R ₄	R ₇	R ₉	R ₁₀
VI'-8	-H	-H	-H	-COOCH ₃
VI'-9	-H	-H	-H	-SO ₂ NH ₂
VI'-10	-H	-H	-H	-COOtBu
VI'-11	-H	-H	-H	-COO CH ₂ CH ₃
VI'-12	-H	-H	-H	-COCH ₃
VI'-13	-H	-H	-H	-CONHCH ₃
VI'-14	-H	-H	-H	-CONH CH ₂ CH ₃
VI'-15	-H	-H	-H	-CONH(CH ₂) ₂ N(CH ₃) ₂
VI'-16	-H	-H	-H	-CONH(CH ₂) ₂ -(<i>N</i> -morpholinyl)
VI'-17	-H	-H	-H	-CONH(CH ₂) ₃ -(<i>N</i> -morpholinyl)
VI'-18	-H	-H	-H	-CONH(CH ₂) ₂ COO CH ₂ CH ₃
VI'-19	-H	-H	-H	-CONH(CH ₂) ₂ COOH
VI'-20	-H	-H	-H	-CONH(CH ₂) ₂ CONHCH ₃
VI'-21	-H	-H	-H	-CONH-piperidine-1-yl
VI'-22	-H	-H	-H	-CONH-(<i>N</i> -morpholinyl)
VI'-23	-H	-H	-H	-CO(CH ₂) ₂ -tetrazole-5-yl
VI'-24	-H	-H	-NHCOCH ₂ N(CH ₃) ₂	-H
VI'-25	-H	-H	-SO ₂ NH(CH ₂) ₃ -(<i>N</i> -morpholinyl)	-H
VI'-26	-H	-NHCOCH ₂ N(CH ₃) ₂	-H	-COOCH ₃
VI'-27	-H	-SO ₂ NH(CH ₂) ₃ -(<i>N</i> -morpholinyl)	-H	-COOCH ₃
VI'-28	-H	-H	-NHCOCH ₂ NMe ₂	-CONHCH ₃
VI'-29	-H	-H	-SO ₂ NH(CH ₂) ₃ -(<i>N</i> -morpholinyl)	-CONHCH ₃
VI'-30	-NH ₂	-H	-NHCOCH ₂ N(CH ₃) ₂	-CONHCH ₃
VI'-31	-OH	-SO ₂ NH(CH ₂) ₃ -(<i>N</i> -morpholinyl)	-H	-CONHCH ₃
VI'-32	-F	-NHCOCH ₂ N(CH ₃) ₂	-H	-CONHCH ₃

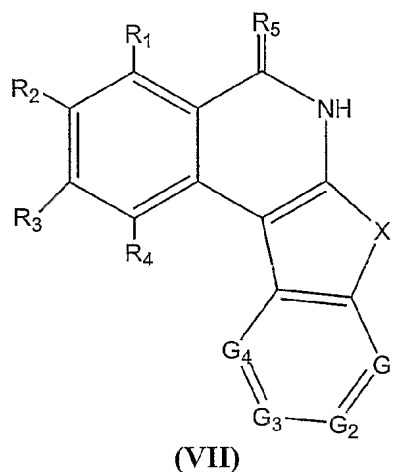
Compound	R ₄	R ₇	R ₉	R ₁₀
VI'-33	-OMe	-H	-SO ₂ NH(CH ₂) ₃ -(N-morpholinyl)	-CONHCH ₃

and pharmaceutically acceptable salts and hydrates thereof.

5

4.10 Tetracyclic Benzamide Derivatives of Formula (VII)

As stated above, the present invention encompasses compounds of Formula (VII):



10 and pharmaceutically acceptable salts and hydrates thereof, where R₁, R₂, R₃, R₄, R₅, G₁, G₂, G₃, G₄, and X are defined above for the Tetracyclic Benzamide Derivatives of Formula (VII).

In one embodiment, R₁-R₄ are hydrogen.

In another embodiment R₅ is O.

15 In another embodiment, at least one of R₁, R₂, R₃, and R₄ is other than hydrogen.

In one embodiment R₁-R₄ is other than -O-(C₁-C₅ alkyl), and -A-B is other than -O-(C₁-C₁₀ alkyl).

In another embodiment X is NH. In still another embodiment X is O.

In a further embodiment X is S. In another embodiment R₄ is NH₂, OCH₃, or

20 NO₂.

In still another embodiment, one of G₁-G₄ is N.

In another embodiment G₁ is N; and G₂-G₄ are C-R₇.

In another embodiment G₂ is N; and G₁, G₃ and G₄ are C-R₇.

In another embodiment G₃ is N; and G₁, G₂ and G₄ are C-R₇.

25 In another embodiment G₄ is N; and G₁, G₂, and G₃ are C-R₇.

In another embodiment G_1 and G_2 are N and G_3 and G_4 are C- R_7 .

In another embodiment G_1 and G_3 are N and G_2 and G_4 are C- R_7 .

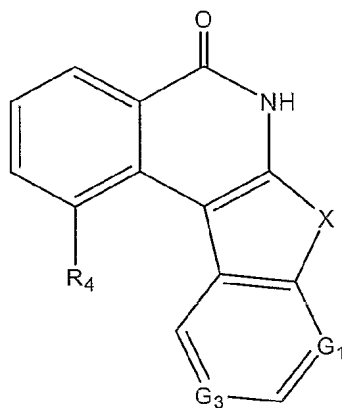
In another embodiment G_1 and G_4 are N and G_2 and G_3 are C- R_7 .

In another embodiment G_2 and G_3 are N and G_1 and G_4 are C- R_7 .

5 In another embodiment G_2 and G_4 are N and G_1 and G_3 are C- R_7 .

In another embodiment G_3 and G_4 are N and G_1 and G_2 are C- R_7 .

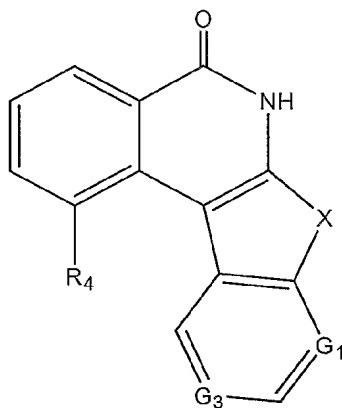
In another embodiment compounds of Formula (VII) have the structure of Formula (VII'):



(VII')

wherein X, G_1 , G_3 , and R_4 are defined above for Formula (VII).

Illustrative compounds of Formula (VII') are set forth below:



(VII')

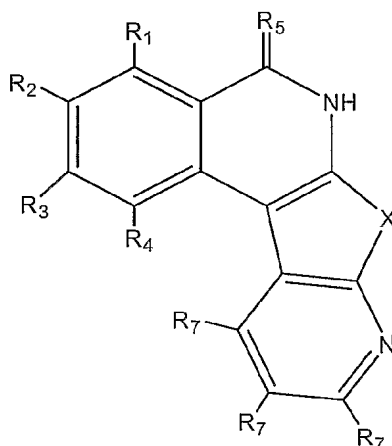
Compound	R_4	G_1	G_3	X
VII'-1	-H	-CH	-N	-NH-
VII'-2	-H	-N	-CH	-NH-
VII'-3	-H	-CH	-N	-N(CH ₃)-

Compound	R ₄	G ₁	G ₃	X
VII'-4	-H	-N	-CH	-N(CH ₃)-
VII'-5	-H	-CH	-N	-C(H)(CH ₂ COOH)-
VII'-6	-H	-N	-CH	-C(H)(CH ₂ CONHCH ₃)-
VII'-7	-H	-CH	-N	-O-
VII'-8	-H	-N	-CH	-O-
VII'-9	-H	-CH	-N	-S-
VII'-10	-H	-N	-CH	-S-
VII'-11	-H	-CH	-N	-N(CONHCH ₃)-
VII'-12	-H	-N	-CH	-N(CONHCH ₂ CH ₃)-
VII'-13	-H	-CH	-N	-N(CONH(CH ₂) ₂ N(CH ₃) ₂)-
VII'-14	-H	-N	-CH	-N(CONH(CH ₂) ₂ -(<i>N</i> -morpholinyl))-
VII'-15	-H	-CH	-N	-C(H)(CONH(CH ₂) ₂ COOCH ₂ CH ₃)-
VII'-16	-H	-N	-CH	-C(H)CONH(CH ₂) ₂ COOH-
VII'-17	-H	-CH	-N	-C(H)(CONH(CH ₂) ₂ CONHCH ₃)-
VII'-18	-H	-N	-CH	-C(H)CONH-piperidine-1-yl-
VII'-19	-H	-CH	-N	-C(H)(CONH-(<i>N</i> -morpholinyl))-
VII'-20	-H	-N	-CH	-C(H)(CO(CH ₂) ₂ -tetrazole-5-yl)-
VII'-21	-NH ₂	-CH	-N	-NH-
VII'-22	-OCH ₃	-N	-CH	-NH-

and pharmaceutically acceptable salts and hydrates thereof.

4.11 Tetracyclic Benzamide Derivatives of Formula (VIIa)

As stated above, the present invention encompasses compounds of Formula (VIIa):

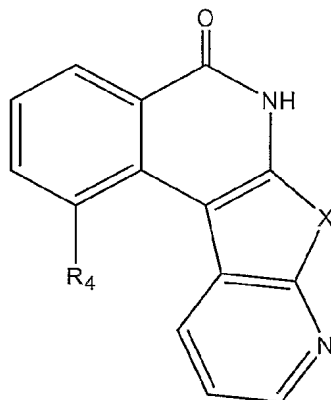


(VIIa)

and pharmaceutically acceptable salts and hydrates thereof, where R_1 , R_2 , R_3 , R_4 , R_5 , R_7 , and X are defined above for the Tetracyclic Benzamide Derivatives of Formula (VIIa).

In one embodiment, R_1 - R_4 are hydrogen. In another embodiment, at least one of R_1 , R_2 , R_3 , R_4 , R_5 , and R_7 , is other than hydrogen. In one embodiment R_1 - R_4 and R_7 is other than -O-(C₁-C₅ alkyl), and -A-B is other than -O-(C₁-C₁₀ alkyl). In another embodiment X is NH. In still another embodiment X is O. In a further embodiment X is S. In another embodiment R_4 is -NH₂, -OCH₃, or -NO₂.

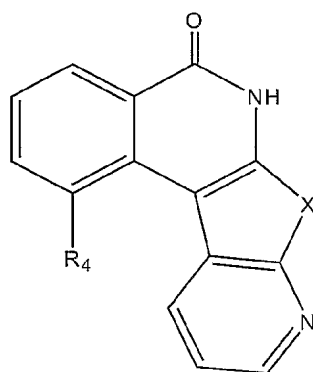
In another embodiment compounds of Formula (VIIa) have the structure of Formula (VIIa'):



(VIIa')

wherein R_4 , and X are defined above for Formula (VIIa).

Illustrative compounds of Formula (VIIa') are set forth below:



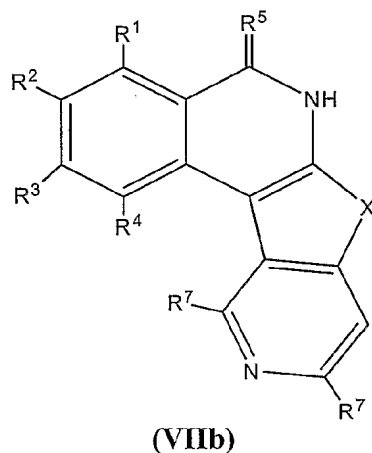
(VIIa')

Compound	R ₄	X
VIIa'-1	-H	-NH-
VIIa'-2	-H	-NCH ₃ -
VIIa'-3	-H	-C(H)(CH ₂ COOH)-
VIIa'-4	-H	-O-
VIIa'-5	-H	-S-
VIIa'-6	-H	-N(CONHCH ₃)-
VIIa'-7	-H	-N(CONH(CH ₂) ₂ N(CH ₃) ₂)-
VIIa'-8	-H	-C(H)(CONH(CH ₂) ₂ COOCH ₂ CH ₃)-
VIIa'-9	-H	-C(H)(CONH(CH ₂) ₂ CONHCH ₃)-
VIIa'-10	-H	-C(H)(CONH-(N-morpholinyl))-
VIIa'-11	-NH ₂	-NH-

5 and pharmaceutically acceptable salts and hydrates thereof.

4.12 Tetracyclic Benzamide Derivatives of Formula (VIIb)

As stated above, the present invention encompasses compounds of Formula (VIIb):



and pharmaceutically acceptable salts and hydrates thereof, where R_1 , R_2 , R_3 , R_4 , R_5 , R_7 , and X are defined above for the Tetracyclic Benzamide Derivatives of Formula (VIIb).

In one embodiment, R_1 - R_4 are hydrogen.

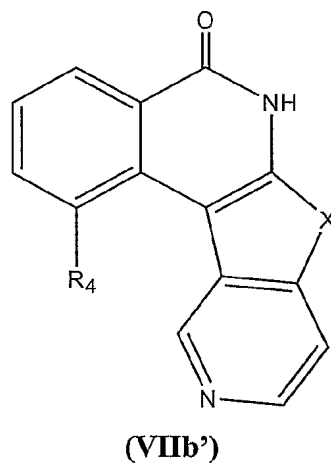
In another embodiment, at least one of R_1 , R_2 , R_3 , R_4 , R_6 , or R_7 , is other than hydrogen.

In one embodiment R_1 - R_4 and R_7 is other than $-O-(C_1-C_5 \text{ alkyl})$, and $-A-B$ is other than $-O-(C_1-C_{10} \text{ alkyl})$.

In another embodiment X is NH. In still another embodiment X is O.

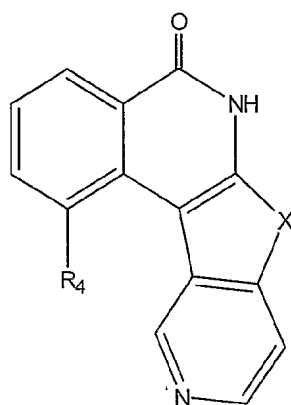
In a further embodiment X is S. In another embodiment R_4 is NH_2 , OCH_3 , or NO_2 .

In another embodiment compounds of Formula (VIIb) have the structure of Formula (VIIb'):



wherein X and R_4 are defined above for Formula (VIIb).

Illustrative compounds of Formula (VIIIb') are set forth below:



(VIIIb')

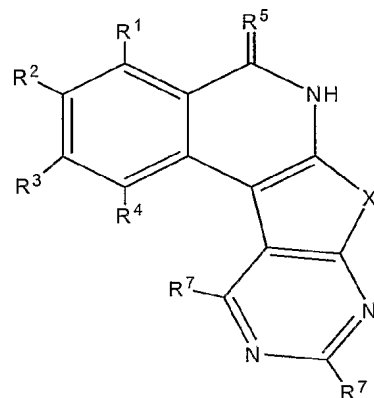
Compound	R ₄	X
VIIIb'-1	-H	-NH-
VIIIb'-2	-H	-NCH ₃ -
VIIIb'-3	-H	-C(H)(CH ₂ CONHCH ₃)-
VIIIb'-4	-H	-O-
VIIIb'-5	-H	-S-
VIIIb'-6	-H	-N(CONHCH ₂ CH ₃)-
VIIIb'-7	-H	-N(CONH(CH ₂) ₂ -(N-morpholinyl))-
VIIIb'-8	-H	-C(H)(CONH(CH ₂) ₂ COOH)-
VIIIb'-9	-H	-C(H)(CONH-piperidine-1-yl)-
VIIIb'-10	-H	-C(H)(CO(CH ₂) ₂ -tetrazole-5-yl)-
VIIIb'-11	-OCH ₃	-NH-

5

and pharmaceutically acceptable salts and hydrates thereof.

4.13 Tetracyclic Benzamide Derivatives of Formula (VIIc)

As stated above, the present invention encompasses compounds of Formula (VIIc):



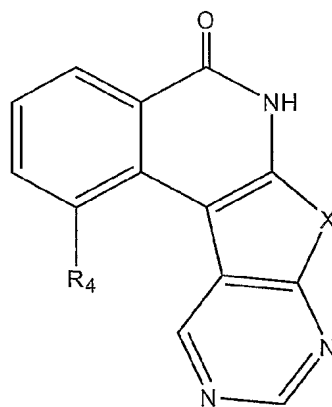
(VIIc)

and pharmaceutically acceptable salts and hydrates thereof, where R_1 , R_2 , R_3 , R_4 , R_5 , R_7 , and X are defined above for the Tetracyclic Benzamide Derivatives of Formula (VIIc).

In one embodiment, R_1 - R_4 are hydrogen. In another embodiment, at least one of R_1 , R_2 , R_3 , R_4 , R_5 , or R_7 , is other than hydrogen. In one embodiment R_1 - R_4 and R_7 is other than

-O-(C_1 - C_5 alkyl), and -A-B is other than -O-(C_1 - C_{10} alkyl). In another embodiment X is NH. In still another embodiment X is O. In a further embodiment X is S. In another embodiment R_4 is -NH₂, -OCH₃, or -NO₂.

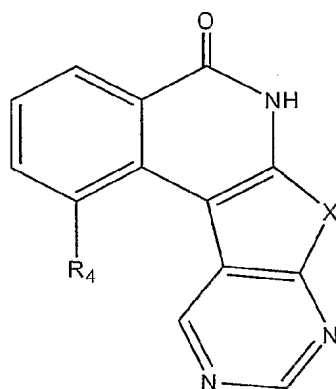
In another embodiment compounds of Formula (VIIc) have the structure of Formula (VIIc'):



(VIIc')

wherein X and R_4 are defined above for Formula (VIIc).

Illustrative compounds of Formula (VIIc) are set forth below:



(VIIc')

Compound	R ₄	X
VIIc'-1	-H	-NH-
VIIc'-2	-H	-NH-
VIIc'-3	-H	-NCH ₃ -
VIIc'-4	-H	-NCH ₃ -
VIIc'-5	-H	-C(H)(CH ₂ COOH)-
VIIc'-6	-H	-C(H)(CH ₂ CONHCH ₃)-
VIIc'-7	-H	-O-
VIIc'-8	-H	-O-
VIIc'-9	-H	-S-
VIIc'-10	-H	-S-
VIIc'-11	-H	-N(CONHCH ₃)-
VIIc'-12	-H	-N(CONHCH ₂ CH ₃)-
VIIc'-13	-H	-N(CONH(CH ₂) ₂ N(CH ₃) ₂)-
VIIc'-14	-H	-N(CONH(CH ₂) ₂ -(N-morpholinyl))-
VIIc'-15	-H	-C(H)(CONH(CH ₂) ₂ COOCH ₂ CH ₃)-
VIIc'-16	-H	-C(H)(CONH(CH ₂) ₂ COOH)-
VIIc'-17	-H	-C(H)(CONH(CH ₂) ₂ CONHCH ₃)-

VIIc'-18	-H	-C(H)(CONH-piperidine-1-yl)-
VIIc'-19	-H	-C(H)(CONH-(<i>N</i> -morpholinyl))-
VIIc'-20	-H	-C(H)(CO(CH ₂) ₂ -tetrazole-5-yl)-
VIIc'-22	-NH ₂	-NH-
VIIc'-22	-OCH ₃	-NH-

and pharmaceutically acceptable salts and hydrates thereof.

4.14 Tetracyclic Benzamide Derivatives Of Formulas (I), (Ia), (Ib), (II), (IIa), (III), (IV), (V), (VI), (VII), (VIIa), (VIIb), and (VIIc)

The Tetracyclic Benzamide Derivatives can exist in a keto or enol tautomeric form. This invention encompasses both the keto and enol forms of the Tetracyclic Benzamide Derivatives. Accordingly, Formulas (I), (Ia) (Ib), (II), (IIa), (III), (IV), (V), (VI), (VII), (VIIa), (VIIb), and (VIIc), although depicting the keto form of the Tetracyclic Benzamide Derivatives, encompass both the keto and enol forms.

The present invention also includes Tetracyclic Benzamide Derivatives, wherein one or more hydrogen, carbon or other atoms are replaced by an isotope thereof. Such compounds are useful as research or diagnostic tools in metabolism pharmacokinetic studies and in binding assays.

4.15 DEFINITIONS

The term “-(C₁-C₁₀)alkyl” as used herein, refers to a straight chain or branched non-cyclic hydrocarbon having from 1 to 10 carbon atoms. Representative straight chain -(C₁-C₁₀)alkyls include -methyl, -ethyl, -*n*-propyl, -*n*-butyl, -*n*-pentyl, -*n*-hexyl, -*n*-heptyl, -*n*-octyl, -*n*-nonyl and -*n*-decyl. Representative branched -(C₁-C₁₀)alkyls include -isopropyl, -*sec*-butyl, -isobutyl, -*tert*-butyl, -isopentyl, -neopentyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 1-ethylbutyl, 2-ethylbutyl, 3-ethylbutyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 2,2-dimethylbutyl, 2,3-dimethylbutyl and 3,3-dimethylbutyl, -isopropyl, -*sec*-butyl, -isobutyl, 1-methylhexyl, 2-methylhexyl, 3-methylhexyl, 4-methylhexyl, 5-methylhexyl, 1,2-dimethylpentyl,

1,3-dimethylpentyl, 1,2-dimethylhexyl, 1,3-dimethylhexyl, 3,3-dimethylhexyl, 1,2-dimethylheptyl, 1,3-dimethylheptyl, and 3,3-dimethylheptyl.

The term “-(C₁-C₉)alkyl” as used herein, refers to a straight chain or branched non-cyclic hydrocarbon having from 1 to 9 carbon atoms. Representative straight chain
 5 -(C₁-C₉)alkyls include -methyl, -ethyl, -*n*-propyl, -*n*-butyl, -*n*-pentyl, -*n*-hexyl, -*n*-heptyl, -*n*-octyl, and -*n*-nonyl. Representative branched -(C₁-C₉)alkyls include -isopropyl, -*sec*-butyl, -isobutyl, -*tert*-butyl, -isopentyl, -neopentyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 1-ethylbutyl, 2-ethylbutyl, 1,1-dimethylbutyl,
 10 1,2-dimethylbutyl, 1,3-dimethylbutyl, 2,2-dimethylbutyl, 2,3-dimethylbutyl and 3,3-dimethylbutyl, -isopropyl, -*sec*-butyl, -isobutyl, 1-methylhexyl, 2-methylhexyl, 3-methylhexyl, 5-methylhexyl, 1,2-dimethylpentyl, 1,3-dimethylpentyl, 1,2-dimethylhexyl, 1,3-dimethylhexyl, 3,3-dimethylhexyl, 1,2-dimethylheptyl, 1,3-dimethylheptyl, and 3,3-dimethylheptyl.

15 The term “-(C₁-C₅)alkyl” as used herein, refers to a straight chain or branched non-cyclic hydrocarbon having from 1 to 5 carbon atoms. Representative straight chain -(C₁-C₅)alkyls include -methyl, -ethyl, -*n*-propyl, -*n*-butyl and -*n*-pentyl. Representative branched -(C₁-C₅)alkyls include -isopropyl, -*sec*-butyl, -isobutyl, -*tert*-butyl, -isopentyl, -neopentyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, 1,1-dimethylpropyl and
 20 1,2-dimethylpropyl.

The term “-(C₂-C₁₀)alkenyl” as used herein, refers to a straight chain or branched non-cyclic hydrocarbon having from 2 to 10 carbon atoms and including at least one carbon-carbon double bond. Representative straight chain and branched (C₂-C₁₀)alkenyls include -vinyl, -allyl, -1-butenyl, -2-butenyl, -isobutylenyl, -1-pentenyl, -2-pentenyl,
 25 -3-methyl-1-butenyl, -2-methyl-2-butenyl, -2,3-dimethyl-2-butenyl, -1-hexenyl, -2-hexenyl, -3-hexenyl, -1-heptenyl, -2-heptenyl, -3-heptenyl, -1-octenyl, -2-octenyl, -3-octenyl, -1-nonenyl, -2-nonenyl, -3-nonenyl, -1-decenyl, -2-decenyl, -3-decenyl and the like.

The term “-(C₃-C₈)cycloalkyl” as used herein, refers to a saturated cyclic hydrocarbon having from 3 to 8 carbon atoms. Representative (C₃-C₈)cycloalkyls include
 30 -cyclopropyl, -cyclobutyl, -cyclopentyl, -cyclohexyl, -cycloheptyl and -cyclooctyl.

The term “-(C₈-C₁₄)bicycloalkyl” as used herein, refers to a bi-cyclic hydrocarbon ring system having from 8 to 14 carbon atoms and at least one saturated cyclic alkyl ring.

Representative $-(C_8-C_{14})$ bicycloalkyls include -indanyl, -1,2,3,4-tetrahydronaphthyl, -5,6,7,8-tetrahydronaphthyl, -perhydronaphthyl and the like.

A "3- to 7-membered monocyclic heterocycle" refers to a monocyclic 3- to 7-membered aromatic or non-aromatic monocyclic cycloalkyl in which 1-4 of the ring carbon atoms have been independently replaced with a N, O or S atom. The 3- to 7-membered monocyclic heterocycles can be attached via a nitrogen, sulfur, or carbon atom. Representative examples of a 3- to 7-membered monocyclic heterocycle group include, but are not limited to, piperidinyl, piperazinyl, morpholinyl, pyrrolyl, oxazinyl, thiazinyl, diazinyl, triazinyl, tetrazinyl, imidazolyl, tetrazolyl, pyrrolidinyl, isoxazolyl, furanyl, furazanyl, pyridinyl, oxazolyl, thiazolyl, thiophenyl, pyrazolyl, triazolyl, and pyrimidinyl.

A "7- to 10-membered bicyclic heterocycle" refers to a bicyclic 7- to 10-membered aromatic or non-aromatic bicyclic cycloalkyl in which 1-4 of the ring carbon atoms have been independently replaced with a N, O or S atom. The 7- to 10-membered bicyclic heterocycles can be attached via a nitrogen, sulfur, or carbon atom. Representative examples of a 7- to 10-membered bicyclic heterocycle group include, but are not limited to, benzimidazolyl, indolyl, isoquinolinyl, indazolyl, quinolinyl, quinazolinyl, purinyl, benzisoxazolyl, benzoxazolyl, benzthiazolyl, benzodiazolyl, benzotriazolyl, isoindolyl and indazolyl.

A "nitrogen-containing 3- to 7-membered monocyclic heterocycle" refers to a 3- to 7-membered monocyclic heterocycle, defined above, which contains at least one ring nitrogen atom. The nitrogen-containing 3- to 7-membered monocyclic heterocycles can be attached via a nitrogen, sulfur, or carbon atom. Representative examples of nitrogen-containing-3- to 7-membered monocyclic heterocycles include, but are not limited to, piperidinyl, piperazinyl, pyrrolyl, oxazinyl, thiazinyl, diazinyl, triazinyl, tetrazinyl, imidazolyl, tetrazolyl, pyrrolidinyl, isoxazolyl, pyridinyl, oxazolyl, thiazolyl, pyrazolyl, triazolyl, pyrimidinyl, and morpholinyl.

A "nitrogen-containing 7- to 10-membered bicyclic heterocycle" refers to a 7- to 10-membered bicyclic heterocycle, defined above, which contains at least one ring nitrogen atom. The nitrogen-containing 7- to 10-membered bicyclic heterocycles can be attached via a nitrogen, sulfur, or carbon atom. Representative nitrogen-containing 7- to 10-membered bicyclic heterocycles include -quinolinyl, -isoquinolinyl, -chromonyl, -indolyl, -isoindolyl, -indoliziny, -indazolyl, -purinyl, -4H-quinoliziny, -isoquinolyl, -quinolyl, -phthalazinyl, -naphthyridinyl -carbazolyl, - β -carbolinyl and the like.

The term “-aryl” as used herein, refers to a phenyl or naphthyl group.

“Halo-substituted-(C₁-C₅ alkyl)” refers to a C₁-C₅ alkyl group, as defined above, wherein one or more of the C₁-C₅ alkyl group's hydrogen atoms has been replaced with -F, -Cl, -Br or -I. Representative examples of an alkylhalo group include, but are not limited to, -CH₂F, -CCl₃, -CF₃, -CH₂Cl, -CH₂CH₂Br, -CH₂CH₂I, -CH₂CH₂CH₂F, -CH₂CH₂CH₂Cl, -CH₂CH₂CH₂CH₂Br, -CH₂CH₂CH₂CH₂I, -CH₂CH₂CH₂CH₂CH₂Br, -CH₂CH₂CH₂CH₂CH₂I, -CH₂CH(Br)CH₃, -CH₂CH(Cl)CH₂CH₃, -CH(F)CH₂CH₃ and -C(CH₃)₂(CH₂Cl).

“Amino-substituted-(C₁-C₅ alkyl)” refers to a C₁-C₅ alkyl group, as defined above, wherein one or more of the C₁-C₅ alkyl group's hydrogen atoms has been replaced with -NH₂. Representative examples of an alkyl amino group include, but are not limited to, -CH₂NH₂, -CH₂CH₂NH₂, -CH₂CH₂CH₂NH₂, -CH₂CH₂CH₂CH₂NH₂, -CH₂CH(NH₂)CH₃, -CH₂CH(NH₂)CH₂CH₃, -CH(NH₂)CH₂CH₃, -C(CH₃)₂(CH₂NH₂), -CH₂CH₂CH₂CH₂NH₂, -CH₂CH₂CH(NH₂)CH₃, -CH₂CH(NH₂)CH₂CH₂CH₃, -CH₂CH(NH₂)CH₂CH₃ and -CH₂C(CH₃)₂(CH₂NH₂).

“-(NH(C₁-C₅ alkyl))” refers to an -NH group, the nitrogen atom of said group being attached to a C₁-C₅ alkyl group, as defined above. Representative examples of an aminoalkyl group include, but are not limited to, -NHCH₃, -NHCH₂CH₃, -NHCH₂CH₂CH₃, -NHCH₂CH₂CH₂CH₃, -NHCH(CH₃)₂, -NHCH₂CH(CH₃)₂, -NHCH₂(CH₃)CH₂CH₃, -NH-CH₂CH₂C(CH₃)₃, -NHCH₂CH₂CH₂CH₂CH₃, -NHCH₂CH(CH₃)₂, -NHCH₂CH₂CH(CH₃)₂, -NHCH₂CH(CH₃)CH₂CH₃ and -NH-CH₂C(CH₃)₃.

“-N(C₁-C₅ alkyl)(C₁-C₅ alkyl)” refers to a nitrogen atom which has attached to it two C₁-C₅ alkyl groups, as defined above. Representative examples of a aminodialkyl group include, but are not limited to, -N(CH₃)₂, -N(CH₂CH₃)(CH₃), -N(CH₂CH₃)₂, -N(CH₂CH₂CH₃)₂, -N(CH₂CH₂CH₂CH₃)₂, -N(CH(CH₃)₂)₂, -N(CH(CH₃)₂)(CH₃), -N(CH₂CH(CH₃)₂)₂, -NH(CH(CH₃)CH₂CH₃)₂, -N(C(CH₃)₃)₂ and -N(C(CH₃)₃)(CH₃).

“-(H₂NC(O))-substituted aryl” refers to an aryl group, as defined above, wherein one of the aryl group's hydrogen atoms has been replaced with one or more -C(O)NH₂ groups. Representative examples of an arylamido group include 2-C(O)NH₂-phenyl, 3-C(O)NH₂-phenyl, 4-C(O)NH₂-phenyl.

“-(H₂NC(O))-substituted pyridyl” refers to an pyridyl group, wherein one of the pyridyl group's hydrogen atoms has been replaced with one or more -C(O)NH₂ groups.

Representative examples of an arylamido group include 2-C(O)NH₂-pyridyl, 3-C(O)NH₂-pyridyl and 4-C(O)NH₂-pyridyl.

“(H₂NC(O))-substituted-(C₁-C₅ alkyl)” refers to a C₁-C₅ alkyl group, as defined above, wherein one of the C₁-C₅ alkyl group’s hydrogen atoms has been replaced with a
 5 -C(O)NH₂ group. Representative examples of an alkylamido group include, but are not limited to, -CH₂C(O)NH₂, -CH₂CH₂C(O)NH₂, -CH₂CH₂CH₂C(O)NH₂,
 -CH₂CH₂CH₂CH₂C(O)NH₂, -CH₂CH₂CH₂CH₂CH₂C(O)NH₂, -CH₂CH(C(O)NH₂)CH₃,
 -CH₂CH(C(O)NH₂)CH₂CH₃, -CH(C(O)NH₂)CH₂CH₃ and -C(CH₃)₂CH₂C(O)NH₂.

“HO-substituted-(C₁-C₅ alkyl)” refers to a C₁-C₅ alkyl group, as defined above,
 10 wherein one of the C₁-C₅ alkyl group’s hydrogen atoms has been replaced with a hydroxyl group. Representative examples of an alkanol group include, but are not limited to, -CH₂OH, -CH₂CH₂OH, -CH₂CH₂CH₂OH, -CH₂CH₂CH₂CH₂OH,
 -CH₂CH₂CH₂CH₂CH₂OH, -CH₂CH(OH)CH₃, -CH₂CH(OH)CH₂CH₃, -CH(OH)CH₂CH₃
 and -C(CH₃)₂CH₂OH.

“Carboxy-substituted-(C₁-C₅ alkyl)” refers to a C₁-C₅ alkyl group, as defined above, wherein one of the C₁-C₅ alkyl group’s hydrogen atoms has been replaced with a
 15 -COOH group. Representative examples of an alkylcarboxy group include, but are not limited to, -CH₂COOH, -CH₂CH₂COOH, -CH₂CH₂CH₂COOH, -CH₂CH₂CH₂CH₂COOH,
 -CH₂CH(COOH)CH₃, -CH₂CH₂CH₂CH₂CH₂COOH, -CH₂CH(COOH)CH₂CH₃,
 20 -CH(COOH)CH₂CH₃ and -C(CH₃)₂CH₂COOH.

The term “glycoside” as used herein refers to a hexose or a pentose sugar forming an α- or β-glycosidic linkage. Representative examples of glycosides include, but are not limited to ribose, deoxyribose, fructose, galactose, glucuronic acid and glucose.

A “subject” is a mammal, *e.g.*, a human, mouse, rat, guinea pig, dog, cat, horse,
 25 cow, pig, or non-human primate, such as a monkey, chimpanzee, or baboon.

The phrase “pharmaceutically acceptable salt,” as used herein, is a salt formed from an acid and a basic nitrogen group of one of the Tetracyclic Benzamide Derivatives. Illustrative salts include, but are not limited, to sulfate, citrate, acetate, oxalate, chloride, bromide, iodide, nitrate, bisulfate, phosphate, acid phosphate, isonicotinate, lactate,
 30 salicylate, acid citrate, tartrate, oleate, tannate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucaronate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzenesulfonate, *p*-toluenesulfonate, and pamoate (*i.e.*, 1,1’-methylene-bis-(2-OH-3-naphthoate)) salts. The term “pharmaceutically acceptable salt” also refers to a salt prepared from a

Tetracyclic benzamide Derivative having an acidic functional group, such as a carboxylic acid functional group or a sulfonic acid functional group, and a pharmaceutically acceptable inorganic or organic base. Suitable bases include, but are not limited to, hydroxides of alkali metals such as sodium, potassium, and lithium; hydroxides of alkaline earth metal such as calcium and magnesium; hydroxides of other metals, such as aluminum and zinc; ammonia, and organic amines, such as unsubstituted or hydroxy-substituted mono-, di-, or tri-alkylamines, dicyclohexylamine; tributyl amine; pyridine; N-methyl, N-ethylamine; diethylamine; triethylamine; mono-, bis-, or tris-(2-OH-lower alkylamines), such as mono-, bis-, or tris-(2-OHethyl)amine, 2-OH *tert*-butylamine, or tris-(hydroxymethyl)methylamine, N,N-di-lower alkyl-N-(hydroxy lower alkyl)-amines, such as N,N-dimethyl-N-(2-hydroxyethyl)amine or tri-(2-OHethyl)amine; N-methyl-D-glucamine; and amino acids such as arginine, lysine, and the like.

An "effective amount" when used in connection a Tetracyclic Benzamide Derivative is an amount effective for: (a) treating or preventing a Condition or (b) inhibiting PARP in an *in vivo* or an *in vitro* cell.

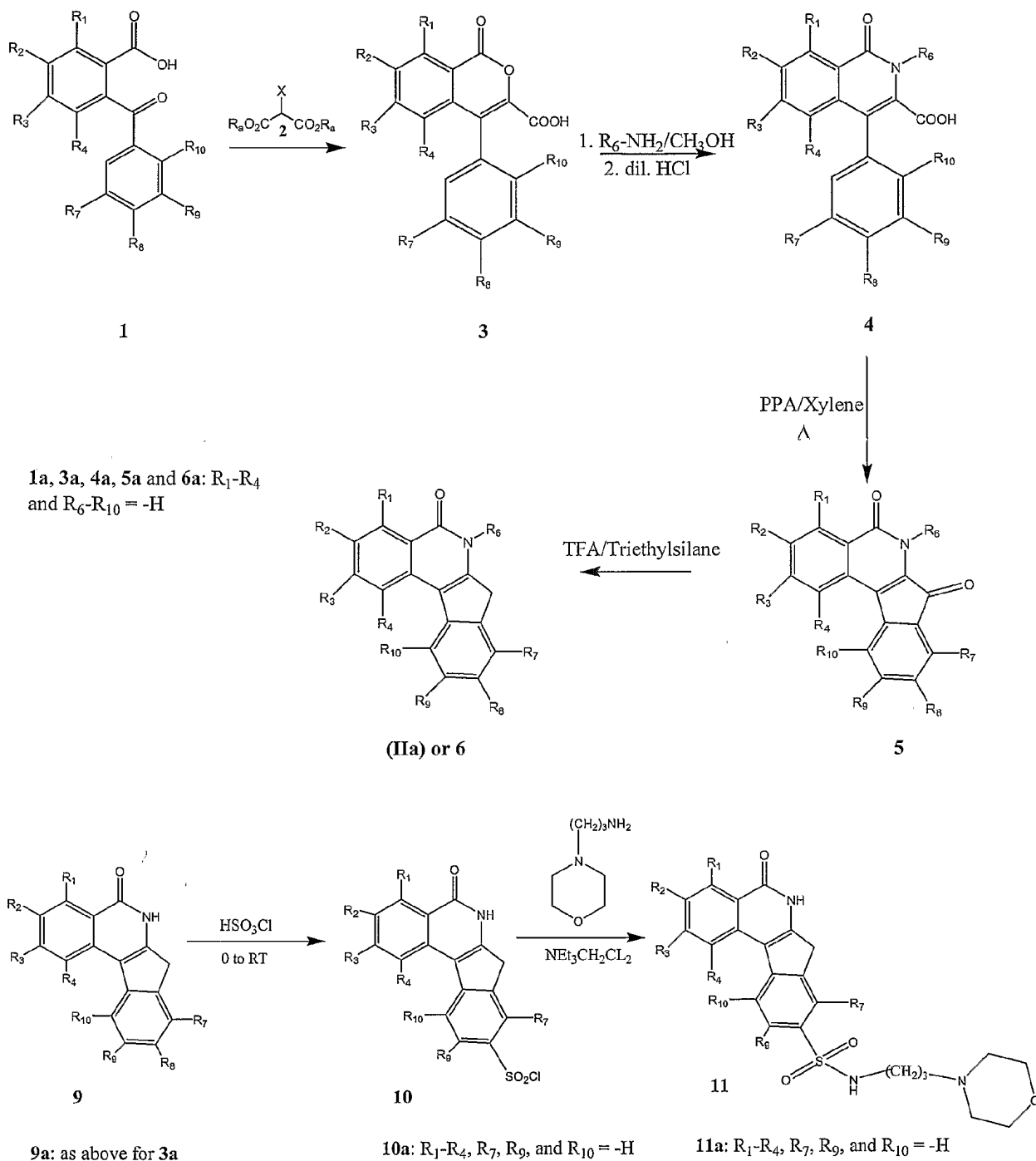
The following abbreviations are used herein and have the indicated definitions: AcOH is acetic acid, CEP is Cecal Ligation and Puncture, DMEM is Dulbecco's Modified Eagle Medium, DMF is *N,N*-dimethylformamide, DMSO is dimethylsulfoxide, Et is ethyl, EtOAc is ethyl acetate, EtOH is ethanol, HEPES is 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid, HPLC is high performance liquid chromatography, LPS is lipopolysaccharide, MeCN is acetonitrile, MeOH is methanol, MS is mass spectrometry, Ms is mesyl (methanesulfonyl), NaBH₄ is sodium borohydride, NEt₃ is triethylamine, NMR is nuclear magnetic resonance, PBS is phosphate-buffered saline (pH 7.4), PARP is poly(ADP-ribose)polymerase, PPA is polyphosphoric acid, Py is pyridine, SDS is dodecyl sulfate (sodium salt), STZ is streptozotocin, TCA is trichloroacetic acid, Tf is triflyl (trifluoromethanesulfonyl), TFA is trifluoroacetic acid, THF is tetrahydrofuran; TLC is thin-layer chromatography, TNF is tumor necrosis factor, TRIS is Tris(hydroxymethyl)aminomethane and Ts is tosyl (*p*-toluenesulfonyl).

4.16 Methods for Making the Tetracyclic Benzamide Derivatives

Examples of synthetic pathways useful for making Tetracyclic Benzamide Derivatives are set forth in the Examples below and generalized in Schemes 1-6.

Scheme 1 illustrates methods useful for making Tetracyclic Benzamide Derivatives of Formula (IIa), where R_1 - R_4 and R_6 - R_{10} are defined for Formula (IIa).

Scheme 1



wherein

10

R_1 - R_4 and R_6 - R_{10} are as defined above for the compounds of Formula (IIa);

each R_a is independently C_1 - C_3 alkyl; and X is -Cl, -Br, -I, -OTf, -OMs or -OTs.

Tetracyclic Benzamide Derivatives of Formula (II) and Formula (IIa) can be made by a method comprising the steps of Scheme 1 above herein.

A compound of Formula 3 can be made by a method comprising contacting a compound of Formula 1 with a compound of Formula 2 in the presence of a base for a
5 time and at a temperature sufficient to make a compound of Formula 3.

In one embodiment R_a is methyl and X is -Br.

In one embodiment about 0.1 to about 10 equivalents of a compound of Formula 2 are used per about 1 equivalent of a compound of Formula 1.

In another embodiment about 0.5 to about 5 equivalents of a compound of
10 Formula 2 are used per about 1 equivalent of a compound of Formula 1.

In still another embodiment, about 1 to about 2 equivalents of a compound of Formula 2 are used per about 1 equivalent of a compound of Formula 1.

In one embodiment about 1 to about 5 equivalents of base are used per about 1 equivalent of a compound of Formula 1.

15 In another embodiment about 2 to about 3 equivalents of base are used per about 1 equivalent of a compound of Formula 1.

Suitable bases for use in the method are organic bases such as triethylamine, diisopropylamine, diisopropylethylamine, pyridine, lutidine and imidazole; and inorganic bases such as alkali metal carbonates, including sodium carbonate, potassium carbonate
20 and cesium carbonate.

In another embodiment, the base is potassium carbonate.

The method can be carried out in the presence of a solvent, such as acetonitrile, methylene chloride, chloroform, THF, DMF, DMSO, ethyl acetate, acetone, benzene, diethyl ether, water or mixtures thereof.

25 In another embodiment, the solvent is DMF.

In still another embodiment, the solvent is substantially anhydrous, i.e., comprises less than about 1% water.

In another embodiment the method is carried out for a time of about 2 hours to about 36 hours.

30 In still another embodiment the method of Scheme 1 is carried out for a time of about 8 hours to about 24 hours.

In yet another embodiment the method of Scheme 1 is carried out for a time of about 12 hours to about 18 hours.

In a further embodiment, the method of Scheme 1 is carried out at a temperature of about 0°C to about 100°C.

In another embodiment, the method of Scheme 1 is carried out at a temperature of about 35°C to about 70°C.

5 In yet another embodiment, the method of Scheme 1 is carried out at a temperature of about 25°C.

A compound of Formula 4 can be made by a method comprising (a) contacting a compound of Formula 3 with ammonia in methanol; and (b) contacting the product of step (a) with dilute acid for a time and at a temperature sufficient to make a compound of
10 Formula 4.

In one embodiment about 1 to about 1000 equivalents of a solution of ammonia in methanol are used per about 1 equivalent of a compound of Formula 3.

In another embodiment about 5 to about 500 equivalents of ammonia in methanol are used per about 1 equivalent of a compound of Formula 3.

15 In still another embodiment, about 10 to about 100 equivalents of ammonia in methanol are used per about 1 equivalent of a compound of Formula 3.

In yet another embodiment about 20 to about 50 equivalents of ammonia in methanol are used per about 1 equivalent of a compound of Formula 3.

In one embodiment the ammonia in methanol is from about 1 N to about 10 N.

20 In another embodiment the ammonia in methanol is from about 3 N to about 7 N.

In one embodiment the dilute acid is from about 0.01 N to about 3 N.

In another embodiment the dilute acid is from about 0.1 N to about 1 N.

In another embodiment, the acid is HCl.

In one embodiment the method is carried out for a time of about 1 hour to about
25 48 hours.

In still another embodiment the method is carried out for a time of about 8 hours to about 36 hours.

In yet another embodiment the method is carried out for a time of about 12 hours to about 24 hours.

30 In one embodiment, the method is carried out at a temperature of about 0°C to about 100°C.

In another embodiment, the method is carried out at a temperature of about 25°C to about 75°C.

In yet another embodiment, the method is carried out at a temperature of about 40°C to about 60°C.

A compound of Formula **5** can be made by a method comprising contacting a compound of Formula **4** with a dehydrating agent for a time and at a temperature
5 sufficient to make a compound of Formula **5**.

In one embodiment about 0.1 to about 10 equivalents of a dehydrating agent are used per about 1 equivalent of a compound of Formula **4**.

In another embodiment about 0.5 to about 5 equivalents of a dehydrating agent are used per about 1 equivalent of a compound of Formula **4**.

10 In still another embodiment, about 1 to about 2 equivalents of a dehydrating agent are used per about 1 equivalent of a compound of Formula **4**.

Suitable dehydrating agents include, but are not limited to, PPA, sulfuric acid, chlorosulfonic acid, sulfuryl chloride and thionyl chloride.

In another embodiment, the dehydrating agent is PPA.

15 The method can be carried out in the presence of a solvent, including, but not limited to, xylenes.

In one embodiment, the solvent is xylenes.

In another embodiment, the solvent is substantially anhydrous, i.e., comprises less than about 1% water.

20 In one embodiment the method is carried out for a time of about 1 hour to about 24 hours.

In still another embodiment the method is carried out for a time of about 4 hours to about 18 hours.

In yet another embodiment the method is carried out for a time of about 6 hours to
25 about 12 hours.

In one embodiment, the method is carried out at a temperature of about 25°C to about 200°C.

In another embodiment, the method is carried out at a temperature of about 100°C to about 160°C.

30 A compound of Formula **(IIa)** can be made by a method comprising contacting a compound of Formula **5** with a reducing agent for a time (e.g. Wolff-Kishner reagents) and at a temperature sufficient to make a compound of Formula **(IIa)**.

In one embodiment about 0.1 to about 10 equivalents of a reducing agent are used per about 1 equivalent of a compound of Formula **5**.

In another embodiment about 0.5 to about 5 equivalents of a reducing agent are used per about 1 equivalent of a compound of Formula 5.

In still another embodiment, about 1 to about 2 equivalents of a reducing agent are used per about 1 equivalent of a compound of Formula 5.

5 Suitable reducing agents for this carbonyl reduction include, but are not limited to, sodium borohydride, diisobutylaluminum hydride, alpineborane, and TFA/triethylsilane.

In one embodiment, the reducing agent is a hydride reducing agent.

In another embodiment, the reducing agent is sodium borohydride.

In another embodiment, the reducing agent is TFA/triethylsilane.

10 The method can be carried out in the presence of a solvent, including, but not limited to, methanol, ethanol, THF and benzene. Alternatively the method can be carried out in the absence of a solvent.

In one embodiment, the solvent is methanol.

In another embodiment, the solvent is substantially anhydrous, i.e., comprises less
15 than about 1% water.

In one embodiment the method is carried out for a time of about 1 minute to about 12 hours.

In still another embodiment the method is carried out for a time of about 5 minutes hours to about 6 hours.

20 In yet another embodiment the method is carried out for a time of about 15 minutes hours to about 2 hours.

In one embodiment, the method is carried out at a temperature of about -20°C to about 40°C.

In another embodiment, the method is carried out at a temperature of about 10°C
25 to about 30°C.

In still another embodiment, the method is carried out at a temperature of about 25°C.

A Tetracyclic Benzamide Derivative of the Formula 9 can be further derivatized using methodology familiar to one skilled in the art of organic synthesis to prepared a
30 variety of analogs of Formula (II) and Formula (IIa) having various substituents at one or more of R₁, R₂, R₃, R₄, R₇, R₈, R₉ and R₁₀. Useful derivatization methods include, but are not limited to, aromatic nucleophilic substitution reactions and aromatic electrophilic substitution reactions, such as nitration, iodination, bromination, chlorination, sulfonylation, sulfonylchlorination, alkylation and acylation. See M.B. Smith and J.

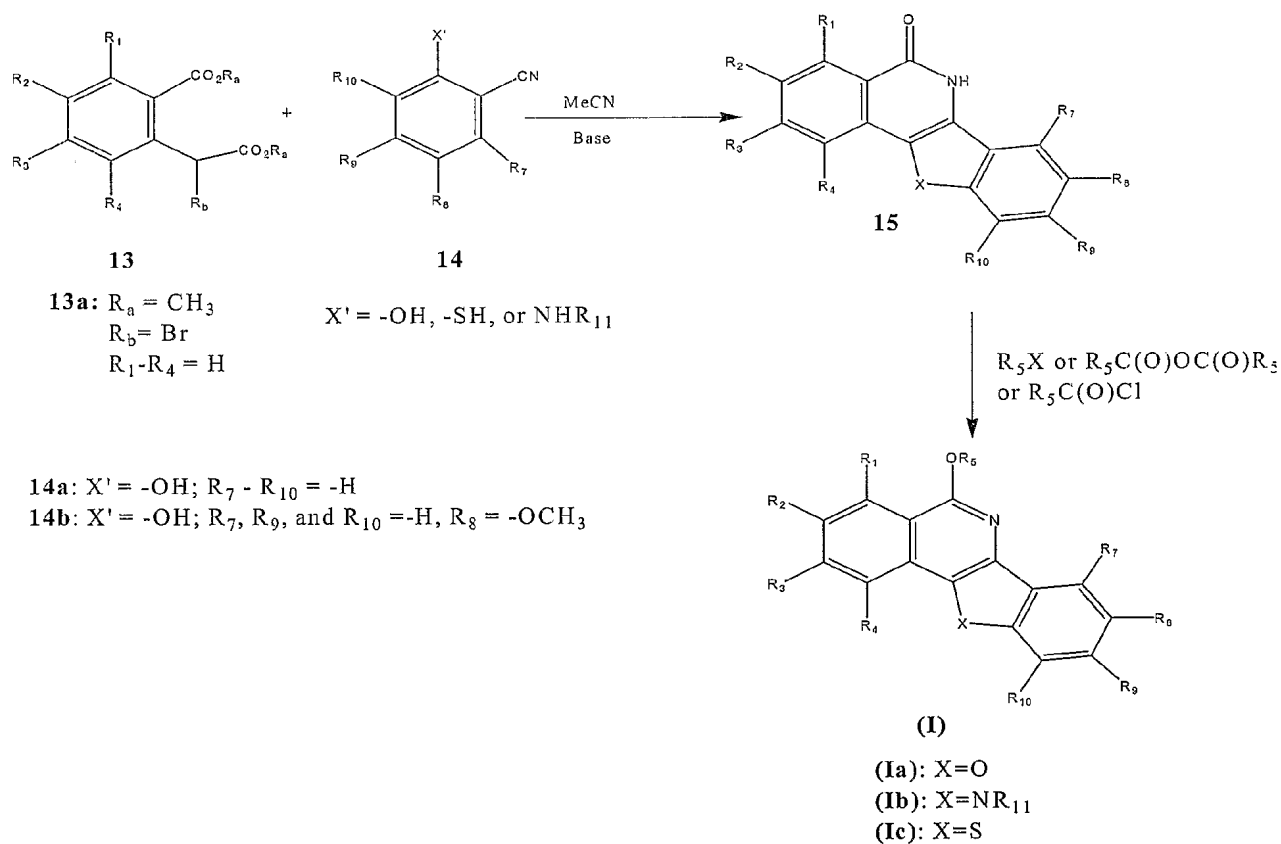
March, *Advanced Organic Chemistry: Reactions, Mechanisms, and Structure* 675-758 and 850-893 (5th ed. 2001).

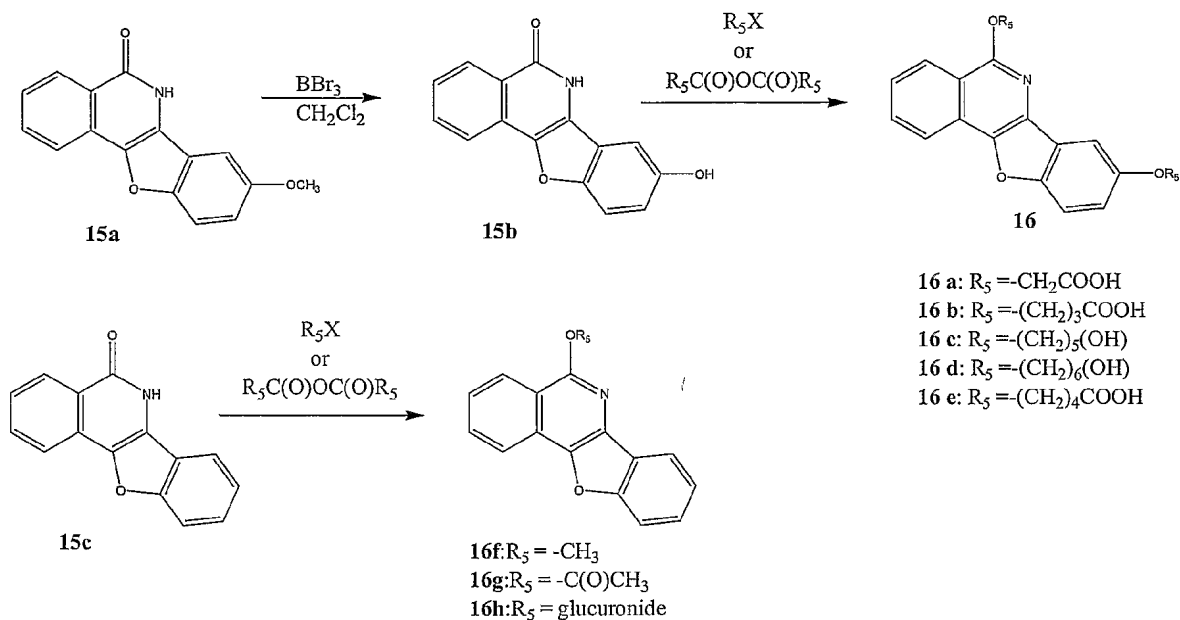
In one embodiment, the Tetracyclic Benzamide Derivative of Formula 9 is transformed into the chlorosulfonyl compound of Formula 10 using chlorosulfonic acid.

- 5 The Chlorosulfonyl compound of Formula 10 is then derivatized to the corresponding 3-(*N*-morpholinyl)-propylsulfonamide derivative of Formula 11 by reacting the chlorosulfonyl compound of 10 with 3-(*N*-morpholinyl)-propylamine in the presence of a triethylamine.

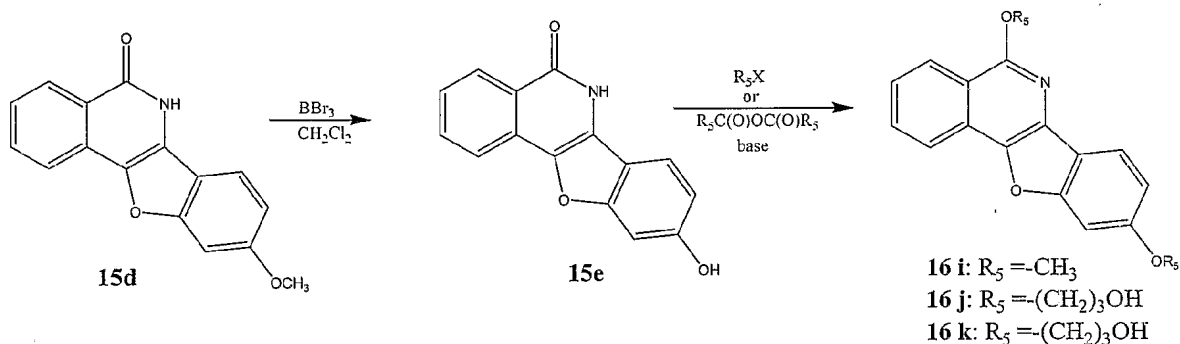
- Scheme 2 below illustrates methods useful for making compounds of Formula (I),
 10 Formula (Ia) and Formula (Ib), wherein R₁-R₄ and R₇-R₁₁ are defined above for the compounds of Formula (I), Formula (Ia) and Formula (Ib); X' is -OH, -NHR₁₁, or -SH; X is -O-, -N(H)-, or -S-; each R_a is independently C₁-C₃ alkyl; and R_b is -Cl, -Br, -I, -OTs, -OMs or -OTf.

Scheme 2





5



A tetracyclic isoquinoline compound of Formula **15** can be prepared by reacting a
 10 homophthalate of Formula **13** with a cyanophenol of Formula **14** in the presence of a
 base, such as triethylamine, sodium carbonate, or potassium carbonate, in a solvent such
 as acetonitrile, acetone or dimethylformamide (DMF).

A compound of Formula **15** can be transformed to a Tetracyclic Benzamide
 Derivative of Formula **(I)** upon treating **15** with an alkylating agent, an acylating agent or
 15 a glucuronidating agent, and further derivatization if necessary.

Suitable alkylating and acylating agents include, but are not limited to,
 alkylhalides, such as iodomethane, iodoethane, 1-iodopropane and 2-bromopropane,
 1-bromopropane, 1-bromobutane, 1-bromopentane and 1-bromohexane, the alkyl group
 of which can be optionally substituted with -OH or -C(O)OH; acyl halides, such as acetyl

chloride and propionyl chloride; and anhydrides, such as acetic anhydride and propionic anhydride.

In one embodiment, the alkylating agent is methyl iodide.

In another embodiment, the alkylating agent is a hydroxy-substituted alkylhalide.

5 In still another embodiment, the alkylating agent is a carboxy-substituted alkylhalide.

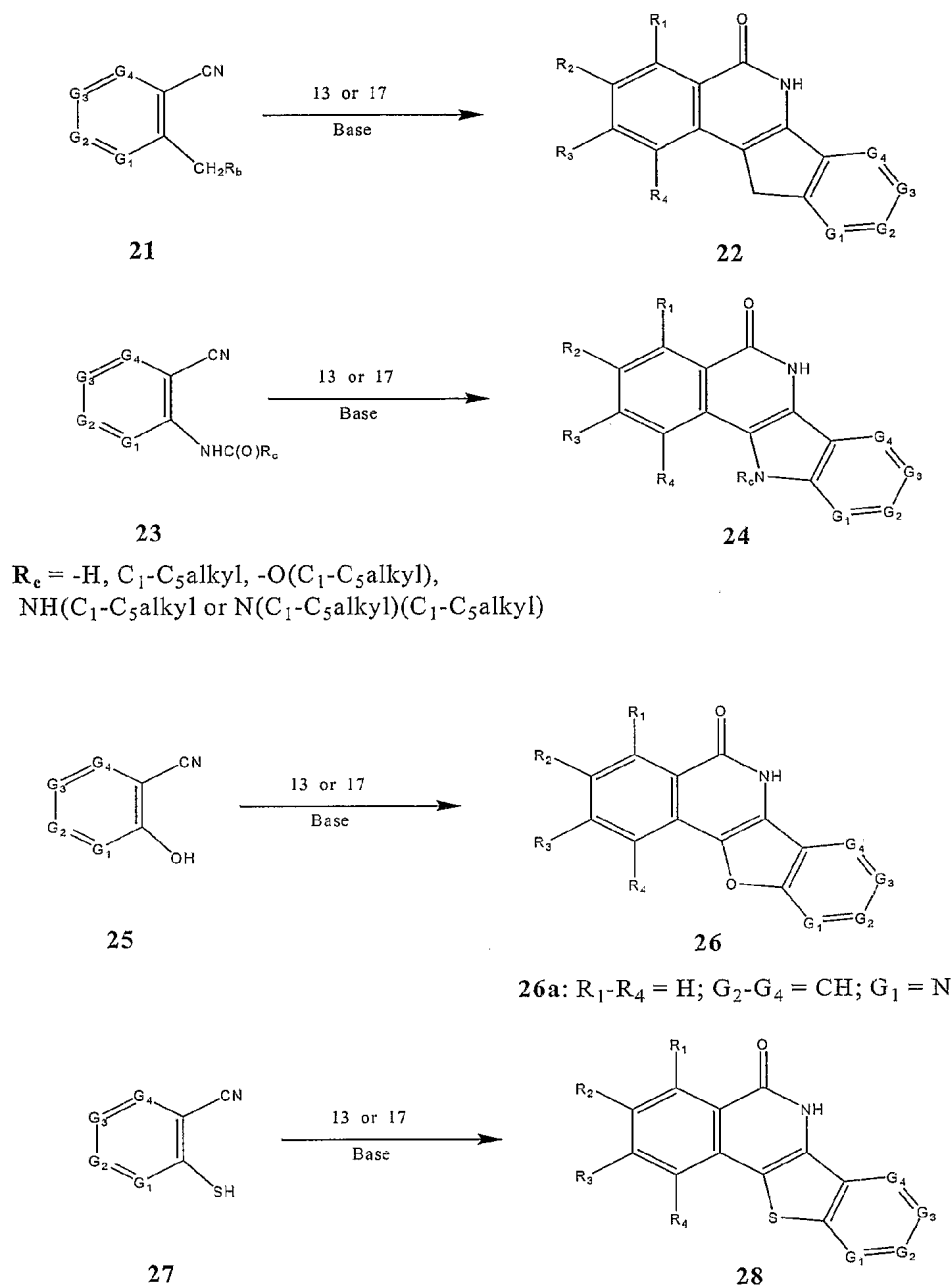
In one embodiment, the acylating agent is acetyl chloride.

In another embodiment, the acylating agent is acetic anhydride.

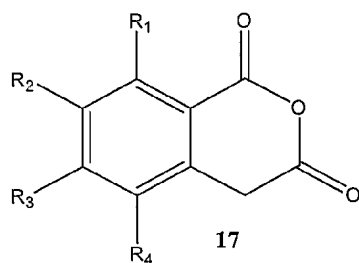
10 In yet another embodiment, R₅ is glucuronidyl and the glucuronidating agent is acetobromo- α -D-glucuronic acid methyl ester.

Scheme 3 below illustrates methodology useful for making Tetracyclic Benzamide Derivatives of Formula III, wherein R₁-R₄ and G₁-G₄ are defined above for the compounds of Formula III; R_b is -Cl, -Br, -I, -OTs, -OMs or -OTf; and R_c is -C₁-C₃ alkyl.

Scheme 3



5 Tetracyclic Benzamide Derivatives Derivatives of Formulas **22**, **24**, **26** and **28** can be made by reacting a homophthalic anhydride of Formula **17**



with a compound of Formula **21**, **23**, **25** or **27**, respectively in the presence of a base.

In an alternate embodiment, Tetracyclic Benzamide Derivatives of Formulas **22**, **24**, **26** and **28** can be made by reacting a homophthalate of Formula **13** with a compound of Formula **21**, **23**, **25** or **27**, respectively in the presence of a base.

5 Suitable bases for use in the methods of Scheme 5 are organic bases such as triethylamine, diisopropylamine, diisopropylethylamine, pyridine, lutidine sodium butoxide, sodium methoxide, and imidazole; and inorganic bases such as alkali metal carbonates, including sodium hydride, sodium carbonate, potassium carbonate and cesium carbonate.

 In one embodiment, the base is triethylamine.

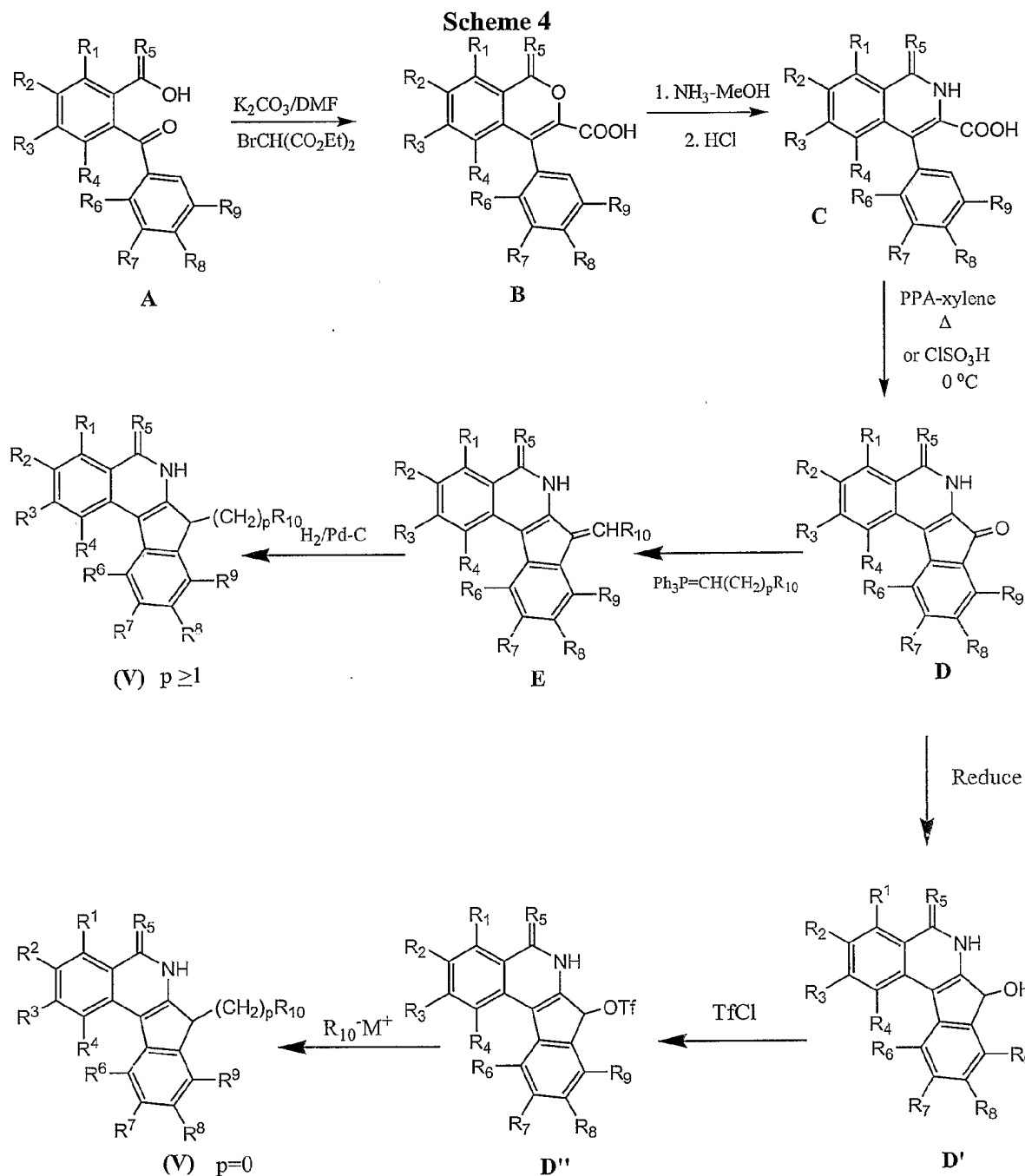
10 In another embodiment, the base is potassium carbonate.

 The method can be carried out in the presence of a solvent, such as acetonitrile, methylene chloride, chloroform, THF, DMF, DMSO, ethyl acetate, acetone, benzene, diethyl ether, water or mixtures thereof.

 In one embodiment, the solvent is acetonitrile.

15 In another embodiment, the solvent is DMF.

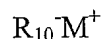
 Scheme 4 below illustrates methods useful for making compounds of Formula (V) wherein R_1 - R_4 and R_7 - R_{10} are defined above for the compounds of Formula (V).



- 5 A ketone of Formula A can be cyclized to the bicyclic intermediates of Formula B using bromo ethyl malonate in the presence of potassium carbonate. The intermediates of Formula B can then be converted to the lactam intermediates of Formula C in the presence of ammonia in methanol. Fridel-Crafts mediated ring closure of C provides the tetracyclic keto intermediates of Formula D which when reacted with a phosphonate or
- 10 phosphorus ylide via a Wittig-Horner procedure provides the Tetracyclic Benzamide

Derivatives of Formula E, whose exocyclic double bond can subsequently be reduced using catalytic hydrogenation to provide the compounds of Formula (V) where $p \geq 2$.

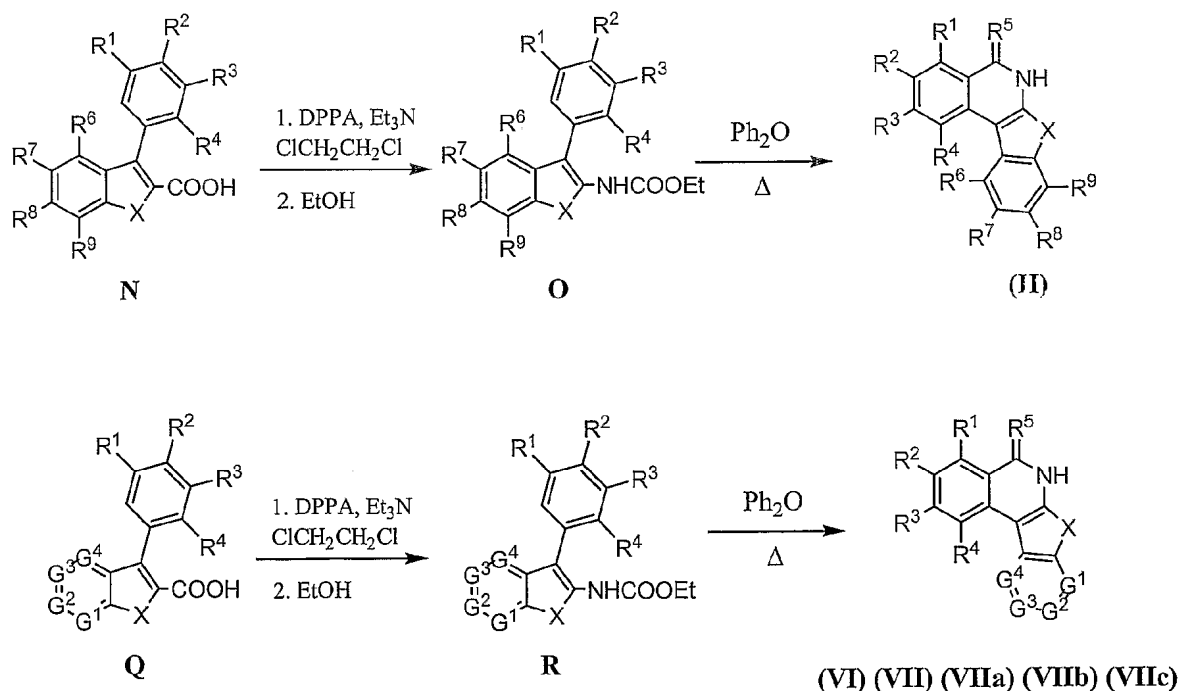
In an alternate embodiment, compounds of Formula (V) where $p = 0$, can be synthesized via intermediates of Formula D. The keto intermediates of Formula D can be reduced to the corresponding alcohol intermediates of Formula D' with subsequent conversion of the alcohol to the triflate intermediates of Formula D'' to produce a good leaving group. The triflate intermediate can then be reacted with nucleophiles of the Formula



where M^+ is a alkali metal such as Na^+ , or K^+ , thereby producing Tetracyclic Benzamide Derivatives of Formula (V) where $p = 0$. The compounds of Formula A can be produced from commercially starting materials using techniques known to one skilled in the art of organic synthesis.

Scheme 5 below illustrates methods useful for making compounds of Formula (II), Formula (VI), Formula (VII), Formula (VIIa), Formula (VIIb), and Formula (VIIc) wherein R_1 - R_4 , R_7 - R_{10} , G_1 - G_4 , and X are defined above for the compounds of Formula (II), Formula (VI), Formula (VII), Formula (VIIa), Formula (VIIb), and Formula (VIIc):

SCHEME 5

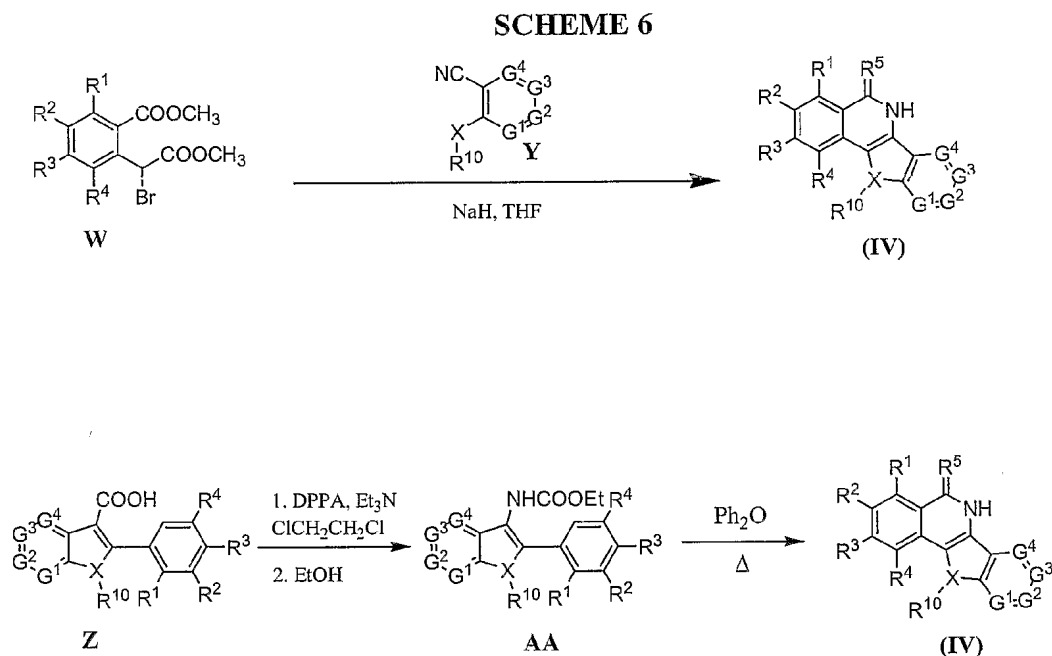


20

The carboxylic acid group of a compound of Formula N can be coupled with DPPA to provide the corresponding carbamate intermediates of Formula O, which can

then be thermally cyclized to provide the Tetracyclic Benzamide derivatives of Formula (II). Using the same synthetic method, the bicyclic carboxylic acids of Formula Q (see Wacker *et al.*, Tet. Lett., 43:5189-5191, 2002; and Bourdais, *et al.*, J. Het. Chem., 12:1111-1115, 1975, for methods useful to make compounds of Formula Q) can be converted to the Tetracyclic Benzamide derivatives of Formula (VI), Formula (VII), Formula (VIIa), Formula (VIIb), and Formula (VIIc) via the intermediacy of the carbamates of Formula R.

Scheme 6 below illustrates methods useful for making compounds of Formula (IV) wherein R₁-R₄, R₇-R₁₀, and G₁-G₄ are defined above for the compounds of Formula (IV):



The Tetracyclic Benzamide Derivatives of Formula (IV) can be made using a one pot coupling/cyclization process by reacting an intermediate of Formula W with an aromatic nitrile of Formula Y in the presence of sodium hydride.

Alternatively, the carboxylic acid group of a compound of Formula Z (see Wacker *et al.*, Tet. Lett., 43:5189-5191, 2002; and Bourdais, *et al.*, J. Het. Chem., 12:1111-1115, 1975, for methods useful to make compounds of Formula Z) can be coupled with DPPA to provide the corresponding carbonate intermediates of Formula AA, which can then be thermally cyclized to provide the Tetracyclic Benzamide Derivatives of Formula (IV).

4.17 Therapeutic Uses of the Tetracyclic Benzamide Derivatives

The invention also includes pharmaceutical compositions comprising an effective amount of a Tetracyclic Benzamide Derivative and a pharmaceutically acceptable carrier or vehicle. The invention includes a Tetracyclic Benzamide Derivative when provided as
5 a pharmaceutically acceptable prodrug, hydrated salt, such as a pharmaceutically acceptable salt, or mixtures thereof.

In accordance with the invention, the Tetracyclic Benzamide Derivatives are administered to a subject in need of treatment or prevention of a Condition.

The Tetracyclic Benzamide Derivatives can be used to treat or prevent an
10 inflammatory disease. Inflammatory diseases can arise where there is an inflammation of the body tissue. These include local inflammatory responses and systemic inflammation. Examples of inflammatory diseases treatable or preventable using the Tetracyclic Benzamide Derivatives include, but are not limited to, organ transplant rejection; chronic inflammatory diseases of the joints, including arthritis, rheumatoid arthritis, osteoarthritis
15 and bone diseases associated with increased bone resorption; inflammatory bowel diseases such as ileitis, ulcerative colitis, Barrett's syndrome, and Crohn's disease; inflammatory lung diseases such as asthma, adult respiratory distress syndrome, and chronic obstructive airway disease; inflammatory diseases of the eye including corneal dystrophy, trachoma, onchocerciasis, uveitis, sympathetic ophthalmitis and
20 endophthalmitis; chronic inflammatory diseases of the gum, including gingivitis and periodontitis; tuberculosis; leprosy; inflammatory diseases of the kidney including uremic complications, glomerulonephritis and nephrosis; inflammatory diseases of the skin including dermatitis, sclerodermatitis, psoriasis and eczema; inflammatory diseases of the central nervous system, including chronic demyelinating diseases of the nervous system,
25 multiple sclerosis, AIDS-related neurodegeneration and Alzheimers disease, infectious meningitis, encephalomyelitis, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis and viral or autoimmune encephalitis; immune-complex vasculitis; systemic lupus erythematosus (SLE); inflammatory diseases of the heart such as cardiomyopathy, ischemic heart disease, hypercholesterolemia, and atherosclerosis; as
30 well as various other diseases that can have significant inflammatory components, including preeclampsia, chronic liver failure, and brain and spinal cord trauma. The inflammatory disease can also be a systemic inflammation of the body, exemplified by gram-positive or gram negative shock, hemorrhagic or anaphylactic shock, or shock

induced by cancer chemotherapy in response to pro-inflammatory cytokines, *e.g.*, shock associated with pro-inflammatory cytokines. Such shock can be induced, *e.g.*, by a chemotherapeutic agent that is administered as a treatment for cancer.

In one embodiment the inflammatory disease is arthritis. In another embodiment
5 the inflammatory disease is colitis.

The Tetracyclic Benzamide Derivatives can be used to treat or prevent a reperfusion disease. Reperfusion refers to the process whereby blood flow in the blood vessels is resumed following ischemia, such as occurs following constriction or obstruction of the vessel. Reperfusion disease can result following a naturally occurring
10 episode, such as a myocardial infarction, stroke, or during a surgical procedure where blood flow in vessels is intentionally or unintentionally blocked. Examples of reperfusion injuries treatable or preventable using the Tetracyclic Benzamide Derivatives include, but are not limited to, intestinal reperfusion disease, myocardial reperfusion disease, and reperfusion disease resulting from cardiopulmonary bypass surgery, thoracoabdominal
15 aneurysm repair surgery, carotid endarterectomy surgery, or hemorrhagic shock.

In one embodiment, the reperfusion disease results from cardiopulmonary bypass surgery, thoracoabdominal aneurysm repair surgery, carotid endarterectomy surgery, or hemorrhagic shock.

In one embodiment, the reperfusion disease is a reoxygenation injury resulting
20 from surgery, particularly that relating to organ transplantation.

The Tetracyclic Benzamide Derivatives can be used to treat or prevent a reoxygenation injury resulting from surgery, particularly that relating to organ transplantation. Examples of reoxygenation injuries treatable or preventable using the Tetracyclic Benzamide Derivatives include, but are not limited to, transplantation of the
25 following organs: heart, lung, liver and kidney.

In one embodiment, a reoxygenation injury resulting from organ transplantation occurs during the organ transplantation.

The Tetracyclic Benzamide Derivatives can be used to treat or prevent an ischemic condition. Examples of ischemic conditions treatable or preventable using the
30 Tetracyclic Benzamide Derivatives include, but are not limited to, stable angina, unstable angina, myocardial ischemia, hepatic ischemia, mesenteric artery ischemia, intestinal ischemia, critical limb ischemia, chronic critical limb ischemia, cerebral ischemia, acute cardiac ischemia, and an ischemic disease of the central nervous system, such as stroke or cerebral ischemia.

In one embodiment, the ischemic condition is myocardial ischemia, stable angina, unstable angina, stroke, ischemic heart disease or cerebral ischemia.

The Tetracyclic Benzamide Derivatives can be used to treat or prevent chronic renal failure. In one embodiment the renal failure is chronic renal failure. In another
5 embodiment, the renal failure is acute renal failure.

The Tetracyclic Benzamide Derivatives can be used to treat or prevent a vascular disease. Examples of vascular diseases treatable or preventable using the Tetracyclic Benzamide Derivatives include, but are not limited to, peripheral arterial occlusion, thromboangitis obliterans, Reynaud's disease and phenomenon, acrocyanosis,
10 erythromelalgia, venous thrombosis, varicose veins, arteriovenous fistula, lymphedema, and lipedema.

In one embodiment the vascular disease is a cardiovascular disease. The Tetracyclic Benzamide Derivatives can be used to treat or prevent cardiovascular diseases. Examples of cardiovascular diseases treatable or preventable using the
15 Tetracyclic Benzamide Derivatives include, but are not limited to, cardiovascular diseases that can be treated or prevented by administering an effective amount of a Tetracyclic Benzamide Derivative include, but are not limited to, chronic heart failure, atherosclerosis, congestive heart failure, circulatory shock, cardiomyopathy, cardiac transplant, myocardial infarction, and a cardiac arrhythmia, such as atrial fibrillation,
20 supraventricular tachycardia, atrial flutter, and paroxysmal atrial tachycardia.

In one embodiment, the cardiovascular disease is chronic heart failure.

In another embodiment, the cardiovascular disease is a cardiac arrhythmia.

In still another embodiment, the cardiac arrhythmia is atrial fibrillation, supraventricular tachycardia, atrial flutter or paroxysmal atrial tachycardia.

25 The Tetracyclic Benzamide Derivatives can be used to treat or prevent diabetes. Examples of diabetes treatable or preventable or preventable using the Tetracyclic Benzamide Derivatives include, but are not limited to, Type I diabetes (Insulin Dependent Diabetes Mellitus), Type II diabetes (Non-Insulin Dependent Diabetes Mellitus), gestational diabetes, insulinopathies, diabetes due to pancreatic disease, diabetes
30 associated with other endocrine diseases (such as Cushing's Syndrome, acromegaly, pheochromocytoma, glucagonoma, primary aldosteronism or somatostatinoma), Type A insulin resistance syndrome, Type B insulin resistance syndrome, lipatrophic diabetes, and diabetes induced by β -cell toxins.

The Tetracyclic Benzamide Derivatives can be used to treat or prevent a diabetic complication. Examples of diabetic complications treatable or preventable or preventable using the Tetracyclic Benzamide Derivatives include, but are not limited to, diabetic cataract, glaucoma, retinopathy, nephropathy, (such as microalbuminuria and progressive diabetic nephropathy), polyneuropathy, gangrene of the feet, atherosclerotic coronary arterial disease, peripheral arterial disease, nonketotic hyperglycemic-hyperosmolar coma, mononeuropathy, autonomic neuropathy, foot ulcer, joint problem, and a skin or mucous membrane complication (such as an infection, a shin spot, a candidal infection or necrobiosis lipidica diabetorumobesity), hyperlipidemia, hypertension, syndrome of insulin resistance, coronary artery disease, retinopathy, diabetic neuropathy, polyneuropathy, mononeuropathy, autonomic neuropathy, foot ulcers, joint problems, fungal infections, and bacterial infections.

4.17.1 Treatment or Prevention of Cancer

The Tetracyclic Benzamide Derivatives can be used to treat or prevent cancer. Examples of cancers treatable or preventable using the Tetracyclic Benzamide Derivatives include, but are not limited to, the cancers disclosed below in Table 1 and metastases thereof.

TABLE 1

20	Solid tumors, including but not limited to:
	fibrosarcoma
	myxosarcoma
	liposarcoma
	chondrosarcoma
25	osteogenic sarcoma
	chordoma
	angiosarcoma
	endotheliosarcoma
	lymphangiosarcoma
30	lymphangioendotheliosarcoma
	synovioma
	mesothelioma
	Ewing's tumor
	leiomyosarcoma
35	rhabdomyosarcoma
	colon cancer

colorectal cancer
kidney cancer
pancreatic cancer
bone cancer
5 breast cancer
ovarian cancer
prostate cancer
esophageal cancer
stomach cancer
10 oral cancer
nasal cancer
throat cancer
squamous cell carcinoma
basal cell carcinoma
15 adenocarcinoma
sweat gland carcinoma
sebaceous gland carcinoma
papillary carcinoma
papillary adenocarcinomas
20 cystadenocarcinoma
medullary carcinoma
bronchogenic carcinoma
renal cell carcinoma
hepatoma
25 bile duct carcinoma
choriocarcinoma
seminoma
embryonal carcinoma
Wilms' tumor
30 cervical cancer
uterine cancer
testicular cancer
small cell lung carcinoma
bladder carcinoma
35 lung cancer
epithelial carcinoma
glioma
glioblastoma multiforme
astrocytoma
40 medulloblastoma
craniopharyngioma
ependymoma
pinealoma
hemangioblastoma
45 acoustic neuroma
oligodendroglioma
meningioma
skin cancer
melanoma
50 neuroblastoma

retinoblastoma

blood-borne cancers, including but not limited to:

5 acute lymphoblastic leukemia ("ALL")
 acute lymphoblastic B-cell leukemia
 acute lymphoblastic T-cell leukemia
 acute myeloblastic leukemia ("AML")
 acute promyelocytic leukemia ("APL")
 acute monoblastic leukemia
 acute erythroleukemic leukemia
 10 acute megakaryoblastic leukemia
 acute myelomonocytic leukemia
 acute nonlymphocytic leukemia
 acute undifferentiated leukemia
 chronic myelocytic leukemia ("CML")
 15 chronic lymphocytic leukemia ("CLL")
 hairy cell leukemia
 multiple myeloma

acute and chronic leukemias:

20 lymphoblastic
 myelogenous
 lymphocytic
 myelocytic leukemias

Lymphomas:

25 Hodgkin's disease
 non-Hodgkin's Lymphoma
 Multiple myeloma
 Waldenström's macroglobulinemia
 Heavy chain disease
 Polycythemia vera

30 In one embodiment, the cancer is pancreatic cancer, colorectal cancer, mesothelioma, a malignant pleural effusion, peritoneal carcinomatosis, peritoneal sarcomatosis, renal cell carcinoma, small cell lung cancer, non-small cell lung cancer, testicular cancer, bladder cancer, breast cancer, head and neck cancer, or ovarian cancer.

In still another embodiment, the subject in need of treatment has
 35 previously undergone treatment for cancer. Such previous treatments include, but are not limited to, prior chemotherapy, radiation therapy, surgery or immunotherapy, such as cancer vaccines.

The Tetracyclic Benzamide Derivatives are also useful for the treatment or prevention of a cancer caused by a virus. For example, human papilloma virus can lead

to cervical cancer (see, *e.g.*, Hernandez-Avila *et al.*, Archives of Medical Research (1997) 28:265-271), Epstein-Barr virus (EBV) can lead to lymphoma (see, *e.g.*, Herrmann *et al.*, J Pathol (2003) 199(2):140-5), hepatitis B or C virus can lead to liver carcinoma (see, *e.g.*, El-Serag, J Clin Gastroenterol (2002) 35(5 Suppl 2):S72-8), human T cell leukemia virus (HTLV)-I can lead to T-cell leukemia (see *e.g.*, Mortreux *et al.*, Leukemia (2003) 17(1):26-38), human herpesvirus-8 infection can lead to Kaposi's sarcoma (see, *e.g.*, Kadow *et al.*, Curr Opin Investig Drugs (2002) 3(11):1574-9), and Human Immune deficiency Virus (HIV) infection contribute to cancer development as a consequence of immunodeficiency (see, *e.g.*, Dal Maso *et al.*, Lancet Oncol (2003) 4(2):110-9).

10

4.17.1.1 Prophylactic Methods

The Tetracyclic Benzamide Derivatives of the Invention can also be administered to prevent the progression of a cancer, including but not limited to the cancers listed in Table 1. Such prophylactic use is indicated in conditions known or suspected of preceding progression to neoplasia or cancer, in particular, where non-neoplastic cell growth consisting of hyperplasia, metaplasia, or most particularly, dysplasia has occurred (for review of such abnormal growth conditions, see Robbins and Angell, 1976, Basic Pathology, 2d Ed., W.B. Saunders Co., Philadelphia, pp. 68-79). Hyperplasia is a form of controlled cell proliferation involving an increase in cell number in a tissue or organ, without significant alteration in structure or function. For example, endometrial hyperplasia often precedes endometrial cancer and precancerous colon polyps often transform into cancerous lesions. Metaplasia is a form of controlled cell growth in which one type of adult or fully differentiated cell substitutes for another type of adult cell. Metaplasia can occur in epithelial or connective tissue cells. A typical metaplasia involves a somewhat disorderly metaplastic epithelium. Dysplasia is frequently a forerunner of cancer, and is found mainly in the epithelia; it is the most disorderly form of non-neoplastic cell growth, involving a loss in individual cell uniformity and in the architectural orientation of cells. Dysplastic cells often have abnormally large, deeply stained nuclei, and exhibit pleomorphism. Dysplasia characteristically occurs where there exists chronic irritation or inflammation, and is often found in the cervix, respiratory passages, oral cavity, and gall bladder.

25
30

Alternatively or in addition to the presence of abnormal cell growth characterized as hyperplasia, metaplasia, or dysplasia, the presence of one or more characteristics of a

transformed phenotype, or of a malignant phenotype, displayed *in vivo* or displayed *in vitro* by a cell sample from a patient, can indicate the desirability of prophylactic/therapeutic administration of the composition of the invention. Such characteristics of a transformed phenotype include morphology changes, looser substratum attachment, loss of contact inhibition, loss of anchorage dependence, protease release, increased sugar transport, decreased serum requirement, expression of fetal antigens, disappearance of the 250,000 dalton cell surface protein, etc. (see also *id.*, at pp. 84-90 for characteristics associated with a transformed or malignant phenotype).

In a specific embodiment, leukoplakia, a benign-appearing hyperplastic or dysplastic lesion of the epithelium, or Bowen's disease, a carcinoma *in situ*, are pre-neoplastic lesions indicative of the desirability of prophylactic intervention.

In another embodiment, fibrocystic disease (cystic hyperplasia, mammary dysplasia, particularly adenosis (benign epithelial hyperplasia)) is indicative of the desirability of prophylactic intervention.

In other embodiments, a patient which exhibits one or more of the following predisposing factors for malignancy can be treated by administration of an amount of a Tetracyclic Benzamide Derivative which is effective to treat or prevent cancer: a chromosomal translocation associated with a malignancy (*e.g.*, the Philadelphia chromosome for chronic myelogenous leukemia, t(14;18) for follicular lymphoma, etc.), familial polyposis or Gardner's syndrome (possible forerunners of colon cancer), benign monoclonal gammopathy (a possible forerunner of multiple myeloma), a first degree kinship with persons having a cancer or precancerous disease showing a Mendelian (genetic) inheritance pattern (*e.g.*, familial polyposis of the colon, Gardner's syndrome, hereditary exostosis, polyendocrine adenomatosis, medullary thyroid carcinoma with amyloid production and pheochromocytoma, Peutz-Jeghers syndrome, neurofibromatosis of Von Recklinghausen, retinoblastoma, carotid body tumor, cutaneous melanocarcinoma, intraocular melanocarcinoma, xeroderma pigmentosum, ataxia telangiectasia, Chediak-Higashi syndrome, albinism, Fanconi's aplastic anemia, and Bloom's syndrome; see Robbins and Angell, 1976, Basic Pathology, 2d Ed., W.B. Saunders Co., Philadelphia, pp. 112-113) etc.), and exposure to carcinogens (*e.g.*, smoking, and inhalation of or contacting with certain chemicals).

In another specific embodiment, the Tetracyclic Benzamide Derivatives are administered to a human patient to prevent progression to breast, colon, ovarian, or cervical cancer.

4.17.2 Therapeutic/Prophylactic Administration and Compositions of the Invention

Due to their activity, the Tetracyclic Benzamide Derivatives are advantageously useful in veterinary and human medicine. As described above, the Tetracyclic Benzamide Derivatives are useful for treating or preventing a Condition in a subject in
5 need thereof.

When administered to a subject, the Tetracyclic Benzamide Derivatives can be administered as a component of a composition that comprises a pharmaceutically acceptable carrier or vehicle. The present compositions, which comprise a Tetracyclic Benzamide Derivative, can be administered orally. The Tetracyclic Benzamide
10 Derivatives of the invention can also be administered by any other convenient route, for example, by infusion or bolus injection, by absorption through epithelial or mucocutaneous linings (*e.g.*, oral, rectal, and intestinal mucosa, *etc.*) and can be administered together with another biologically active agent. Administration can be systemic or local. Various delivery systems are known, *e.g.*, encapsulation in liposomes,
15 microparticles, microcapsules, capsules, *etc.*, and can be administered.

Methods of administration include, but are not limited to, intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, epidural, oral, sublingual, intracerebral, intravaginal, transdermal, rectal, by inhalation, or topical, particularly to the ears, nose, eyes, or skin. In some instances, administration will result
20 in the release of the Tetracyclic Benzamide Derivatives into the bloodstream. The mode of administration is left to the discretion of the practitioner.

In one embodiment, the Tetracyclic Benzamide Derivatives are administered orally.

In other embodiments, it can be desirable to administer the Tetracyclic Benzamide
25 Derivatives locally. This can be achieved, for example, and not by way of limitation, by local infusion during surgery, topical application, *e.g.*, in conjunction with a wound dressing after surgery, by injection, by means of a catheter, by means of a suppository or enema, or by means of an implant, said implant being of a porous, non-porous, or gelatinous material, including membranes, such as sialastic membranes, or fibers.

30 In certain embodiments, it can be desirable to introduce the Tetracyclic Benzamide Derivatives into the central nervous system or gastrointestinal tract by any suitable route, including intraventricular, intrathecal, and epidural injection, and enema.

Intraventricular injection can be facilitated by an intraventricular catheter, for example, attached to a reservoir, such as an Ommaya reservoir.

Pulmonary administration can also be employed, *e.g.*, by use of an inhaler of nebulizer, and Formulation with an aerosolizing agent, or via perfusion in a fluorocarbon
5 oar, synthetic pulmonary surfactant. In certain embodiments, the Tetracyclic Benzamide Derivatives can be Formulated as a suppository, with traditional binders and excipients such as triglycerides.

In another embodiment the Tetracyclic Benzamide Derivatives can be delivered in a vesicle, in particular a liposome (*see* Langer, *Science* 249:1527-1533 (1990) and Treat
10 or prevent *et al.*, *Liposomes in the Therapy of Infectious Disease and Cancer* 317-327 and 353-365 (1989)).

In yet another embodiment the Tetracyclic Benzamide Derivatives can be delivered in a controlled-release system or sustained-release system (*see, e.g.*, Goodson, in *Medical Applications of Controlled Release*, *supra*, vol. 2, pp. 115-138 (1984)). Other
15 controlled or sustained-release systems discussed in the review by Langer, *Science* 249:1527-1533 (1990) can be used. In one embodiment a pump can be used (Langer, *Science* 249:1527-1533 (1990); Sefton, *CRC Crit. Ref. Biomed. Eng.* 14:201 (1987); Buchwald *et al.*, *Surgery* 88:507 (1980); and Saudek *et al.*, *N. Engl. J Med.* 321:574 (1989)). In another embodiment polymeric materials can be used (*see Medical*
20 *Applications of Controlled Release* (Langer and Wise eds., 1974); *Controlled Drug Bioavailability, Drug Product Design and Performance* (Smolen and Ball eds., 1984); Ranger and Peppas, *J. Macromol. Sci. Rev. Macromol. Chem.* 2:61 (1983); Levy *et al.*, *Science* 228:190 (1935); During *et al.*, *Ann. Neural.* 25:351 (1989); and Howard *et al.*, *J. Neurosurg.* 71:105 (1989)).

25 In yet another embodiment, a controlled- or sustained-release system can be placed in proximity of a target of the Tetracyclic Benzamide Derivatives, *e.g.*, the spinal column, brain, skin, lung, or gastrointestinal tract, thus requiring only a fraction of the systemic dose.

The present compositions can optionally comprise a suitable amount of a
30 pharmaceutically acceptable excipient so as to provide the form for proper administration to the animal.

Such pharmaceutical excipients can be liquids, such as water and oils, including those of petroleum, animal, vegetable, or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. The pharmaceutical excipients can be saline, gum

acacia; gelatin, starch paste, talc, keratin, colloidal silica, urea and the like. In addition, auxiliary, stabilizing, thickening, lubricating, and coloring agents can be used. In one embodiment the pharmaceutically acceptable excipients are sterile when administered to a subject. Water is a particularly useful excipient when the Tetracyclic Benzamide

5 Derivative is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid excipients, particularly for injectable solutions. Suitable pharmaceutical excipients also include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the
10 like. The present compositions, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents.

The present compositions can take the form of solutions, suspensions, emulsion, tablets, pills; pellets, capsules, capsules containing liquids, powders, sustained-release
Formulations, suppositories, emulsions, aerosols, sprays, suspensions, or any other form
15 suitable for use. In one embodiment the composition is in the form of a capsule (see *e.g.* U.S. Patent No. 5,698,155). Other examples of suitable pharmaceutical excipients are described in *Remington's Pharmaceutical Sciences* 1447-1676 (Alfonso R. Gennaro eds., 19th ed. 1995), incorporated herein by reference.

In one embodiment the Tetracyclic Benzamide Derivatives are Formulated in
20 accordance with routine procedures as a composition adapted for oral administration to human beings. Compositions for oral delivery can be in the form of tablets, lozenges, aqueous or oily suspensions, granules, powders, emulsions, capsules, syrups, or elixirs for example. Orally administered compositions can contain one or more agents, for example, sweetening agents such as fructose, aspartame or saccharin; flavoring agents such as
25 peppermint, oil of wintergreen, or cherry; coloring agents; and preserving agents, to provide a pharmaceutically palatable preparation. Moreover, where in tablet or pill form, the compositions can be coated to delay disintegration and absorption in the gastrointestinal tract thereby providing a sustained action over an extended period of time. Selectively permeable membranes surrounding an osmotically active driving a
30 Tetracyclic Benzamide Derivative are also suitable for orally administered compositions. In these latter platforms, fluid from the environment surrounding the capsule is imbibed by the driving compound, which swells to displace the agent or agent composition through an aperture. These delivery platforms can provide an essentially zero order delivery profile as opposed to the spiked profiles of immediate release Formulations. A

time-delay material such as glycerol monostearate or glycerol stearate can also be used. Oral compositions can include standard excipients such as mannitol, lactose, starch, magnesium stearate, sodium saccharin, cellulose, and magnesium carbonate. In one embodiment the excipients are of pharmaceutical grade.

5 In another embodiment the Tetracyclic Benzamide Derivatives can be Formulated for intravenous administration. Typically, compositions for intravenous administration comprise sterile isotonic aqueous buffer. Where necessary, the compositions can also include a solubilizing agent. Compositions for intravenous administration can optionally include a local anesthetic such as lignocaine to lessen pain at the site of the injection.

10 Generally, the ingredients are supplied either separately or mixed together in unit dosage form, for example, as a dry lyophilized-powder or water free concentrate in a hermetically sealed container such as an ampule or sachette indicating the quantity of active agent. Where the Tetracyclic Benzamide Derivatives are to be administered by infusion, they can be dispensed, for example, with an infusion bottle containing sterile
15 pharmaceutical grade water or saline. Where the Tetracyclic Benzamide Derivatives are administered by injection, an ampule of sterile water for injection or saline can be provided so that the ingredients can be mixed prior to administration.

 The Tetracyclic Benzamide Derivatives can be administered by controlled-release or sustained-release means or by delivery devices that are well known to those of ordinary
20 skill in the art. Examples include, but are not limited to, those described in U.S. Patent Nos. 3,845,770; 3,916,899; 3,536,809; 3,598,123; 4,008,719; 5,674,533; 5,059,595; 5,591,767; 5,120,548; 5,073,543; 5,639,476; 5,354,556; and 5,733,556, each of which is incorporated herein by reference. Such dosage forms can be used to provide controlled- or sustained-release of one or more active ingredients using, for example,
25 hydropropylmethyl cellulose, other polymer matrices, gels, permeable membranes, osmotic systems, multilayer coatings, microparticles, liposomes, microspheres, or a combination thereof to provide the desired release profile in varying proportions. Suitable controlled- or sustained-release Formulations known to those skilled in the art, including those described herein, can be readily selected for use with the active
30 ingredients of the invention. The invention thus encompasses single unit dosage forms suitable for oral administration such as, but not limited to, tablets, capsules, gelcaps, and caplets that are adapted for controlled- or sustained-release.

 Controlled- or sustained-release pharmaceutical compositions can have a common goal of improving drug therapy over that achieved by their non-controlled or

non-sustained counterparts. In one embodiment a controlled- or sustained-release composition comprises a minimal amount of a Tetracyclic Benzamide Derivative to cure or control the condition in a minimum amount of time. Advantages of controlled- or sustained-release compositions include extended activity of the drug, reduced dosage frequency, and increased patient compliance. In addition, controlled- or sustained-release compositions can favorably affect the time of onset of action or other characteristics, such as blood levels of the Tetracyclic Benzamide Derivative, and can thus reduce the occurrence of adverse side effects.

Controlled- or sustained-release compositions can initially release an amount of a Tetracyclic Benzamide Derivative that promptly produces the desired therapeutic or prophylactic effect, and gradually and continually release other amounts of the Tetracyclic Benzamide Derivative to maintain this level of therapeutic or prophylactic effect over an extended period of time. To maintain a constant level of the Tetracyclic Benzamide Derivative in the body, the Tetracyclic Benzamide Derivative can be released from the dosage form at a rate that will replace the amount of Tetracyclic Benzamide Derivative being metabolized and excreted from the body. Controlled- or sustained-release of an active ingredient can be stimulated by various conditions, including but not limited to, changes in pH, changes in temperature, concentration or availability of enzymes, concentration or availability of water, or other physiological conditions or compounds.

The amount of the Tetracyclic Benzamide Derivative that is effective in the treatment or prevention of a Condition can be determined by standard clinical techniques. In addition, *in vitro* or *in vivo* assays can optionally be employed to help identify optimal dosage ranges. The precise dose to be employed will also depend on the route of administration, and the seriousness of the condition being treated and should be decided according to the judgment of the practitioner and each patient's circumstances in view of, *e.g.*, published clinical studies. Effective dosage amounts of the present invention, when used for the indicated effects, range from about 0.05 to about 1000 mg of Tetracyclic Benzamide Derivative per day. Compositions for *in vivo* or *in vitro* use can contain about 0.5, 1.0, 2.5, 5.0, 10.0, 15.0, 25.0, 50.0, 100.0, 250.0, 500.0 or 1000.0 mg of Tetracyclic Benzamide Derivative. In one embodiment, the compositions are in the form of a tablet that can be scored. Effective plasma levels of the Tetracyclic Benzamide Derivatives can range from about 0.002 mg to about 50 mg per kg of body weight per day.

Tetracyclic Benzamide Derivatives can be administered in a single daily dose, or the total daily dosage can be administered in divided doses of two, three or four times daily. Furthermore, Tetracyclic Benzamide Derivatives can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using those
5 forms of transdermal skin patches well known to those of ordinary skill in that art. To be administered in the form of a transdermal delivery system, the dosage administration can be continuous rather than intermittent throughout the dosage regimen. Other illustrative topical preparations include creams, ointments, lotions, aerosol sprays and gels, wherein the concentration of Tetracyclic Benzamide Derivative ranges from about 0.1% to about
10 15%, w/w or w/v.

The Tetracyclic Benzamide Derivatives can be assayed *in vitro* or *in vivo* for the desired therapeutic or prophylactic activity prior to use in humans. Animal model systems can be used to demonstrate safety and efficacy.

The present methods for treating or preventing a Condition in a subject in need
15 thereof can further comprise administering another therapeutic agent to the subject being administered a Tetracyclic Benzamide Derivative. In one embodiment the other therapeutic agent is administered in an effective amount.

Effective amounts of the other therapeutic agents are well known to those skilled in the art. However, it is well within the skilled artisan's purview to determine the other
20 therapeutic agent's optimal effective amount range. In one embodiment of the invention, where, another therapeutic agent is administered to a subject, the effective amount of the Tetracyclic Benzamide Derivative is less than its effective amount would be where the other therapeutic agent is not administered. In this case, without being bound by theory, it is believed that the Tetracyclic Benzamide Derivatives and the other therapeutic agent
25 act synergistically to treat or prevent a Condition.

In one embodiment the other therapeutic agent is an anti-inflammatory agent. Anti-inflammatory agents include but are not limited to adrenocorticosteroids, such as cortisol, cortisone, fludrocortisone, prednisone, prednisolone, 6a-methylprednisolone, triamcinolone, betamethasone, and dexamethasone; and non-steroidal anti-inflammatory
30 agents (NSAIDs), such as aspirin, acetaminophen, indomethacin, sulindac, tolmetin, diclofenac, ketorolac, ibuprofen, naproxen, flurbiprofen, ketoprofen, fenoprofen, oxaprozin, mefenamic acid, meclofenamic acid, piroxicam, meloxicam, nabumetone, rofecoxib, celecoxib, etodolac, and nimesulide.

In one embodiment the other therapeutic agent is an anti-renal failure agent. Anti-renal failure agents include but are not limited to ACE (angiotensin-converting enzyme) inhibitors, such as captopril, enalaprilat, lisinopril, benazepril, fosinopril, trandolapril, quinapril, and ramipril; diuretics, such as mannitol, glycerin, furosemide, toseamide, tripamide, chlorothiazide, methyclothiazide, indapamide, amiloride, and spironolactone; and fibric acid agents, such as clofibrate, gemfibrozil, fenofibrate, ciprofibrate, and bezafibrate.

In one embodiment the other therapeutic agent is an anti-diabetic agent. Anti-diabetic agents include but are not limited to glucagons; somatostatin; diazoxide; sulfonylureas, such as tolbutamide, acetohexamide, tolazamide, chlorpropamide, glybenclamide, glipizide, glimepiride, and glimepiride; insulin secretagogues, such as repaglinide, and nateglinide; biguanides, such as metformin and phenformin; thiazolidinediones, such as pioglitazone, rosiglitazone, and troglitazone; and α -glucosidase inhibitors, such as acarbose and miglitol.

In one embodiment the other therapeutic agent is an anti-cardiovascular disease agent. Anti-cardiovascular disease agents include but are not limited to carnitine; thiamine; and muscarinic receptor antagonists, such as atropine, scopolamine, homatropine, tropicamide, pirenzepine, ipratropium, tiotropium, and tolterodine.

The other therapeutic agent can also be an agent useful for reducing any potential side effects of a Tetracyclic Benzamide Derivatives. For example, the other therapeutic agent can be an antiemetic agent. Examples of useful antiemetic agents include, but are not limited to, metoclopramide, domperidone, prochlorperazine, promethazine, chlorpromazine, trimethobenzamide, ondansetron, granisetron, hydroxyzine, acetylleucine monoethanolamine, alizapride, azasetron, benzquinamide, bietanautine, bromopride, buclizine, clebopride, cyclizine, dimenhydrinate, diphenidol, dolasetron, meclizine, methallatal, metopimazine, nabilone, oxypendyl, pipamazine, scopolamine, sulpiride, tetrahydrocannabinol, thiethylperazine, thioproperazine, tropisetron, and mixtures thereof.

The present methods for the treatment or prevention of cancer can further comprise administering another anticancer agent. In one embodiment, the methods comprise the sequential administration of a Tetracyclic Benzamide Derivative and another anticancer agent. In another embodiment, the methods comprise the administration of a composition comprising a pharmaceutically acceptable carrier, a Tetracyclic Benzamide Derivative, and another anticancer agent.

The Tetracyclic Benzamide Derivative and the other anticancer agent can act additively or synergistically. A synergistic use of a Tetracyclic Benzamide Derivative and another anticancer agent permits the use of lower dosages of one or more of these agents and/or less frequent administration of said agents to a subject with cancer. The ability to utilize lower dosages of a Tetracyclic Benzamide Derivative and/or additional anticancer agents and/or to administer said agents less frequently can reduce the toxicity associated with the administration of said agents to a subject without reducing the efficacy of said agents in the treatment of cancer. In addition, a synergistic effect can result in the improved efficacy of these agents in the treatment of cancer and/or the reduction of adverse or unwanted side effects associated with the use of either agent alone.

In one embodiment, the Tetracyclic Benzamide Derivative and the anticancer agent can act synergistically when administered in doses typically employed when such agents are used as monotherapy for the treatment of cancer. In another embodiment, the Tetracyclic Benzamide Derivative and the anticancer agent can act synergistically when administered in doses that are less than doses typically employed when such agents are used as monotherapy for the treatment of cancer.

Suitable additional anticancer agents useful in the methods and compositions of the present invention include, but are not limited to, gemcitabine, capecitabine, methotrexate, taxol, taxotere, mercaptopurine, thioguanine, hydroxyurea, cytarabine, cyclophosphamide, ifosfamide, nitrosoureas, cisplatin, carboplatin, mitomycin, dacarbazine, procarbazine, etoposide, teniposide, campathecins, bleomycin, doxorubicin, idarubicin, daunorubicin, dactinomycin, plicamycin, mitoxantrone, L-asparaginase, doxorubicin, epirubicin, 5-fluorouracil, taxanes such as docetaxel and paclitaxel, leucovorin, levamisole, irinotecan, estramustine, etoposide, nitrogen mustards, BCNU, nitrosoureas such as carmustine and lomustine, vinca alkaloids such as vinblastine, vincristine and vinorelbine, platinum complexes such as cisplatin, carboplatin and oxaliplatin, imatinib mesylate, hexamethylmelamine, topotecan, tyrosine kinase inhibitors, tyrphostins herbimycin A, genistein, erbstatin, and lavendustin A.

In one embodiment, the additional anticancer agent can be, but is not limited to, a drug listed in Table 2.

TABLE 2

Alkylating agents

Nitrogen mustards:	Cyclophosphamide
	Ifosfamide
	Trofosfamide
	Chlorambucil
Nitrosoureas:	Carmustine (BCNU)
	Lomustine (CCNU)
Alkylsulphonates:	Busulfan
	Treosulfan
Triazenes:	Dacarbazine
Platinum containing complexes:	Cisplatin
	Carboplatin
	Aroplatin
	Oxaliplatin
<u>Plant Alkaloids</u>	
Vinca alkaloids:	Vincristine
	Vinblastine
	Vindesine
	Vinorelbine
Taxoids:	Paclitaxel
	Docetaxel
<u>DNA Topoisomerase Inhibitors</u>	
Epipodophyllins:	Etoposide
	Teniposide
	Topotecan
	9-aminocamptothecin
	Camptothecin
	Crisnatol
Mitomycins:	Mitomycin C
	Anti-metabolites
<u>Anti-folates:</u>	
DHFR inhibitors:	Methotrexate
	Trimetrexate

IMP dehydrogenase Inhibitors:	Mycophenolic acid Tiazofurin Ribavirin EICAR
Ribonucleotide reductase Inhibitors:	Hydroxyurea Deferoxamine
<u>Pyrimidine analogs:</u>	
Uracil analogs:	5-Fluorouracil Fluoxuridine Doxifluridine Ralitrexed
Cytosine analogs:	Cytarabine (ara C) Cytosine arabinoside Fludarabine Gemcitabine Capecitabine
<u>Purine analogs:</u>	Mercaptopurine Thioguanine
<u>DNA Antimetabolites:</u>	3-HP 2'-deoxy-5-fluorouridine 5-HP alpha-TGDR aphidicolin glycinate ara-C 5-aza-2'-deoxycytidine beta-TGDR cyclocytidine guanazole inosine glycidialdehyde macebecin II Pyrzoloimidazole
<u>Hormonal therapies:</u>	

Receptor antagonists:

Anti-estrogen:

Tamoxifen

Raloxifene

Megestrol

LHRH agonists:

Goserelin

Leuprolide acetate

Anti-androgens:

Flutamide

Bicalutamide

Retinoids/Retinoids

Cis-retinoic acid

Vitamin A derivative:

All-trans retinoic acid (ATRA-IV)

Vitamin D3 analogs:

EB 1089

CB 1093

KH 1060

Photodynamic therapies:

Vertoporphin (BPD-MA)

Phthalocyanine

Photosensitizer Pc4

Demethoxy-hypocrellin A
(2BA-2-DMHA)Cytokines:Interferon- α Interferon- β Interferon- γ

Tumor necrosis factor

Angiogenesis Inhibitors:Angiostatin (plasminogen
fragment)

antiangiogenic antithrombin III

Angiozyme

ABT-627

Bay 12-9566

Benefin

Bevacizumab

BMS-275291

cartilage-derived inhibitor (CDI)

CAI
CD59 complement fragment
CEP-7055
Col 3
Combretastatin A-4
Endostatin (collagen XVIII
fragment)
Fibronectin fragment
Gro-beta
Halofuginone
Heparinases
Heparin hexasaccharide fragment
HMOV833
Human chorionic gonadotropin
(hCG)
IM-862
Interferon alpha/beta/gamma
Interferon inducible protein (IP-
10)
Interleukin-12
Kringles 5 (plasminogen fragment)
Marimastat
Metalloproteinase inhibitors
(TIMPs)
2-Methoxyestradiol
MMI 270 (CGS 27023A)
MoAb IMC-1C11
Neovastat
NM-3
Panzem
PI-88
Placental ribonuclease inhibitor
Plasminogen activator inhibitor

Platelet factor-4 (PF4)
Prinomastat
Prolactin 16kD fragment
Proliferin-related protein (PRP)
PTK 787/ZK 222594
Retinoids
Solimastat
Squalamine
SS 3304
SU 5416
SU6668
SU11248
Tetrahydrocortisol-S
Tetrathiomolybdate
Thalidomide
Thrombospondin-1 (TSP-1)
TNP-470
Transforming growth factor-beta
(TGF-b)
Vasculostatin
Vasostatin (calreticulin fragment)
ZD6126
ZD 6474
farnesyl transferase inhibitors
(FTI)
Bisphosphonates
Allocolchicine
Halichondrin B
Colchicine
colchicine derivative
dolstatin 10
Maytansine
Rhizoxin

Antimitotic agents:

Thiocolchicine

trityl cysteine

Others:

Isoprenylation inhibitors:

Dopaminergic neurotoxins: 1-methyl-4-phenylpyridinium ion

Cell cycle inhibitors: Staurosporine

Actinomycins: Actinomycin D

Dactinomycin

Bleomycins: Bleomycin A2

Bleomycin B2

Peplomycin

Anthracyclines: Daunorubicin

Doxorubicin (adriamycin)

Idarubicin

Epirubicin

Pirarubicin

Zorubicin

Mitoxantrone

MDR inhibitors: Verapamil

Ca²⁺ ATPase inhibitors: Thapsigargin

Other additional anticancer agents that can be used in the compositions and methods of the present invention include, but are not limited to: acivicin; aclarubicin; acodazole hydrochloride; acronine; adozelesin; aldesleukin; altretamine; ambomycin;

5 ametantrone acetate; aminoglutethimide; amsacrine; anastrozole; anthramycin; asparaginase; asperlin; azacitidine; azetepa; azotomycin; batimastat; benzodepa; bicalutamide; bisantrene hydrochloride; bisnafide dimesylate; bizelesin; bleomycin sulfate; brequinar sodium; bropirimine; busulfan; cactinomycin; calusterone; caracemide; carbetimer; carboplatin; carmustine; carubicin hydrochloride; carzelesin; cedefingol;

10 chlorambucil; cirolemycin; cisplatin; cladribine; crisnatol mesylate; cyclophosphamide; cytarabine; dacarbazine; dactinomycin; daunorubicin hydrochloride; decitabine; dexormaplatin; dezaguanine; dezaguanine mesylate; diaziquone; docetaxel; doxorubicin; doxorubicin hydrochloride; droloxifene; droloxifene citrate; dromostanolone propionate;

- duazomycin; edatrexate; eflornithine hydrochloride; elsamitrucin; enloplatin; enpromate; epipropidine; epirubicin hydrochloride; erbulozole; esorubicin hydrochloride; estramustine; estramustine phosphate sodium; etanidazole; etoposide; etoposide phosphate; etoprine; fadrozole hydrochloride; fazarabine; fenretinide; floxuridine;
- 5 fludarabine phosphate; fluorouracil; flurocitabine; fosquidone; fostriecin sodium; gemcitabine hydrochloride; hydroxyurea; idarubicin hydrochloride; ifosfamide; ilmoforesine; interleukin II (including recombinant interleukin II, or rIL2), interferon alfa-2 α ; interferon alfa-2 β ; interferon alfa-n1 ; interferon alfa-n3; interferon beta-1 α ; interferon gamma-1 β ; iproplatin; irinotecan hydrochloride; lanreotide acetate; letrozole;
- 10 leuprolide acetate; liarozole hydrochloride; lometrexol sodium; lomustine; losoxantrone hydrochloride; masoprocol; maytansine; mechlorethamine hydrochloride; megestrol acetate; melengestrol acetate; melphalan; menogaril; mercaptopurine; methotrexate; methotrexate sodium; metoprine; meturedapa; mitindomide; mitocarcin; mitocromin; mitogillin; mitomalcin; mitomycin; mitosper; mitotane; mitoxantrone hydrochloride;
- 15 mycophenolic acid; nocodazole; nogalamycin; ormaplatin; oxisuran; paclitaxel; pegaspargase; peliomycin; pentamustine; peplomycin sulfate; perfosfamide; pipobroman; pipsulfan; piroxantrone hydrochloride; plicamycin; plomestane; porfimer sodium; porfiromycin; prednimustine; procarbazine hydrochloride; puromycin; puromycin hydrochloride; pyrazofurin; riboprine; rogletimide; safingol; safingol hydrochloride;
- 20 semustine; simtrazene; sparfosate sodium; sparsomycin; spirogermanium hydrochloride; spiromustine; spiroplatin; streptonigrin; streptozocin; sulofenur; talisomycin; tecogalan sodium; tegafur; teloxantrone hydrochloride; temoporfin; teniposide; teroxirone; testolactone; thiamiprine; thioguanine; thiotepa; tiazofurin; tirapazamine; toremifene citrate; trestolone acetate; triciribine phosphate; trimetrexate; trimetrexate glucuronate;
- 25 triptorelin; tubulozole hydrochloride; uracil mustard; uredepa; vapreotide; verteporfin; vinblastine sulfate; vincristine sulfate; vindesine; vindesine sulfate; vinepidine sulfate; vinyglycinate sulfate; vinleurosine sulfate; vinorelbine tartrate; vinrosidine sulfate; vinzolidine sulfate; vorozole; zeniplatin; zinostatin; zorubicin hydrochloride.

- Further anticancer drugs that can be used in the methods and compositions of the
- 30 invention include, but are not limited to: 20-epi-1,25 dihydroxyvitamin D3; 5-ethynyluracil; abiraterone; aclarubicin; acylfulvene; adecypenol; adozelesin; aldesleukin; ALL-TK antagonists; altretamine; ambamustine; amidox; amifostine; aminolevulinic acid; amrubicin; amsacrine; anagrelide; anastrozole; andrographolide; angiogenesis inhibitors; antagonist D; antagonist G; antarelix; anti-dorsalizing morphogenetic protein-

1; antiandrogen, prostatic carcinoma; antiestrogen; antineoplaston; antisense
oligonucleotides; aphidicolin glycinate; apoptosis gene modulators; apoptosis regulators;
apurinic acid; ara-CDP-DL-PTBA; arginine deaminase; asulacrine; atamestane;
atrimustine; axinastatin 1; axinastatin 2; axinastatin 3; azasetron; azatoxin; azatyrosine;
5 baccatin III derivatives; balanol; batimastat; BCR/ABL antagonists; benzochlorins;
benzoylstauroporine; beta lactam derivatives; beta-alethine; betaclamycin B; betulinic
acid; bFGF inhibitor; bicalutamide; bisantrene; bisaziridinylspermine; bisnafide;
bistratene A; bizelesin; breflate; bropirimine; budotitane; buthionine sulfoximine;
calcipotriol; calphostin C; camptothecin derivatives; canarypox IL-2; carboxamide-
10 amino-triazole; carboxyamidotriazole; CaRest M3; CARN 700; cartilage derived
inhibitor; carzelesin; casein kinase inhibitors (ICOS); castanospermine; cecropin B;
cetorelix; chlorIns; chloroquinoxaline sulfonamide; cicaprost; cis-porphyrin; cladribine;
clomifene analogues; clotrimazole; collismycin A; collismycin B; combretastatin A4;
combretastatin analogue; conagenin; crambescidin 816; crisnatol; cryptophycin 8;
15 cryptophycin A derivatives; curacin A; cyclopentanthraquinones; cycloplatam;
cypemycin; cytarabine ocfosfate; cytolytic factor; cytostatin; dacliximab; decitabine;
dehydrodidemnin B; deslorelin; dexamethasone; dexifosfamide; dexrazoxane;
dexverapamil; diaziquone; didemnin B; didox; diethylnorspermine; dihydro-5-acytidine;
dihydrotaxol; dioxamycin; diphenyl spiromustine; docetaxel; docosanol; dolasetron;
20 doxifluridine; droloxifene; dronabinol; duocarmycin SA; ebselen; ecomustine; edelfosine;
edrecolomab; eflornithine; elemene; emitefur; epirubicin; epristeride; estramustine
analogue; estrogen agonists; estrogen antagonists; etanidazole; etoposide phosphate;
exemestane; fadrozole; fazarabine; fenretinide; filgrastim; finasteride; flavopiridol;
flezelastine; fluasterone; fludarabine; fluorodaunorubicin hydrochloride; forfenimex;
25 formestane; fostriecin; fotemustine; gadolinium texaphyrin; gallium nitrate; galocitabine;
ganirelix; gelatinase inhibitors; gemcitabine; glutathione inhibitors; hepsulfam; heregulin;
hexamethylene bisacetamide; hypericin; ibandronic acid; idarubicin; idoxifene;
idramantone; ilmofosine; ilomastat; imidazoacridones; imiquimod; immunostimulant
peptides; insulin-like growth factor-1 receptor inhibitor; interferon agonists; interferons;
30 interleukins; iobenguane; iododoxorubicin; ipomeanol, 4-; iroplact; irsogladine;
isobengazole; isohomohalicondrin B; itasetron; jasplakinolide; kahalalide F; lamellarin-N
triacetate; lanreotide; leinamycin; lenograstim; lentinan sulfate; leptolstatin; letrozole;
leukemia inhibiting factor; leukocyte alpha interferon;
leuprolide+estrogen+progesterone; leuprorelin; levamisole; liarozole; linear polyamine

analogue; lipophilic disaccharide peptide; lipophilic platinum complexes; lissoclinamide
 7; lobaplatin; lombricine; lometrexol; lonidamine; losoxantrone; lovastatin; loxoribine;
 lurtotecan; lutetium texaphyrin; lysofylline; lytic peptides; maitansine; mannostatin A;
 marimastat; masoprocold; maspin; matrilysin inhibitors; matrix metalloproteinase
 5 inhibitors; menogaril; merbarone; meterelin; methioninase; metoclopramide; MIF
 inhibitor; mifepristone; miltefosine; mirimostim; mismatched double stranded RNA;
 mitoguazone; mitolactol; mitomycin analogues; mitonafide; mitotoxin fibroblast growth
 factor-saporin; mitoxantrone; mofarotene; molgramostim; monoclonal antibody, human
 chorionic gonadotrophin; monophosphoryl lipid A+myobacterium cell wall sk;
 10 mopidamol; multiple drug resistance gene inhibitor; multiple tumor suppressor 1-based
 therapy; mustard anticancer agents; mycaperoxide B; mycobacterial cell wall extract;
 myriaporone; N-acetyldinaline; N-substituted benzamides; nafarelin; nagrestip;
 naloxone+pentazocine; napavin; naphterpin; nartograstim; nedaplatin; nemorubicin;
 neridronic acid; neutral endopeptidase; nilutamide; nisamycin; nitric oxide modulators;
 15 nitroxide antioxidant; nitrullyn; O6-benzylguanine; octreotide; okicenone;
 oligonucleotides; onapristone; ondansetron; ondansetron; oracin; oral cytokine inducer;
 ormaplatin; osaterone; oxaliplatin; oxaunomycin; paclitaxel; paclitaxel analogues;
 paclitaxel derivatives; palauamine; palmitoylrhizoxin; pamidronic acid; panaxytriol;
 panomifene; parabactin; pazelliptine; pegaspargase; peldesine; pentosan polysulfate
 20 sodium; pentostatin; pentozole; perflubron; perfosfamide; perillyl alcohol;
 phenazinomycin; phenylacetate; phosphatase inhibitors; picibanil; pilocarpine
 hydrochloride; pirarubicin; piritrexim; placetin A; placetin B; plasminogen activator
 inhibitor; platinum complex; platinum complexes; platinum-triamine complex; porfimer
 sodium; porfiromycin; prednisone; propyl bis-acridone; prostaglandin J2; proteasome
 25 inhibitors; protein A-based immune modulator; protein kinase C inhibitor; protein kinase
 C inhibitors, microalgal; protein tyrosine phosphatase inhibitors; purine nucleoside
 phosphorylase inhibitors; purpurins; pyrazoloacridine; pyridoxylated hemoglobin
 polyoxyethylene conjugate; raf antagonists; raltitrexed; ramosetron; ras farnesyl protein
 transferase inhibitors; ras inhibitors; ras-GAP inhibitor; retelliptine demethylated;
 30 rhenium Re 186 etidronate; rhizoxin; ribozymes; RII retinamide; rogletimide; rohitukine;
 romurtide; roquinimex; rubiginone B1; ruboxyl; safingol; saintopin; SarCNU; sarcophytol
 A; sargramostim; Sdi 1 mimetics; semustine; senescence derived inhibitor 1; sense
 oligonucleotides; signal transduction inhibitors; signal transduction modulators; single
 chain antigen binding protein; sizofiran; sobuzoxane; sodium borocaptate; sodium

phenylacetate; solverol; somatomedin binding protein; sonermin; sparfosic acid; spicamycin D; spiromustine; splenopentin; spongistatin 1; squalamine; stem cell inhibitor; stem-cell division inhibitors; stipiamide; stromelysin inhibitors; sulfinosine; superactive vasoactive intestinal peptide antagonist; suradista; suramin; swainsonine;

5 synthetic glycosaminoglycans; tallimustine; tamoxifen methiodide; tauromustine; tazarotene; tecogalan sodium; tegafur; tellurapyrylium; telomerase inhibitors; temoporfin; temozolomide; teniposide; tetrachlorodecaoxide; tetrazomine; thaliblastine; thiocoraline; thrombopoietin; thrombopoietin mimetic; thymalfasin; thymopoietin receptor agonist; thymotrigan; thyroid stimulating hormone; tin ethyl etiopurpurin; tirapazamine;

10 titanocene bichloride; topsentin; toremifene; totipotent stem cell factor; translation inhibitors; tretinoin; triacetyluridine; triciribine; trimetrexate; triptorelin; tropisetron; turosteride; tyrosine kinase inhibitors; tyrphostins; UBC inhibitors; ubenimex; urogenital sinus-derived growth inhibitory factor; urokinase receptor antagonists; vapreotide; variolin B; vector system, erythrocyte gene therapy; velaresol; veramine; verdins;

15 verteporfin; vinorelbine; vinxaltine; vitaxin; vorozole; zanoterone; zeniplatin; zilascorb; and zinostatin stimalamer.

4.17.1.3 Multi-Modality Therapy For Cancer

The Tetracyclic Benzamide Derivatives can be administered to a subject that has undergone or is currently undergoing one or more additional anticancer treatment modalities including, but not limited to, surgery, radiation therapy, or immunotherapy,

20 such as cancer vaccines.

In one embodiment, the invention provides methods for treating cancer comprising (a) administering to a subject in need thereof an amount of a Tetracyclic Benzamide Derivative effective to treat or prevent cancer; and (b) administering to said

25 subject one or more additional anticancer treatment modalities including, but not limited to, surgery, radiation therapy, or immunotherapy, such as a cancer vaccine.

In one embodiment, the additional anticancer treatment modality is radiation therapy.

In another embodiment, the additional anticancer treatment modality is

30 surgery.

In still another embodiment, the additional anticancer treatment modality is immunotherapy.

In a specific embodiment, the Tetracyclic Benzamide Derivatives are administered concurrently with radiation therapy. In another specific embodiment, the additional anticancer treatment modality is administered prior or subsequent to the Tetracyclic Benzamide Derivative, preferably at least an hour, five hours, 12 hours, a day, 5 a week, a month, more preferably several months (e.g., up to three months), prior or subsequent to administration of the Tetracyclic Benzamide Derivatives.

When the additional anticancer treatment modality is radiation therapy, any radiation therapy protocol can be used depending upon the type of cancer to be treated. For example, but not by way of limitation, X-ray radiation can be administered; 10 in particular, high-energy megavoltage (radiation of greater than 1 MeV energy) can be used for deep tumors, and electron beam and orthovoltage X-ray radiation can be used for skin cancers. Gamma-ray emitting radioisotopes, such as radioactive isotopes of radium, cobalt and other elements, can also be administered.

Additionally, the invention provides methods of treatment of cancer using 15 the Tetracyclic Benzamide Derivatives as an alternative to chemotherapy or radiation therapy where the chemotherapy or the radiation therapy results in negative side effects, in the subject being treated. The subject being treated can, optionally, be treated with another anticancer treatment modality such as surgery, radiation therapy, or immunotherapy, depending on which treatment is found to be acceptable or bearable.

20 The Tetracyclic Benzamide Derivatives can also be used in an *in vitro* or *ex vivo* fashion, such as for the treatment of certain cancers, including, but not limited to leukemias and lymphomas, such treatment involving autologous stem cell transplants. This can involve a multi-step process in which the animal's autologous hematopoietic stem cells are harvested and purged of all cancer cells, the patient's remaining bone- 25 marrow cell population is then eradicated via the administration of high doses of the Tetracyclic Benzamide Derivatives and/or high dose radiation therapy, and the stem cell graft is infused back into the animal. Supportive care is then provided while bone marrow function is restored and the subject recovers.

A Tetracyclic Benzamide Derivative and the other therapeutic agent can act 30 additively or, in one embodiment synergistically. In one embodiment a Tetracyclic Benzamide Derivative is administered concurrently with another therapeutic agent. In one embodiment a composition comprising an effective amount of a Tetracyclic Benzamide Derivative and an effective amount of another therapeutic agent can be administered. Alternatively, a composition comprising an effective amount of a

Tetracyclic Benzamide Derivative and a different composition comprising an effective amount of another therapeutic agent can be concurrently administered. In another embodiment an, effective amount of a Tetracyclic Benzamide Derivative is administered prior or subsequent to administration of an effective amount of another therapeutic agent.

- 5 In this embodiment the Tetracyclic Benzamide Derivative is administered while the other therapeutic agent exerts its therapeutic effect, or the other therapeutic agent is administered while the Tetracyclic Benzamide Derivative exerts its preventative or therapeutic effect for treating or preventing a Condition.

- A composition of the invention is prepared by a method comprising admixing a
10 Tetracyclic Benzamide Derivative or a pharmaceutically acceptable salt and a pharmaceutically acceptable carrier or vehicle. Admixing can be accomplished using methods well known for admixing a compound (or salt) and a pharmaceutically acceptable carrier or vehicle. In one embodiment the Tetracyclic Benzamide Derivative or the pharmaceutically acceptable salt of the Compound is present in the composition in
15 an effective amount.

4.17.3 Kits

The invention encompasses kits that can simplify the administration of a Tetracyclic Benzamide Derivative to a subject.

- 20 A typical kit of the invention comprises a unit dosage form of a Tetracyclic Benzamide Derivative. In one embodiment the unit dosage form is a container, which can be sterile, containing an effective amount of a Tetracyclic Benzamide Derivative and a pharmaceutically acceptable carrier or vehicle. The kit can further comprise a label or printed instructions instructing the use of the Tetracyclic Benzamide Derivative to treat or
25 prevent a Condition. The kit can also further comprise a unit dosage form of another therapeutic agent, for example, a container containing an effective amount of the other therapeutic agent. In one embodiment the kit comprises a container containing an effective amount of a Tetracyclic Benzamide Derivative and an effective amount of another therapeutic agent. Examples of other therapeutic agents include, but are not
30 limited to, those listed above.

Kits of the invention can further comprise a device that is useful for administering the unit dosage forms. Examples of such a device includes, but are not limited to, a syringe, a drip bag, a patch, an inhaler, and an enema bag.

The following examples are set forth to assist in understanding the invention and should not, of course, be construed as specifically limiting the invention described and claimed herein. Such variations of the invention, including the substitution of all equivalents now known or later developed, which would be within the purview of those skilled in the art, and changes in Formulation or minor changes in experimental design, are to be considered to fall within the scope of the invention incorporated herein.

5. EXAMPLES

5.1.1 Example 1: Preparation of Illustrative Tetracyclic Benzamide Derivatives

5.1.2 General Methods

Proton NMR spectra were obtained using a Varian 300 MHz spectrophotometer and chemical shift values (δ) are reported in parts per million (ppm). TLC was performed using TLC plates precoated with silica gel 60 F-254, and preparative TLC was performed using precoated Whatman 60A TLC plates. All intermediates and final compounds were characterized on the basis of ^1H NMR and MS data.

15 a) **Preparation of 4-Phenyl-3-isocoumarincarboxylic acid (3a):**

Following the procedure described in Natsugary *et al.*, *J Med. Chem.* 38, 3106-3120 (1995), compound **3a** (Scheme 1) was synthesized. A suspension of **1a** (33.9 g, 0.15 mol) (Scheme 1), potassium carbonate (41.4 g, 0.3 mol) and diethyl bromomalonate (28.17 mL, 0.165 mol) in DMF (250 mL) was stirred at room temperature for 15 h. The reaction mixture was then diluted using cold water and extracted into ethyl acetate. The ethyl acetate layer was dried over sodium sulfate, and concentrated *in vacuo* to afford a crude residue to which was added glacial acetic acid (1.0 L) and concentrated HCl (800 mL). The resulting solution was heated at reflux for 6 h. The reaction mixture was cooled to room temperature and poured on ice water. The solid precipitate was filtered, washed with water and dried using vacuum to provide compound **3a** as a white solid. Yield = 32.6 g (84%).

b) **Preparation of 4-Phenyl-3-isoquinolinonecarboxylic acid (4a)(Scheme 1):**

A stirred suspension of **3a** (1.4 g, 0.0052 mol) in ammonia-methanol (7 N, 125 mL) was heated at reflux for 23 h, then cooled to room temperature. The reaction mixture

was concentrated *in vacuo*, and the residue obtained was acidified with 10% aqueous HCl. The resulting solid was filtered, washed with water and dried under vacuum to provide compound **4a**. Yield = 1.225 g (89%).

c) Preparation of 6H, 7-oxoindeno[2,1-c]isoquinolinone (5a) (Scheme 1):

5 *Using PPA:*

To a stirred suspension of compound **4a** (0.225 g, 0.85 mmol) in xylenes (20 mL) was added polyphosphoric acid (0.600 g). The resulting reaction mixture was heated at reflux for 6 h. The reaction mixture was cooled to room temperature and concentrated *in vacuo* to provide a crude residue, which was poured on ice. The resulting solid was
10 filtered, washed with water, and dried under vacuum to provide compound **5a**. Yield = 155 mg (74%).

Using chlorosulfonic acid:

Similarly, compound **4a** (500 mg, 0.0019 mol) was suspended up in chlorosulfonic acid (2.5 mL) at 0°C for 5 min, and the reaction mixture was stirred at
15 room temperature for 5 min. After the reaction mixture became homogeneous, it was slowly poured on ice. The resultant red-colored solid precipitate was filtered, washed with water, and dried to provide compound **5a**. Yield = 395 mg (85%).

d) Reduction of (5a) to 6H,7H-Hydroxyindeno[2,1-c]isoquinolin-5-one (6a) (Compounds of Formula IIa) (Scheme 1):

20 To a stirred suspension of **5a** (1.0 g, 4.0 mmol) in methanol (25 mL) was slowly added solid sodium borohydride (385 mg) at room temperature. The resulting reaction mixture was stirred for 15 min. The reaction mixture was then poured on an ice-cold 1 N HCl solution, and the resulting solid was filtered, washed with water, and dried under vacuum to provide compound **6a** (Formula IIa). Yield = 0.940 g (93%).

25 **e) Preparation of 5-Oxo-5,7-dihydro-6H-indeno[2,1-c]isoquinoline-9-sulfonyl chloride (10a) (Scheme 1):**

Compound **9a** (210 mg, 0.9 mmol) was slowly added to a solution of chlorosulphonic acid (2.0 mL) at 0°C for 5 min, and at room temperature for 5 min. After the reaction mixture became homogeneous, it was slowly poured on ice. The solid that

precipitated was filtered, washed with water, and dried to provide compound **10a** (180 mg, 60%).

f) 5-Oxo-5,7-dihydro-6H-indeno[2,1-c]isoquinoline-9-sulfonic acid (3-morpholin-4-yl-propyl)-amide (11a) (Scheme 1):

5 A suspension of **10a** (110 mg, 0.33 mmol) in methylene chloride (10 mL) was treated with 4-(3-morpholino)-1-propylamine (240 mg, 1.66 mmol) and triethylamine (1 eq), and the reaction mixture was stirred at room temperature for 1 h. The resulting mixture was diluted with ethyl acetate, and the solid that precipitated was filtered, washed with ether and dried to provide compound **11a**. Yield = 65 mg (45%).

10 **g) Preparation of 2-(bromo-methoxycarbonyl-methyl)-benzoic acid methyl ester (α -Bromodimethylhomophthalate) (13a) (Scheme 2):**

Dimethylhomophthalate (83.1 g, Aldrich Chemical Co.) was dissolved in dichloromethane (2 L), and N-bromosuccinimide (121 g, 1.7 eq) was added. The resulting suspension was irradiated for 18 h with a 500 wt quartz-halogen lamp, which
15 brought the reaction mixture to reflux. The reaction mixture was then washed sequentially with saturated aqueous sodium bicarbonate (4 L), saturated aqueous sodium bisulfite (2 L), and saturated aqueous sodium chloride (2 L). The organic phase was dried using sodium sulfate with a small amount of silica added to remove polar impurities. The organic phase was filtered and concentrated *in vacuo* to provide compound **13a** (Scheme
20 2) as a dark orange oil. Yield = 120.3 g (100%).

h) Preparation of 8-Methoxy-6H-11-oxa-6-aza-benzo[a]fluoren-5-one (15a) (Scheme 2):

A mixture of α -Bromodimethylhomophthalate (**13a**) (1.16 g) and 2-hydroxy-5-methoxy-benzonitrile (**14b**), 0.6 g, 4 mmol, 1.0 eq) was dissolved by warming in
25 acetonitrile (6 mL). Triethylamine (5.6 mL, 10 eq) was then added. The reaction mixture was heated at reflux for 48 h under inert atmosphere, then cooled to room temperature. The reaction mixture was diluted with saturated sodium bicarbonate (40 mL), and the resulting suspension was allowed to stir for 2 h, and was then filtered. The resulting filtercake was washed sequentially with 1 N HCl (2 x 50 mL), acetonitrile (2 x 50 mL)
30 and dichloromethane (50 mL), then dried in a vacuum oven at 50°C for three days to provide compound **15a** as a white solid. Yield = 0.81 mg (76%).

i) Preparation of 8-Hydroxy-6*H*-11-oxa-6-aza-benzo [*a*]fluoren-5-one (15b) (Scheme 2):

8-Methoxy-6*H*-11-oxa-6-aza-benzo[*a*]fluoren-5-one (**15a**) (5.0 g) was cooled using an ice bath, and boron tribromide (1 M in methylene chloride, 95 mL, 95 mmol, 5 eq) was added in a steady stream under nitrogen. The reaction was heated at reflux under inert atmosphere for 2 h, then cooled to room temperature and poured into water (150 mL). The resulting suspension was allowed to stir for 1 h, filtered, and the solids were washed with water (2 x 200 mL). The solids were then suspended in of 5 N sodium hydroxide (600 mL), then using heating. The resulting solution was cooled to 0°C using an ice bath and the solution acidified to pH 1 using con c. HCl. The resulting precipitate was vacuum filtered, and the solids were washed sequentially with water (3 x 300 mL), and diethyl ether (300 mL), then dried overnight using a vacuum oven at 50°C to provide compound **15b** as a gray solid. Yield = 4.74 g (100%).

j) Preparation of 6*H*-11-oxa-6-aza-benzo[*a*]fluoren-5-one (15c):

Using the method of Example **h** and substituting **14b** with 2-hydroxy-benzonitrile (**14a**), compound **15c** was prepared.

k) Preparation of 9-Methoxy-6*H*-11-oxa-6-aza-benzo[*a*]fluoren-5-one (15d):

Using the method of Example **h** and substituting **14b** with 2-hydroxy-4-methoxy-benzonitrile (**14c**), compound **15d** was prepared.

l) Preparation of 9-Hydroxy-6*H*-11-oxa-6-aza-benzo[*a*]fluoren-5-one (15e):

Using the method of Example **i** and substituting compound **15a** with compound **15d**, compound **15e** was prepared.

m) Preparation of Compound 16a (Scheme 2):

To a solution of compound **15b** (0.755 mmol) in acetone (4 mL) was added 2-bromoacetic acid (2.1 eq) and potassium carbonate (1.04 g, 10 eq). The resultant mixture was heated at reflux for 15 h under nitrogen atmosphere. The reaction mixture was poured into 20 mL of 1 N aqueous sodium hydroxide, stirred 0.5 h, and filtered. The solids were washed twice with 10 mL volumes of water, then stirred for 1 h in 20 mL of 1 N aqueous hydrochloric acid. The solids were vacuum filtered, washed twice with 10 mL

of water, twice with 10 mL of ether, and dried *in vacuo* to provide compound **16a** in 75% yield.

n) Preparation of Compound 16b:

Using the method of Example **m** and substituting 2-bromoacetic acid with
5 3-bromo-1-propanol, compound **16b** was prepared from compound **15b**.

o) Preparation of Compound 16c:

Using the method of Example **m** and substituting 2-bromoacetic acid with
5-bromo-1-pentanol, compound **16c** was prepared from compound **15b**.

p) Preparation of Compound 16d:

10 Using the method of Example **m** and substituting 2-bromoacetic acid with
6-bromo-1-hexanol, compound **16d** was prepared from compound **15b**.

q) Preparation of Compound 16e:

Using the method of Example **m** and substituting 2-bromoacetic acid with
5-bromo-1-pentanoic acid, compound **16e** was prepared from compound **15b**.

15 **r) Preparation of Compound 16f:**

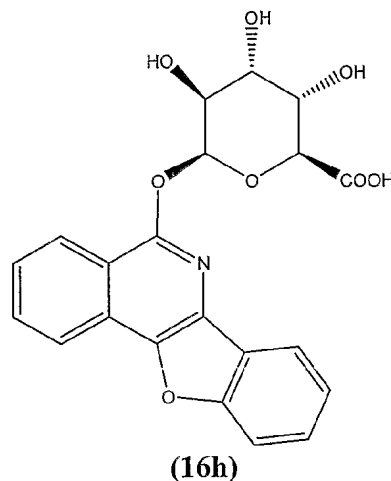
To a solution of compound **15c** (0.755 mmol) in acetone (4 mL) was added
iodomethane (52 μ L, 1.1 eq) and potassium carbonate (1.04 g, 10 eq). The resultant
mixture was heated at reflux for 15 h under nitrogen atmosphere. The reaction mixture
was poured into 20 mL of 1 N aqueous sodium hydroxide, stirred 0.5 h, and filtered. The
20 resultant solids were washed twice with 10 mL of water, then stirred for 1 h in 20 mL of 1
N aqueous hydrochloric acid. The resultant solids were vacuum filtered, washed twice
with 10 mL of water, twice with 10 mL of ether, and dried *in vacuo* to provide 165 mg
(78%) of compound **16f**.

s) Preparation of Acetic acid 11-oxa-6-aza-benzo[a]fluoren-5-yl ester (16g):

25 To a solution of compound **15c** (500 mg, 2.13 mmol) in pyridine (10 mL) was
added acetic anhydride (4 mL). The resultant mixture was heated at 100°C for 9 h, then
cooled slowly to room temperature overnight. The solvent was removed on the rotary

evaporator and the residual oil was extracted into 50 mL ethyl acetate. The organic layer was washed with 50 mL of 1 N aqueous hydrochloric acid, dried (sodium sulfate), and the solvent removed *in vacuo* to provide 308 mg (52% yield) of compound **16g** as a white powder.

5 **t) Preparation of 1-(11-Oxa-6-aza-benzo[*a*]fluoren-5-yloxy)- β -D-glucuronic acid (16h):**



Preparation of methyl ester intermediate:

10 6*H*-11-Oxa-6-aza benzo[*a*]fluoren-5-one (**15c**) (500 mg, 2.13 mmol) (Scheme 2), silver carbonate (2.35 g, 4 eq), 4 angstrom molecular sieves (1.8 g), and 100 mL toluene were combined in a 500 mL 3- neck flask equipped with a dean-stark trap, a condenser, and an addition funnel. The mixture was brought to reflux under nitrogen atmosphere, and 30 mL of distillate were collected over 1 h. The addition funnel was charged with
 15 acetobromo- α -D-glucuronic acid methyl ester (930 mg, 1.1 eq) dissolved in 25 mL toluene, and this solution was added dropwise over 0.5 h to the refluxing reaction mixture. The reaction mixture was heated at reflux for another 6 h, then slowly cooled to room temperature overnight. The resulting suspension was vacuum filtered to remove solids, and the filter cake was washed three times with 100 mL of ethyl acetate. The
 20 filtrate was concentrated to an oil on the rotary evaporator. The oil was loaded directly on a column of 30 g silica and purified by flash chromatography, eluting with 19:1 dichloromethane: ethyl acetate to provide of the intermediate compound 1-(11-Oxa-6-aza-benzo[*a*]fluoren-5-yloxy)2,3,4-tri-*O*-acetyl- β -D-glucuronic acid methyl ester as a white powder.

Ester Hydrolysis to Provide Compound 16h:

1-(11-Oxa-6-aza-benzo[*a*]fluoren-5-yloxy)-2,3,4-tri-*O*-acetyl- β -D-glucuronic acid methyl ester (779 mg, 1.81 mmol) was dissolved in 30 mL acetone, and 8 mL of 1 N aqueous sodium hydroxide followed by 12 mL water were added dropwise. The resultant mixture was stirred for 0.5 h, over which time a precipitate formed. The reaction mixture was titrated to pH 5 with 1 N aqueous hydrochloric acid and vacuum filtered. The resultant solids were washed with 30 mL of acetone and dried *in vacuo* to give 288 mg (50%) of compound **16h** as a white powder.

u) 5,9-Dimethoxy-11-oxa-6-aza-benzo[*a*]fluorine (16i):

9-Methoxy-6*H*-11-oxa-6-aza-benzo[*a*]fluorine-5-one (200 mg, 0.755 mmol) was suspended in 4 mL acetone and to the suspension were added . Methyl iodide (52 μ L, 1.1 eq) and potassium carbonate (1.04 g, 10 eq). The mixture was allowed to reflux overnight under nitrogen atmosphere. Additional methyl iodide (25 μ L, 0.5 eq) and acetone (4 mL) were added and the reaction refluxed overnight under nitrogen. The reaction mixture was poured into 20 mL of 1 N aqueous sodium hydroxide, stirred 0.5 h, and filtered. The resultant solids were washed twice with 10 mL of water, then stirred for 1 h in 20 mL of 1 N aqueous hydrochloric acid. The solids were vacuum filtered, washed twice with 10 mL of water, then twice with 10 mL volumes of ether. The solids were dried *in vacuo* to give 165 mg (78%) of compound **16i** as a white powder.

20 v) Preparation of Compound 16j:

Using the method of Example **m** and substituting: 1) 2-bromoacetic acid with 3-bromo-1-propanol, and 2) compound **15b** with compound **15c**, compound **16j** was prepared.

w) Preparation of Compound 16k

25 Using the method of Example **m** and substituting: 1) 2-bromoacetic acid with 6-bromo-1-hexanol, and 2) compound **15b** with compound **15c**, compound **16k** was prepared.

x) Preparation of 9-Methyl-6*H*-11-oxa-6,10-diaza-benzo[*a*]fluoren-5-one (26a)

To a solution of α -bromodimethylhomophthalate (2.00 g, 6.97 mmol) in DMF (15 mL) was added 3-cyano-2-hydroxy-6-methylpyridine (1.03 g, 1.1 eq) and potassium carbonate (4.82 g, 5 eq). The resulting mixture was allowed to stir at 100°C for 4 h under inert atmosphere. The reaction was cooled to room temperature and concentrated *in vacuo*. The resulting solid residue was diluted with 1 N aqueous HCl (60 mL) and stirred for 30 min. The resulting suspension was filtered and the solids were washed with water. The aqueous filtrate was extracted with EtOAc (2 x 50 mL). The collected solids were added to the combined EtOAc extracts, and the resulting solution was dried over sodium sulfate, filtered and concentrated *in vacuo* to afford a crude residue. The crude residue was recrystallized from toluene at -20°C over 18 h, vacuum filtered and dried to provide compound **26a** as a yellow solid. Yield = 500 mg (29%).

5.1.3 Example 2. Effect of Illustrative Tetracyclic Benzamide Derivatives on PARP activity in cultured macrophages, using a whole-cell based assay and a purified enzyme assay.

Demonstration of illustrative Tetracyclic Benzamide Derivatives' ability to inhibit PARP and prevent peroxynitrite induced cytotoxicity was shown using methods described in Virag et al., *Br. J. Pharmacol.*, 1999, 126(3):769-77; and *Immunology* 1998, 94(3):345-55. RAW mouse macrophages were cultured in DMEM medium with high glucose and supplemented with 10% fetal bovine serum. Cells were used at 80% confluence in 12-well plates. Cells were pretreated with various concentrations (100 nM - 1 μ M) of a Tetracyclic Benzamide Derivative for 10 min. Peroxynitrite, a prototypical oxidant which induces DNA single strand breakage, was used to induce PARP activation. Peroxynitrite was diluted in phosphate buffered saline (PBS) (pH 11.0) and added to the cells in a bolus of 50 μ l. Cells were then incubated for 20 min. Peroxynitrite was decomposed by incubation for 30 min at pH 7.0, used as a control, and failed to influence the parameter studied. After the 20 min incubation, the cells were spun, the medium was aspirated and the cells were resuspended in 0.5 mL assay buffer (56 mM HEPES pH 7.5, 28 mM KCl, 28 mM NaCl, 2 mM MgCl₂, 0.01% w/v digitonin and 0.125 μ M NAD⁺ and 0.5 μ Ci/ml ³H-NAD⁺). Following an incubation in assay buffer, (10 min at 37°C), PARP activity was measured as follows: 200 μ l ice cold 50% w/v TCA was added and the samples were incubated for 4 h at 4°C. Samples were then spun (10 min @ 10,000 g) and pellets washed twice with ice cold 5% w/v TCA and solubilized overnight in 250 μ l 2% w/v SDS/0.1 N NaOH at 37°C. The contents of the tubes were added to 6.5 mL

ScintiSafe Plus scintillation liquid (Fisher Scientific) and radioactivity was determined using a liquid scintillation counter (Wallac, Gaithersburg, MD). The results shown in Table 3 demonstrate that the illustrative Tetracyclic Benzamide Derivatives significantly and dose-dependently inhibit the activation of PARP in the macrophage assay.

5

Table 3. Inhibitory effect of various novel substituted Tetracyclic Benzamide Derivatives on PARP activation in cultured murine macrophages.

Compound No.	% PARP inhibition at 1 μ M	% PARP inhibition at 300 nM	% PARP inhibition at 100 nM
9a	70	56	NT
11	70	9	NT
16a	56	64	47
16b	29	26	25
16c	68	47	39
16d	NT	38	3
16e	57	56	33
16f	56	59	40
16g	67	66	40
16h	NT	56	32
26a	61	54	36

NT-Not Tested

- 10 The potency of inhibition on purified PARP enzyme was subsequently determined for selected Tetracyclic Benzamide Derivatives, and the potency was compared with that of 3-aminobenzamide, a prototypical benchmark PARP inhibitor. The assay was performed in 96 well ELISA plates according to instructions provided with a commercially available PARP inhibition assay kit (Trevigen, Gaithersburg, MD).
- 15 Briefly, wells were coated with 1 mg/mL histone (50 μ l/well) at 4°C overnight. Plates were then washed four times with PBS and then blocked by adding 50 μ l Strep-Diluent (supplied with the kit). After incubation (1 h, room temperature), the plates were washed four times with PBS. Appropriate dilutions of PARP inhibitors were combined with 2x

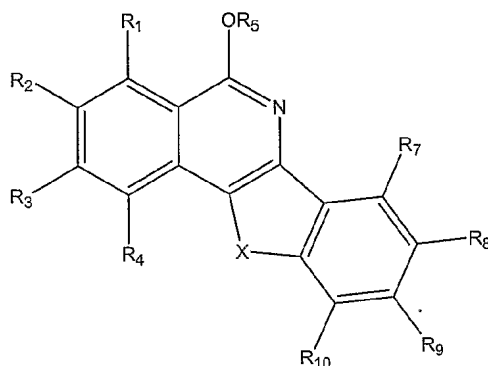
PARP cocktail (1.95 mM NAD⁺, 50 μM biotinylated NAD⁺ in 50 mM TRIS pH 8.0, 25 mM MgCl₂) and high specific activity PARP enzyme (both were supplied with the kit) in a volume of 50 μl. The reaction was allowed to proceed for 30 min at room temperature. After 4 washes in PBS, incorporated biotin was detected by peroxidase-conjugated streptavidin (1:500 dilution) and TACS Sapphire substrate. The assay confirmed the results of the macrophage-based PARP assay. For example, the PARP inhibitor **16a** exerted 56% inhibition of PARP activity in this assay at 1 μM, and thus was approximately 56,000 times more potent than the reference compound 3-aminobenzamide at this concentration. These results indicate that compounds 9a, 11, 16a-16h and 26a, illustrative Tetracyclic Benzamide Derivatives, are useful for treating or preventing a Condition.

The present invention is not to be limited in scope by the specific embodiments disclosed in the examples which are intended as illustrations of a few aspects of the invention and any embodiments that are functionally equivalent are within the scope of this invention. Indeed, various modifications of the invention in addition to those shown and described herein will become apparent to those skilled in the art and are intended to fall within the scope of the appended claims.

A number of references have been cited, the entire disclosures of which have been incorporated herein in their entirety.

What is claimed is:

1. A compound of the Formula:



(I)

or a pharmaceutically acceptable salt or hydrate thereof,

wherein:

R₅ is -C₁-C₁₀ alkyl, halo-substituted-(C₁-C₅ alkyl), HO-substituted-(C₁-C₅ alkyl), carboxy-substituted-(C₁-C₅ alkyl), -C(O)-C₁-C₁₀ alkyl, -C(O)-aryl, -C(O)-(3- to 7-membered monocyclic heterocycle), -C(O)-(7- to 10-membered bicyclic heterocycle) or -glycoside;

X is -C(O)-, -CH₂-, -CH(halo)-, -(C(OH)((CH₂)_nCH₃))-, -(C(OH)(aryl))-, -O-, -NH-, -S-, -CH(NR₁₁R₁₂)- or -N(SO₂Y)-, wherein Y is -OH, -NH₂, -(C₁-C₅ alkyl)-(3- to 7-membered monocyclic heterocycle), or -(C₁-C₅ alkyl)-(7- to 10-membered bicyclic heterocycle) and n is an integer ranging from 0-5;

R₁₁ and R₁₂ are independently -hydrogen or -C₁-C₉ alkyl, or N, R₁₁ and R₁₂ are taken together to form a -(nitrogen-containing 3- to 7-membered monocyclic heterocycle), or a -(nitrogen-containing 7- to 10-membered bicyclic heterocycle);

R₁, R₂, R₃, R₄, R₇, R₈, R₉ and R₁₀ are independently -hydrogen, -halo, -hydroxy, -O-(C₁-C₅ alkyl), -C₁-C₁₀ alkyl, halo-substituted-(C₁-C₅ alkyl), -C₂-C₁₀ alkenyl, -C₃-C₈-cycloalkyl, -aryl, -NH₂, amino-substituted-(C₁-C₅ alkyl), -C(O)OH, -C(O)O(C₁-C₅ alkyl), -OC(O)(C₁-C₅ alkyl), NO₂ or -A-B;

A is -SO₂-, -SO₂NH-, -NHCO-, -NHCONH-, -O-, -CO-, -OC(O)-, -C(O)O-, -CONH-, -CON(C₁-C₄ alkyl)-, -NH-, -CH₂-, -S- or -C(S)-;

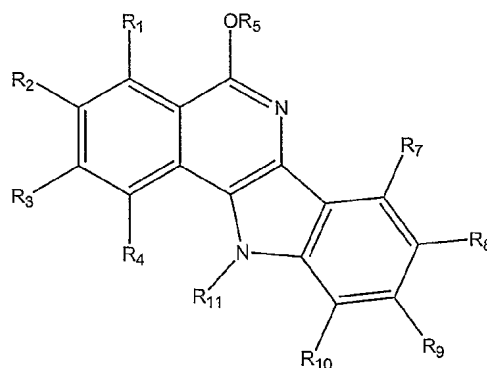
B is -C₁-C₁₀ alkyl, -C₂-C₁₀ alkenyl, -(nitrogen-containing 3- to 7-membered monocyclic heterocycle), -(nitrogen-containing 7- to 10-membered bicyclic heterocycle), -(3- to 7-membered monocyclic heterocycle), -(7- to 10-membered bicyclic heterocycle),

- C₃-C₈ cycloalkyl, -aryl, -NZ₁Z₂, -(C₁-C₅ alkylene)-NZ₁Z₂, amino-substituted-(C₁-C₅ alkyl), -N(C₁-C₅ alkyl)(C₁-C₅ alkyl), -(C₁-C₅ alkyl)-(3- to 7-membered monocyclic heterocycle), or -(C₁-C₅ alkyl)-(7- to 10-membered bicyclic heterocycle), - (H₂NC(O))-substituted aryl, -(H₂NC(O))-substituted pyridyl, -C(O)OH,
- 5 -C(O)O-(C₁-C₅ alkyl), -C(O)O-phenyl or -C(NH)NH₂, each of which is unsubstituted or substituted with one or more of -O-(C₁-C₅ alkyl), -halo, halo-substituted-(C₁-C₅ alkyl), HO-substituted-(C₁-C₅ alkyl), amino-substituted-(C₁-C₅ alkyl), -hydroxy, -NO₂, -NH₂, -CN, -NH(C₁-C₅ alkyl), -N(C₁-C₅ alkyl)(C₁-C₅ alkyl), -(nitrogen-containing 3- to 7-membered monocyclic heterocycle), 7- to 10-membered bicycloheterocyclic amine, -C₁-
- 10 C₁₀ alkyl, -C₂-C₁₀ alkenyl, -C₂-C₁₀ alkynyl, -aryl, -benzyl, -(C(O)NH₂)-substituted(C₁-C₅ alkyl), carboxy-substituted-(C₁-C₅ alkyl), -C(O)OH, -C₁-C₅-alkylene-C(O)O-(C₁-C₅ alkyl) or -C₁-C₅ alkylene-OC(O)-(C₁-C₅ alkyl); and

- Z₁ and Z₂ are independently -H or -C₁-C₁₀ alkyl, which is unsubstituted or substituted with one or more of -halo, -OH or -N(Z₃)(Z₄), where Z₃ and Z₄ are
- 15 independently, -H or -C₁-C₅ alkyl, which is unsubstituted or substituted with one or more of -halo, -hydroxy or -NH₂; or N, Z₃ and Z₄ are taken together to form a -(nitrogen-containing 3- to 7-membered monocyclic heterocycle) or a -(nitrogen-containing 7- to 10-membered bicyclic heterocycle); or N, Z₁ and Z₂ are taken together to form a -(nitrogen-containing 3- to 7-membered monocyclic heterocycle), or a -(nitrogen-
- 20 containing 7- to 10-membered bicyclic heterocycle).

2. The compound or the pharmaceutically acceptable salt of the compound of claim 1, wherein X is-O-.

3. A compound of the Formula



25

(Ib)

or a pharmaceutically acceptable salt or hydrate thereof,

wherein:

R_5 is $-C_1-C_{10}$ alkyl, halo-substituted- (C_1-C_5) alkyl, HO-substituted- (C_1-C_5) alkyl, carboxy-substituted- (C_1-C_5) alkyl, $-C(O)-C_1-C_{10}$ alkyl, $-C(O)-$ aryl, $-C(O)-(3- \text{ to } 7-$ membered monocyclic heterocycle), $-C(O)-(7- \text{ to } 10-$ membered bicyclic heterocycle) or - glycoside;

R_{11} $-H$, $-C_1-C_5$ alkyl, $-$ aryl, $-C(O)-C_1-C_5$ alkyl, or $-SO_2Y$, wherein Y is $-OH$, $-NH_2$ or $-(C_1-C_5)$ alkyl- $(3- \text{ to } 7-$ membered monocyclic heterocycle), or $-(C_1-C_5)$ alkyl- $(7- \text{ to } 10-$ membered bicyclic heterocycle);

$R_1, R_2, R_3, R_4, R_7, R_8, R_9$ and R_{10} are independently $-hydrogen$, $-halo$, $-hydroxy$, $-O-(C_1-C_5)$ alkyl, $-C_1-C_{10}$ alkyl, halo-substituted- (C_1-C_5) alkyl, $-C_2-C_{10}$ alkenyl, $-C_3-C_8$ -cycloalkyl, $-aryl$, $-NH_2$, amino-substituted- (C_1-C_5) alkyl, $-C(O)OH$, $-C(O)O(C_1-C_5)$ alkyl, $-OC(O)(C_1-C_5)$ alkyl, NO_2 or $-A-B$;

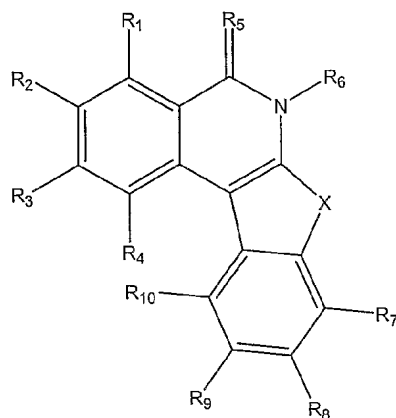
A is $-SO_2-$, $-SO_2NH-$, $-NHCO-$, $-NHCONH-$, $-O-$, $-CO-$, $-OC(O)-$, $-C(O)O-$, $-CONH-$, $-CON(C_1-C_4)$ alkyl-, $-NH-$, $-CH_2-$, $-S-$ or $-C(S)-$;

B is $-C_1-C_{10}$ alkyl, $-C_2-C_{10}$ alkenyl, $-(\text{nitrogen-containing } 3- \text{ to } 7-$ membered monocyclic heterocycle), $-(\text{nitrogen-containing } 7- \text{ to } 10-$ membered bicyclic heterocycle), $-(3- \text{ to } 7-$ membered monocyclic heterocycle), $-(7- \text{ to } 10-$ membered bicyclic heterocycle), $-C_3-C_8$ cycloalkyl, $-aryl$, $-NZ_1Z_2$, $-(C_1-C_5)$ alkylene- NZ_1Z_2 , amino-substituted- (C_1-C_5) alkyl, $-N(C_1-C_5)$ alkyl- (C_1-C_5) alkyl, $-(C_1-C_5)$ alkyl- $(3- \text{ to } 7-$ membered monocyclic heterocycle), or $-(C_1-C_5)$ alkyl- $(7- \text{ to } 10-$ membered bicyclic heterocycle), $-(H_2NC(O))$ -substituted aryl, $-(H_2NC(O))$ -substituted pyridyl, $-C(O)OH$, $-C(O)O-(C_1-C_5)$ alkyl, $-C(O)O$ -phenyl or $-C(NH)NH_2$, each of which is unsubstituted or substituted with one or more of $-O-(C_1-C_5)$ alkyl, $-halo$, halo-substituted- (C_1-C_5) alkyl, HO-substituted- (C_1-C_5) alkyl, amino-substituted- (C_1-C_5) alkyl, $-hydroxy$, $-NO_2$, $-NH_2$, $-CN$, $-NH(C_1-C_5)$ alkyl, $-N(C_1-C_5)$ alkyl- (C_1-C_5) alkyl, $-(\text{nitrogen-containing } 3- \text{ to } 7-$ membered monocyclic heterocycle), $7- \text{ to } 10-$ membered bicycloheterocyclic amine, $-C_1-C_{10}$ alkyl, $-C_2-C_{10}$ alkenyl, $-C_2-C_{10}$ alkynyl, $-aryl$, $-benzyl$, $-(H_2NC(O))$ -substituted- (C_1-C_5) alkyl, carboxy-substituted- (C_1-C_5) alkyl, $-C(O)OH$, $-C_1-C_5$ -alkylene- $C(O)O-(C_1-C_5)$ alkyl or $-C_1-C_5$ alkylene- $OC(O)-(C_1-C_5)$ alkyl; and

Z_1 and Z_2 are independently $-H$ or $-C_1-C_{10}$ alkyl, which is unsubstituted or substituted with one or more of $-halo$, $-OH$ or $-N(Z_3)(Z_4)$, where Z_3 and Z_4 are independently, $-H$ or $-C_1-C_5$ alkyl, which is unsubstituted or substituted with one or more of $-halo$, $-hydroxy$ or $-NH_2$; or N , Z_3 and Z_4 are taken together to form a $-(\text{nitrogen-}$

containing 3- to 7-membered monocyclic heterocycle) or a -(nitrogen-containing 7- to 10-membered bicyclic heterocycle); or N, Z₁ and Z₂ are taken together to form a -(nitrogen-containing 3- to 7-membered monocyclic heterocycle), or a -(nitrogen-containing 7- to 10-membered bicyclic heterocycle).

5 4. A compound of the Formula



(II)

or a pharmaceutically acceptable salt or hydrate thereof,
wherein:

10 R₅ is O, NH or S;

R₆ is -H or C₁-C₄ alkyl;

X is -C(O)-, -CH₂-, -CH(halo)-, -(C(OH)((CH₂)_nCH₃))-, -(C(OH)(aryl))-, -O-, -NH-, -S-, -CH(NR₁₁R₁₂)- or -N(SO₂Y)-, wherein Y is -OH, -NH₂, -(C₁-C₅ alkyl)-(3- to 7-

15 heterocycle) and n is an integer ranging from 0-5;

R₁₁ and R₁₂ are independently -hydrogen or -C₁-C₉ alkyl, or N, R₁₁ and R₁₂ are taken together to form a -(nitrogen-containing 3- to 7-membered monocyclic heterocycle), or a -(nitrogen-containing 7- to 10-membered bicyclic heterocycle);

20 R₁, R₂, R₃, R₄, R₇, R₈, R₉ and R₁₀ are independently -hydrogen, -halo, -hydroxy, -O-(C₁-C₅ alkyl), -C₁-C₁₀ alkyl, halo-substituted-(C₁-C₅ alkyl), -C₂-C₁₀ alkenyl, -C₃-C₈-cycloalkyl, -aryl, -NH₂, amino-substituted-(C₁-C₅ alkyl), -C(O)OH, -C(O)O(C₁-C₅ alkyl), -OC(O)(C₁-C₅ alkyl), NO₂ or -A-B;

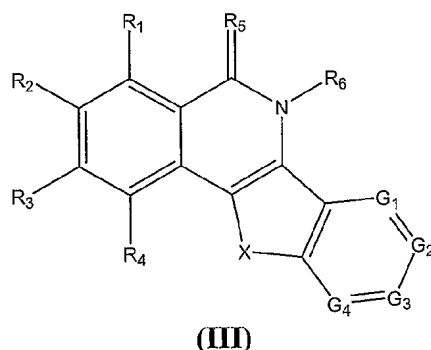
A is -SO₂-, -SO₂NH-, -NHCO-, -NHCONH-, -O-, -CO-, -OC(O)-, -C(O)O-, -CONH-, -CON(C₁-C₄ alkyl)-, -NH-, -CH₂-, -S- or -C(S)-;

25 B is -C₁-C₁₀ alkyl, -C₂-C₁₀ alkenyl, -(nitrogen-containing 3- to 7-membered monocyclic heterocycle), -(nitrogen-containing 7- to 10-membered bicyclic heterocycle),

- (3- to 7-membered monocyclic heterocycle), -(7- to 10-membered bicyclic heterocycle),
 -C₃-C₈ cycloalkyl, -aryl, -NZ₁Z₂, -(C₁-C₅ alkylene)-NZ₁Z₂, amino-substituted-(C₁-C₅
 alkyl), -N(C₁-C₅ alkyl)(C₁-C₅ alkyl), -(C₁-C₅ alkyl)-(3- to 7-membered
 monocyclic heterocycle), or -(C₁-C₅ alkyl)-(7- to 10-membered bicyclic heterocycle), -
 5 (H₂NC(O))-substituted aryl, -(H₂NC(O))-substituted pyridyl, -C(O)OH,
 -C(O)O-(C₁-C₅ alkyl), -C(O)O-phenyl or -C(NH)NH₂, each of which is unsubstituted or
 substituted with one or more of -O-(C₁-C₅ alkyl), -halo, halo-substituted-(C₁-C₅ alkyl),
 HO-substituted-(C₁-C₅ alkyl), amino-substituted-(C₁-C₅ alkyl), -hydroxy, -NO₂, -NH₂,
 -CN, -NH(C₁-C₅ alkyl), -N(C₁-C₅ alkyl)(C₁-C₅ alkyl), -(nitrogen-containing 3- to 7-
 10 membered monocyclic heterocycle), 7- to 10-membered bicycloheterocyclic amine, -C₁-
 C₁₀ alkyl, -C₂-C₁₀ alkenyl, -C₂-C₁₀ alkynyl, -aryl, -benzyl, -(H₂NC(O))-substituted(C₁-
 C₅ alkyl), carboxy-substituted-(C₁-C₅ alkyl), -C(O)OH, -C₁-C₅-alkylene-C(O)O-(C₁-C₅
 alkyl) or -C₁-C₅ alkylene-OC(O)-(C₁-C₅ alkyl); and
 Z₁ and Z₂ are independently -H or -C₁-C₁₀ alkyl, which is unsubstituted or
 15 substituted with one or more of -halo, -OH or -N(Z₃)(Z₄), where Z₃ and Z₄ are
 independently, -H or -C₁-C₅ alkyl, which is unsubstituted or substituted with one or more
 of -halo, -hydroxy or -NH₂; or N, Z₃ and Z₄ are taken together to form a -(nitrogen-
 containing 3- to 7-membered monocyclic heterocycle) or a -(nitrogen-containing 7- to
 10-membered bicyclic heterocycle); or N, Z₁ and Z₂ are taken together to form a -
 20 (nitrogen-containing 3- to 7-membered monocyclic heterocycle), or a -(nitrogen-
 containing 7- to 10-membered bicyclic heterocycle).

5. The compound or the pharmaceutically acceptable salt of the compound of claim 4, wherein X is -CH₂- and R₅ is -O-.

6. A compound of the Formula



5 or a pharmaceutically acceptable salt or hydrate thereof,

wherein:

R₅ is O, NH or S;

R₆ is -H or -C₁-C₄ alkyl;

X is -C(O)-, -CH₂-, -CH(halo)-, -(C(OH)((CH₂)_nCH₃))-, -(C(OH)(aryl))-, -O-, -
 10 NH-, S-, -CH(NR₁₁R₁₂)- or -N(SO₂Y)-, wherein Y is -OH, -NH₂, -(C₁-C₅ alkyl)-(3- to 7-
 membered monocyclic heterocycle), or -(C₁-C₅ alkyl)-(7- to 10-membered bicyclic
 heterocycle) and n is an integer ranging from 0-5;

R₁₁ and R₁₂ are independently -hydrogen or -C₁-C₉ alkyl, or N, R₁₁ and R₁₂ are
 taken together to form a -(nitrogen-containing 3- to 7-membered monocyclic
 15 heterocycle), or a -(nitrogen-containing 7- to 10-membered bicyclic heterocycle);

one of G₁-G₄ is C-R₇ and the remaining G₁-G₄ are independently N or C-R₇;

R₁, R₂, R₃, and R₄ are independently -hydrogen, -halo, -hydroxy, -O-(C₁-C₅ alkyl),
 -C₁-C₁₀ alkyl, halo-substituted-(C₁-C₅ alkyl), -C₂-C₁₀ alkenyl, -C₃-C₈-cycloalkyl, -aryl, -
 NH₂, amino-substituted-(C₁-C₅ alkyl), -C(O)OH, -C(O)O(C₁-C₅ alkyl), -OC(O)(C₁-C₅
 20 alkyl), NO₂ or -A-B;

A is -SO₂-, -SO₂NH-, -NHCO-, -NHCONH-, -O-, -CO-, -OC(O)-, -C(O)O-,
 -CONH-, -CON(C₁-C₄ alkyl)-, -NH-, -CH₂-, -S- or -C(S)-;

B is -C₁-C₁₀ alkyl, -C₂-C₁₀ alkenyl, -(nitrogen-containing 3- to 7-membered
 monocyclic heterocycle), -(nitrogen-containing 7- to 10-membered bicyclic heterocycle),
 25 -(3- to 7-membered monocyclic heterocycle), -(7- to 10-membered bicyclic heterocycle),
 -C₃-C₈ cycloalkyl, -aryl, -NZ₁Z₂, -(C₁-C₅ alkylene)-NZ₁Z₂, amino-substituted-(C₁-C₅
 alkyl), -N(C₁-C₅ alkyl)(C₁-C₅ alkyl), -(C₁-C₅ alkyl)-(3- to 7-membered
 monocyclic heterocycle), or -(C₁-C₅ alkyl)-(7- to 10-membered bicyclic heterocycle), -
 (H₂NC(O))-substituted aryl, -(H₂NC(O))-substituted pyridyl, -C(O)OH,
 30 -C(O)O-(C₁-C₅ alkyl), -C(O)O-phenyl or -C(NH)NH₂, each of which is unsubstituted or

substituted with one or more of -O-(C₁-C₅ alkyl), -halo, halo-substituted-(C₁-C₅ alkyl), HO-substituted-(C₁-C₅ alkyl), amino-substituted-(C₁-C₅ alkyl), -hydroxy, -NO₂, -NH₂, -CN, -NH(C₁-C₅ alkyl), -N(C₁-C₅ alkyl)(C₁-C₅ alkyl), -(nitrogen-containing 3- to 7-membered monocyclic heterocycle), 7- to 10-membered bicycloheterocyclic amine, -C₁-C₁₀ alkyl, -C₂-C₁₀ alkenyl, -C₂-C₁₀ alkynyl, -aryl, -benzyl, -(H₂NC(O))-substituted(C₁-C₅ alkyl), carboxy-substituted-(C₁-C₅ alkyl), -C(O)OH, -C₁-C₅-alkylene-C(O)O-(C₁-C₅ alkyl) or -C₁-C₅ alkylene-OC(O)-(C₁-C₅ alkyl); and

Z₁ and Z₂ are independently -H or -C₁-C₁₀ alkyl, which is unsubstituted or substituted with one or more of -halo, -OH or -N(Z₃)(Z₄), where Z₃ and Z₄ are independently, -H or -C₁-C₅ alkyl, which is unsubstituted or substituted with one or more of -halo, -hydroxy or -NH₂; or N, Z₃ and Z₄ are taken together to form a -(nitrogen-containing 3- to 7-membered monocyclic heterocycle) or a -(nitrogen-containing 7- to 10-membered bicyclic heterocycle); or N, Z₁ and Z₂ are taken together to form a -(nitrogen-containing 3- to 7-membered monocyclic heterocycle), or a -(nitrogen-containing 7- to 10-membered bicyclic heterocycle);

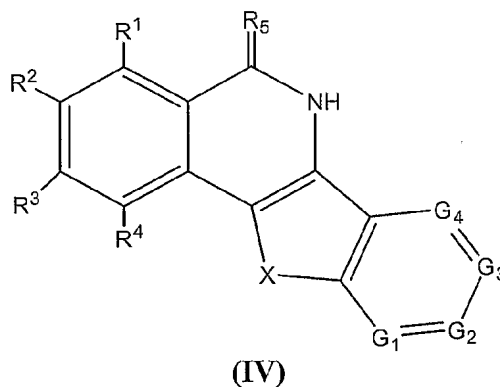
each R₇ is independently -H, -C₁-C₆ alkyl, -O-(C₁-C₆ alkyl), -S-(C₁-C₆ alkyl), -SO₂NH(C₁-C₆ alkyl) or C(O)NH-(C₁-C₆ alkyl).

7. The compound of claim 6 wherein R₆ is hydrogen.

8. The compound of claim 6 wherein R₅ is O.

9. The compound of claim 6 wherein G₄ is N.

10. A compound of the Formula:



or a pharmaceutically acceptable salt or hydrate thereof, wherein:

R₅ is O, NH or S;

X is -C(O)-, -CH₂-, -CH(halo)-, -CH(OH)-, -(C(OH)((CH₂)_mCH₃))-, -(C(OH)(aryl))-, -O-, -N(Z₅)-, -S-, -CH(NR₁₁R₁₂)- or -N(SO₂Y)-, wherein Y is -OH, -NH₂, -(C₁-C₅ alkyl)-(3- to 7-membered monocyclic heterocycle), or -(C₁-C₅ alkyl)-(7- to 10-membered bicyclic heterocycle) and m is an integer ranging from 0-5;

- 5 R₁₁ and R₁₂ are independently -hydrogen or -C₁-C₉ alkyl, or N, R₁₁ and R₁₂ are taken together to form a -(nitrogen-containing 3- to 7-membered monocyclic heterocycle), or a -(nitrogen-containing 7- to 10-membered bicyclic heterocycle);
- one of G₁-G₄ is C-R₇ and the remaining G₁-G₄ are independently N or C-R₇;
- R₁, R₂, R₃, and R₄ are independently -hydrogen, -halo, -hydroxy, -O-(C₁-C₅ alkyl),
- 10 -C₁-C₁₀ alkyl, halo-substituted-(C₁-C₅ alkyl), -C₂-C₁₀ alkenyl, -C₃-C₈-cycloalkyl, -aryl, -NH₂, amino-substituted-(C₁-C₅ alkyl), -C(O)OH, -C(O)O(C₁-C₅ alkyl), -OC(O)(C₁-C₅ alkyl), NO₂ or -A-B;

A is -SO₂-, -SO₂NH-, -NHCO-, -NHCONH-, -O-, -CO-, -OC(O)-, -C(O)O-, -CONH-, -CON(C₁-C₄ alkyl)-, -NH-, -CH₂-, -S- or -C(S)-;

- 15 B is -C₁-C₁₀ alkyl, -C₂-C₁₀ alkenyl, -(nitrogen-containing 3- to 7-membered monocyclic heterocycle), -(nitrogen-containing 7- to 10-membered bicyclic heterocycle), -(3- to 7-membered monocyclic heterocycle), -(7- to 10-membered bicyclic heterocycle), -C₃-C₈ cycloalkyl, -aryl, -NZ₁Z₂, -(C₁-C₅ alkylene)-NZ₁Z₂, amino-substituted-(C₁-C₅ alkyl), -N(C₁-C₅ alkyl)(C₁-C₅ alkyl), -(C₁-C₅ alkyl)-(3- to 7-membered
- 20 monocyclic heterocycle), or -(C₁-C₅ alkyl)-(7- to 10-membered bicyclic heterocycle), -(H₂NC(O))-substituted aryl, -(H₂NC(O))-substituted pyridyl, -C(O)OH, -C(O)O-(C₁-C₅ alkyl), -C(O)O-phenyl or -C(NH)NH₂, each of which is unsubstituted or substituted with one or more of -O-(C₁-C₅ alkyl), -halo, halo-substituted-(C₁-C₅ alkyl), HO-substituted-(C₁-C₅ alkyl), amino-substituted-(C₁-C₅ alkyl), -hydroxy, -NO₂, -NH₂,
- 25 -CN, -NH(C₁-C₅ alkyl), -N(C₁-C₅ alkyl)(C₁-C₅ alkyl), -(nitrogen-containing 3- to 7-membered monocyclic heterocycle), 7- to 10-membered bicycloheterocyclic amine, -C₁-C₁₀ alkyl, -C₂-C₁₀ alkenyl, -C₂-C₁₀ alkynyl, -aryl, -benzyl, -(H₂NC(O))-substituted(C₁-C₅ alkyl), carboxy-substituted-(C₁-C₅ alkyl), -C(O)OH, -C₁-C₅-alkylene-C(O)O-(C₁-C₅ alkyl) or -C₁-C₅ alkylene-OC(O)-(C₁-C₅ alkyl);

- 30 Z₁ and Z₂ are independently -H or -C₁-C₁₀ alkyl, which is unsubstituted or substituted with one or more of -halo, -OH or -N(Z₃)(Z₄), where Z₃ and Z₄ are independently, -H or -C₁-C₅ alkyl, which is unsubstituted or substituted with one or more of -halo, -hydroxy or -NH₂; or N, Z₃ and Z₄ are taken together to form a -(nitrogen-containing 3- to 7-membered monocyclic heterocycle) or a -(nitrogen-containing 7- to

10-membered bicyclic heterocycle); or N, Z₁ and Z₂ are taken together to form a – (nitrogen-containing 3- to 7-membered monocyclic heterocycle), or a –(nitrogen-containing 7- to 10-membered bicyclic heterocycle);

each R₇ is independently -H, -C₁-C₆ alkyl, -O-(C₁-C₆ alkyl), -S-(C₁-C₆ alkyl),

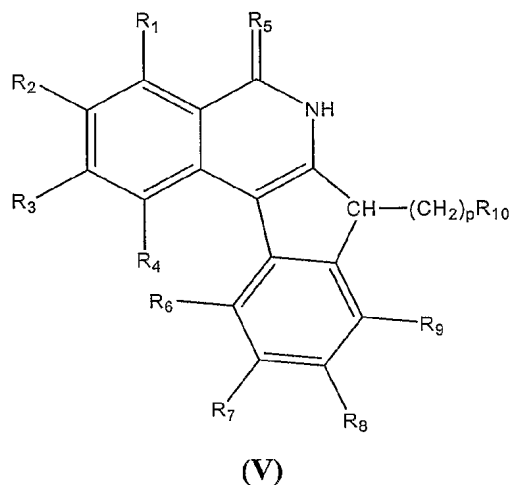
5 -SO₂NH(C₁-C₆ alkyl) or C(O)NH-(C₁-C₆ alkyl);

Z₅ is -H, -C₁-C₅ alkyl, -(CH₂)_n-CN, -(CH₂)_n-aryl, -(CH₂)_n-(3- to 7-membered monocyclic heterocycle), -(CH₂)_n-(7- to 10-membered bicyclic heterocycle), -(CH₂)_n-COO-(C₁-C₅ alkyl), -(CH₂)_n-COO-aryl, -(CH₂)_n-COOH, -CONH-(CH₂)_n-COOH, -CONH-(CH₂)_n-COO-(C₁-C₅ alkyl), -CONH-(CH₂)_n-aryl, -CONHNH-(C₁-C₅ alkyl), -CONHNH-aryl, -(CH₂)_n-CONH₂, -(CH₂)_n-CONH-(C₁-C₅ alkyl), -(CH₂)_n-CONH-aryl, -(CH₂)_n-CONH-(CH₂)_q-aryl, -(CH₂)_n-CONH-(CH₂)_q-(3- to 7-membered monocyclic heterocycle), -(CH₂)_n-CONH-(CH₂)_q-(3- to 7-membered monocyclic heterocycle), -(CH₂)_n-CONH-(CH₂)_q-CONH₂, -(CH₂)_n-CONH-(CH₂)_q-CONH-(C₁-C₅ alkyl), -(CH₂)_n-CONH-(CH₂)_q-CON(C₁-C₅ alkyl)₂, -C(O)(CH₂)_n-(C₁-C₅ alkyl), -C(O)(CH₂)_n-aryl, -C(O)(CH₂)_n-COOH, -C(O)(CH₂)_n-COO-(C₁-C₅ alkyl), -C(O)(CH₂)_n-COO-(3- to 7-membered monocyclic heterocycle), -C(O)(CH₂)_n-COO-(7- to 10-membered bicyclic heterocycle), -C(O)(CH₂)_n-phenyl, -C(O)(CH₂)_n-(3- to 7-membered monocyclic heterocycle), -C(O)(CH₂)_n-phenyl, -C(O)(CH₂)_n-(7- to 10-membered bicyclic heterocycle), -C(O)O(CH₂)_n-phenyl, -C(O)O(CH₂)_n-(3- to 7-membered monocyclic heterocycle), -C(O)(CH₂)_n-phenyl, -C(O)(CH₂)_n-(7- to 10-membered bicyclic heterocycle), -C(O)N((CH₂)_n-phenyl)₂, -C(O)N((CH₂)_n-phenyl)((CH₂)_q-3- to 7-membered monocyclic heterocycle), -C(O)N((CH₂)_n-phenyl)((CH₂)_q-7- to 10-membered bicyclic heterocycle), -C(O)N((CH₂)_n-(3- to 7-membered monocyclic heterocycle))₂, -C(O)N((CH₂)_n-7- to 10-membered bicyclic heterocycle)₂, or -SO₂NH₂;

25 each n is an integer ranging from 0 to 10; and

q is an integer ranging from 0 to 10.

11. A compound of Formula



5 or a pharmaceutically acceptable salt or hydrate thereof,

wherein:

R₅ is O, S, or NH;

R₁, R₂, R₃, R₄, R₆, R₇, R₈, and R₉ are independently -hydrogen, -halo, -hydroxy, -NH₂ NO₂, or -A-B;

10 A is -SO₂-, -SO₂NH-, -NHCO-, -NHCONH-, -O-, -CO-, -OC(O)-, -C(O)O-, -CONH-, -CON(C₁-C₄ alkyl)-, -NH-, -CH₂-, -S- or -C(S)-;

B is -C₁-C₁₀ alkyl, -C₂-C₁₀ alkenyl, -(nitrogen-containing 3- to 7-membered monocyclic heterocycle), -(nitrogen-containing 7- to 10-membered bicyclic heterocycle), -(3- to 7-membered monocyclic heterocycle), -(7- to 10-membered bicyclic heterocycle),
 15 -C₃-C₈ cycloalkyl, -aryl, -NZ₁Z₂, -(C₁-C₅ alkylene)-NZ₁Z₂, amino-substituted-(C₁-C₅ alkyl), -N(C₁-C₅ alkyl)(C₁-C₅ alkyl), -(C₁-C₅ alkyl)-(3- to 7-membered monocyclic heterocycle), or -(C₁-C₅ alkyl)-(7- to 10-membered bicyclic heterocycle), -
 (H₂NC(O))-substituted aryl, -(H₂NC(O))-substituted pyridyl, -C(O)OH, -C(O)O-(C₁-C₅ alkyl), -C(O)O-phenyl or -C(NH)NH₂, each of which is unsubstituted or
 20 substituted with one or more of -O-(C₁-C₅ alkyl), -halo, halo-substituted-(C₁-C₅ alkyl), HO-substituted-(C₁-C₅ alkyl), amino-substituted-(C₁-C₅ alkyl), -hydroxy, -NO₂, -NH₂, -CN, -NH(C₁-C₅ alkyl), -N(C₁-C₅ alkyl)(C₁-C₅ alkyl), -(nitrogen-containing 3- to 7-membered monocyclic heterocycle), 7- to 10-membered bicycloheterocyclic amine, -C₁-C₁₀ alkyl, -C₂-C₁₀ alkenyl, -C₂-C₁₀ alkynyl, -aryl, -benzyl, -(H₂NC(O))-substituted(C₁-
 25 C₅ alkyl), carboxy-substituted-(C₁-C₅ alkyl), -C(O)OH, -C₁-C₅-alkylene-C(O)O-(C₁-C₅ alkyl) or -C₁-C₅ alkylene-OC(O)-(C₁-C₅ alkyl); and

Z_1 and Z_2 are independently -H or -C₁-C₁₀ alkyl, which is unsubstituted or substituted with one or more of -halo, -OH or -N(Z_3)(Z_4), where Z_3 and Z_4 are independently, -H or -C₁-C₅ alkyl, which is unsubstituted or substituted with one or more of -halo, -hydroxy or -NH₂; or N, Z_3 and Z_4 are taken together to form a -(nitrogen-
 5 containing 3- to 7-membered monocyclic heterocycle) or a -(nitrogen-containing 7- to 10-membered bicyclic heterocycle); or N, Z_1 and Z_2 are taken together to form a -(nitrogen-containing 3- to 7-membered monocyclic heterocycle), or a -(nitrogen-containing 7- to 10-membered bicyclic heterocycle);

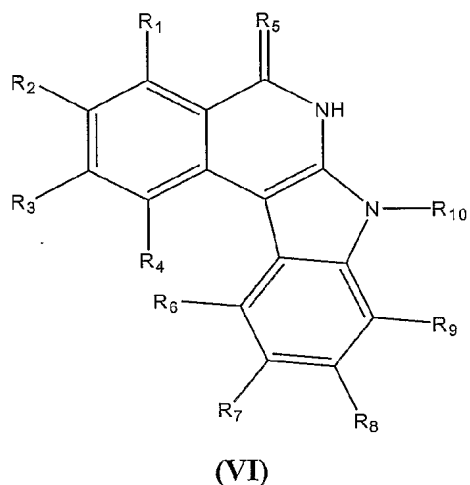
R_{10} is -H, -C₁-C₅ alkyl, -(CH₂)_n-CN, -(CH₂)_n-aryl, -(CH₂)_n-(3- to 7-membered
 10 monocyclic heterocycle), -(CH₂)_n-(7- to 10-membered bicyclic heterocycle), -(CH₂)_n-COO-(C₁-C₅ alkyl), -(CH₂)_n-COO-aryl, -(CH₂)_n-COOH, -CONH-(CH₂)_n-COOH, -CONH-(CH₂)_n-COO-(C₁-C₅ alkyl), -CONH-(CH₂)_n-aryl, -CONHNH-(C₁-C₅ alkyl), -CONHNH-aryl, -(CH₂)_n-CONH₂, -(CH₂)_n-CONH-(C₁-C₅ alkyl), -(CH₂)_n-CONH-aryl, -(CH₂)_n-CONH-(CH₂)_q-aryl, -(CH₂)_n-CONH-(CH₂)_q-(3- to 7-membered monocyclic
 15 heterocycle), -(CH₂)_n-CONH-(CH₂)_q-(3- to 7-membered monocyclic heterocycle), -(CH₂)_n-CONH-(CH₂)_q-CONH₂, -(CH₂)_n-CONH-(CH₂)_q-CONH-(C₁-C₅ alkyl), -(CH₂)_n-CONH-(CH₂)_q-CON(C₁-C₅ alkyl)₂, -C(O)(CH₂)_n-(C₁-C₅ alkyl), -C(O)(CH₂)_n-aryl, -C(O)(CH₂)_n-COOH, -C(O)(CH₂)_n-COO-(C₁-C₅alkyl), -C(O)(CH₂)_n-COO-(3- to 7-membered monocyclic heterocycle), -C(O)(CH₂)_n-COO-(7- to 10-membered bicyclic
 20 heterocycle), -C(O)(CH₂)_n-phenyl, -C(O)(CH₂)_n-(3- to 7-membered monocyclic heterocycle), -C(O)(CH₂)_n-phenyl, -C(O)(CH₂)_n-(7- to 10-membered bicyclic heterocycle), -C(O)O(CH₂)_n-phenyl, -C(O)O(CH₂)_n-(3- to 7-membered monocyclic heterocycle), -C(O)(CH₂)_n-phenyl, -C(O)(CH₂)_n-(7- to 10-membered bicyclic heterocycle), -C(O)N((CH₂)_n-phenyl)₂, -C(O)N((CH₂)_n-phenyl)((CH₂)_q-3- to 7-membered
 25 monocyclic heterocycle), -C(O)N((CH₂)_n-phenyl)((CH₂)_q-7- to 10-membered bicyclic heterocycle), -C(O)N((CH₂)_n-(3- to 7-membered monocyclic heterocycle))₂, -C(O)N((CH₂)_n-7- to 10-membered bicyclic heterocycle)₂, or -SO₂NH₂;

each n is an integer ranging from 0 to 10;

p is an integer ranging from 0 to 5, with p being other than 0 when R_{10} is -H; and

30 q is an integer ranging from 0 to 10.

12. A compound of the Formula



5 or a pharmaceutically acceptable salt or hydrate thereof,

wherein:

R_5 is O, S, or NH;

$R_1, R_2, R_3, R_4, R_6, R_7, R_8,$ and R_9 are independently -hydrogen, -halo, -hydroxy, - NH_2 , NO_2 , or -A-B;

10 A is $-SO_2-$, $-SO_2NH-$, $-NHCO-$, $-NHCONH-$, $-O-$, $-CO-$, $-OC(O)-$, $-C(O)O-$, $-CONH-$, $-CON(C_1-C_4 \text{ alkyl})-$, $-NH-$, $-CH_2-$, $-S-$ or $-C(S)-$;

B is $-C_1-C_{10}$ alkyl, $-C_2-C_{10}$ alkenyl, -(nitrogen-containing 3- to 7-membered monocyclic heterocycle), -(nitrogen-containing 7- to 10-membered bicyclic heterocycle), -(3- to 7-membered monocyclic heterocycle), -(7- to 10-membered bicyclic heterocycle),
 15 $-C_3-C_8$ cycloalkyl, -aryl, $-NZ_1Z_2$, $-(C_1-C_5 \text{ alkylene})-NZ_1Z_2$, amino-substituted- $(C_1-C_5 \text{ alkyl})$, $-N(C_1-C_5 \text{ alkyl})(C_1-C_5 \text{ alkyl})$, $-(C_1-C_5 \text{ alkyl})$ -(3- to 7-membered monocyclic heterocycle), or $-(C_1-C_5 \text{ alkyl})$ -(7- to 10-membered bicyclic heterocycle), - $(H_2NC(O))$ -substituted aryl, $-(H_2NC(O))$ -substituted pyridyl, $-C(O)OH$, $-C(O)O-(C_1-C_5 \text{ alkyl})$, $-C(O)O$ -phenyl or $-C(NH)NH_2$, each of which is unsubstituted or
 20 substituted with one or more of $-O-(C_1-C_5 \text{ alkyl})$, -halo, halo-substituted- $(C_1-C_5 \text{ alkyl})$, HO-substituted- $(C_1-C_5 \text{ alkyl})$, amino-substituted- $(C_1-C_5 \text{ alkyl})$, -hydroxy, $-NO_2$, $-NH_2$, $-CN$, $-NH(C_1-C_5 \text{ alkyl})$, $-N(C_1-C_5 \text{ alkyl})(C_1-C_5 \text{ alkyl})$, -(nitrogen-containing 3- to 7-membered monocyclic heterocycle), 7- to 10-membered bicycloheterocyclic amine, $-C_1-C_{10}$ alkyl, $-C_2-C_{10}$ alkenyl, $-C_2-C_{10}$ alkynyl, -aryl, -benzyl, $-(H_2NC(O))$ -substituted $(C_1-C_5 \text{ alkyl})$, carboxy-substituted- $(C_1-C_5 \text{ alkyl})$, $-C(O)OH$, $-C_1-C_5$ -alkylene- $-C(O)O-(C_1-C_5 \text{ alkyl})$ or $-C_1-C_5$ alkylene- $OC(O)-(C_1-C_5 \text{ alkyl})$;

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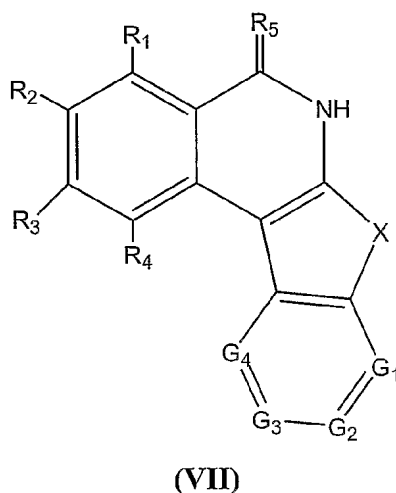
Z_1 and Z_2 are independently -H or -C₁-C₁₀ alkyl, which is unsubstituted or substituted with one or more of -halo, -OH or -N(Z_3)(Z_4), where Z_3 and Z_4 are independently, -H or -C₁-C₅ alkyl, which is unsubstituted or substituted with one or more of -halo, -hydroxy or -NH₂; or N, Z_3 and Z_4 are taken together to form a -(nitrogen-containing 3- to 7-membered monocyclic heterocycle) or a -(nitrogen-containing 7- to 10-membered bicyclic heterocycle); or N, Z_1 and Z_2 are taken together to form a -(nitrogen-containing 3- to 7-membered monocyclic heterocycle), or a -(nitrogen-containing 7- to 10-membered bicyclic heterocycle);

R_{10} is -H, -C₁-C₅ alkyl, -(CH₂)_n-CN, -(CH₂)_n-aryl, -(CH₂)_n-(3- to 7-membered monocyclic heterocycle), -(CH₂)_n-(7- to 10-membered bicyclic heterocycle), -(CH₂)_n-COO-(C₁-C₅ alkyl), -(CH₂)_n-COO-aryl, -(CH₂)_n-COOH, -CONH-(CH₂)_n-COOH, -CONH-(CH₂)_n-COO-(C₁-C₅ alkyl), -CONH-(CH₂)_n-aryl, -CONHNH-(C₁-C₅ alkyl), -CONHNH-aryl, -(CH₂)_n-CONH₂, -(CH₂)_n-CONH-(C₁-C₅ alkyl), -(CH₂)_n-CONH-aryl, -(CH₂)_n-CONH-(CH₂)_q-aryl, -(CH₂)_n-CONH-(CH₂)_q-(3- to 7-membered monocyclic heterocycle), -(CH₂)_n-CONH-(CH₂)_q-(7- to 10-membered bicyclic heterocycle), -(CH₂)_n-CONH-(CH₂)_q-CONH₂, -(CH₂)_n-CONH-(CH₂)_q-CONH-(C₁-C₅ alkyl), -(CH₂)_n-CONH-(CH₂)_q-CON(C₁-C₅ alkyl)₂, -C(O)(CH₂)_n-(C₁-C₅ alkyl), -C(O)(CH₂)_n-aryl, -C(O)(CH₂)_n-COOH, -C(O)(CH₂)_n-COO-(C₁-C₅ alkyl), -C(O)(CH₂)_n-COO-(3- to 7-membered monocyclic heterocycle), -C(O)(CH₂)_n-COO-(7- to 10-membered bicyclic heterocycle), -C(O)(CH₂)_n-phenyl, -C(O)(CH₂)_n-(3- to 7-membered monocyclic heterocycle), -C(O)(CH₂)_n-phenyl, -C(O)(CH₂)_n-(7- to 10-membered bicyclic heterocycle), -C(O)O(CH₂)_n-phenyl, -C(O)O(CH₂)_n-(3- to 7-membered monocyclic heterocycle), -C(O)(CH₂)_n-phenyl, -C(O)(CH₂)_n-(7- to 10-membered bicyclic heterocycle), -C(O)N((CH₂)_n-phenyl)₂, -C(O)N((CH₂)_n-phenyl)((CH₂)_q-3- to 7-membered monocyclic heterocycle), -C(O)N((CH₂)_n-phenyl)((CH₂)_q-7- to 10-membered bicyclic heterocycle), -C(O)N((CH₂)_n-(3- to 7-membered monocyclic heterocycle))₂, -C(O)N((CH₂)_n-7- to 10-membered bicyclic heterocycle)₂, or -SO₂NH₂;

each n is an integer ranging from 0 to 10; and

q is an integer ranging from 0 to 10.

13. A compound of the Formula



5 or a pharmaceutically acceptable salt or hydrate thereof,

wherein

R_5 is O, NH or S;

X is -C(O)-, -CH₂-, -CH(halo)-, -CH(OH)-, -(C(OH)((CH₂)_mCH₃))-, -
 (C(OH)(aryl))-, -O-, -N(Z₅)-, -S-, -CH(NR₁₁R₁₂)- or -N(SO₂Y)-, wherein Y is -OH, -
 10 NH₂, -(C₁-C₅ alkyl)-(3- to 7-membered monocyclic heterocycle), or -(C₁-C₅ alkyl)-(7- to
 10-membered bicyclic heterocycle) and m is an integer ranging from 0-5;

R₁₁ and R₁₂ are independently -hydrogen or -C₁-C₉ alkyl, or N, R₁₁ and R₁₂ are
 taken together to form a -(nitrogen-containing 3- to 7-membered monocyclic
 heterocycle), or a -(nitrogen-containing 7- to 10-membered bicyclic heterocycle);

15 one of G₁-G₄ is C-R₇ and the remaining G₁-G₄ are independently N or C-R₇;

R₁, R₂, R₃, and R₄ are independently -hydrogen, -halo, -hydroxy, -O-(C₁-C₅ alkyl),
 -C₁-C₁₀ alkyl, halo-substituted-(C₁-C₅ alkyl), -C₂-C₁₀ alkenyl, -C₃-C₈-cycloalkyl, -aryl, -
 NH₂, amino-substituted-(C₁-C₅ alkyl), -C(O)OH, -C(O)O(C₁-C₅ alkyl), -OC(O)(C₁-C₅
 alkyl), NO₂ or -A-B;

20 A is -SO₂-, -SO₂NH-, -NHCO-, -NHCONH-, -O-, -CO-, -OC(O)-, -C(O)O-,
 -CONH-, -CON(C₁-C₄ alkyl)-, -NH-, -CH₂-, -S- or -C(S)-;

B is -C₁-C₁₀ alkyl, -C₂-C₁₀ alkenyl, -(nitrogen-containing 3- to 7-membered
 monocyclic heterocycle), -(nitrogen-containing 7- to 10-membered bicyclic heterocycle),
 -(3- to 7-membered monocyclic heterocycle), -(7- to 10-membered bicyclic heterocycle),
 25 -C₃-C₈ cycloalkyl, -aryl, -NZ₁Z₂, -(C₁-C₅ alkylene)-NZ₁Z₂, amino-substituted-(C₁-C₅
 alkyl), -N(C₁-C₅ alkyl)(C₁-C₅ alkyl), -(C₁-C₅ alkyl)-(3- to 7-membered

monocyclic heterocycle), or $-(C_1-C_5 \text{ alkyl})-(7- \text{ to } 10\text{-membered bicyclic heterocycle})$, $-(H_2NC(O))$ -substituted aryl, $-(H_2NC(O))$ -substituted pyridyl, $-C(O)OH$, $-C(O)O-(C_1-C_5 \text{ alkyl})$, $-C(O)O$ -phenyl or $-C(NH)NH_2$, each of which is unsubstituted or substituted with one or more of $-O-(C_1-C_5 \text{ alkyl})$, -halo, halo-substituted- $(C_1-C_5 \text{ alkyl})$,
 5 HO -substituted- $(C_1-C_5 \text{ alkyl})$, amino-substituted- $(C_1-C_5 \text{ alkyl})$, -hydroxy, $-NO_2$, $-NH_2$, $-CN$, $-NH(C_1-C_5 \text{ alkyl})$, $-N(C_1-C_5 \text{ alkyl})(C_1-C_5 \text{ alkyl})$, $-(\text{nitrogen-containing } 3- \text{ to } 7\text{-membered monocyclic heterocycle})$, $7- \text{ to } 10\text{-membered bicycloheterocyclic amine}$, $-C_1-C_{10} \text{ alkyl}$, $-C_2-C_{10} \text{ alkenyl}$, $-C_2-C_{10} \text{ alkynyl}$, -aryl, -benzyl, $-(H_2NC(O))$ -substituted- $(C_1-C_5 \text{ alkyl})$, carboxy-substituted- $(C_1-C_5 \text{ alkyl})$, $-C(O)OH$, $-C_1-C_5\text{-alkylene-}C(O)O-(C_1-C_5$
 10 $\text{alkyl})$ or $-C_1-C_5 \text{ alkylene-OC(O)}-(C_1-C_5 \text{ alkyl})$;

Z_1 and Z_2 are independently $-H$ or $-C_1-C_{10} \text{ alkyl}$, which is unsubstituted or substituted with one or more of -halo, $-OH$ or $-N(Z_3)(Z_4)$, where Z_3 and Z_4 are independently, $-H$ or $-C_1-C_5 \text{ alkyl}$, which is unsubstituted or substituted with one or more of -halo, -hydroxy or $-NH_2$; or N , Z_3 and Z_4 are taken together to form a $-(\text{nitrogen-}$
 15 $\text{containing } 3- \text{ to } 7\text{-membered monocyclic heterocycle})$ or a $-(\text{nitrogen-containing } 7- \text{ to } 10\text{-membered bicyclic heterocycle})$; or N , Z_1 and Z_2 are taken together to form a $-(\text{nitrogen-containing } 3- \text{ to } 7\text{-membered monocyclic heterocycle})$, or a $-(\text{nitrogen-containing } 7- \text{ to } 10\text{-membered bicyclic heterocycle})$;

each R_7 is independently $-H$, $-C_1-C_6 \text{ alkyl}$, $-O-(C_1-C_6 \text{ alkyl})$, $-S-(C_1-C_6 \text{ alkyl})$,
 20 $-SO_2NH(C_1-C_6 \text{ alkyl})$ or $C(O)NH-(C_1-C_6 \text{ alkyl})$;

Z_5 is $-H$, $-C_1-C_5 \text{ alkyl}$, $-(CH_2)_n-CN$, $-(CH_2)_n\text{-aryl}$, $-(CH_2)_n\text{-(} 3- \text{ to } 7\text{-membered monocyclic heterocycle)}$, $-(CH_2)_n\text{-(} 7- \text{ to } 10\text{-membered bicyclic heterocycle)}$, $-(CH_2)_n\text{-COO-}(C_1-C_5 \text{ alkyl})$, $-(CH_2)_n\text{-COO-aryl}$, $-(CH_2)_n\text{-COOH}$, $-CONH-(CH_2)_n\text{-COOH}$, $-CONH-(CH_2)_n\text{-COO-}(C_1-C_5 \text{ alkyl})$, $-CONH-(CH_2)_n\text{-aryl}$, $-CONHNH-(C_1-C_5 \text{ alkyl})$, $-CONHNH\text{-aryl}$, $-(CH_2)_n\text{-CONH}_2$, $-(CH_2)_n\text{-CONH-}(C_1-C_5 \text{ alkyl})$, $-(CH_2)_n\text{-CONH-aryl}$, $-(CH_2)_n\text{-CONH-}(CH_2)_q\text{-aryl}$, $-(CH_2)_n\text{-CONH-}(CH_2)_q\text{-(} 3- \text{ to } 7\text{-membered monocyclic heterocycle)}$, $-(CH_2)_n\text{-CONH-}(CH_2)_q\text{-(} 3- \text{ to } 7\text{-membered monocyclic heterocycle)}$, $-(CH_2)_n\text{-CONH-}(CH_2)_q\text{-CONH}_2$, $-(CH_2)_n\text{-CONH-}(CH_2)_q\text{-CONH-}(C_1-C_5 \text{ alkyl})$, $-(CH_2)_n\text{-CONH-}(CH_2)_q\text{-CON-}(C_1-C_5 \text{ alkyl})_2$, $-C(O)(CH_2)_n\text{-(} C_1-C_5 \text{ alkyl)}$, $-C(O)(CH_2)_n\text{-aryl}$, $-C(O)(CH_2)_n\text{-COOH}$, $-C(O)(CH_2)_n\text{-COO-}(C_1-C_5 \text{ alkyl})$, $-C(O)(CH_2)_n\text{-COO-}(3- \text{ to } 7\text{-membered monocyclic heterocycle})$, $-C(O)(CH_2)_n\text{-COO-}(7- \text{ to } 10\text{-membered bicyclic heterocycle})$, $-C(O)(CH_2)_n\text{-phenyl}$, $-C(O)(CH_2)_n\text{-(} 3- \text{ to } 7\text{-membered monocyclic heterocycle)}$, $-C(O)(CH_2)_n\text{-phenyl}$, $-C(O)(CH_2)_n\text{-(} 7- \text{ to } 10\text{-membered bicyclic heterocycle)}$, $-C(O)O(CH_2)_n\text{-phenyl}$, $-C(O)O(CH_2)_n\text{-(} 3- \text{ to } 7\text{-membered monocyclic}$
 30

- heterocycle), -C(O)(CH₂)_n-phenyl, -C(O)(CH₂)_n-(7- to 10-membered bicyclic heterocycle), -C(O)N((CH₂)_n-phenyl)₂, -C(O)N((CH₂)_n-phenyl)((CH₂)_q-3- to 7-membered monocyclic heterocycle), -C(O)N((CH₂)_n-phenyl)((CH₂)_q 7- to 10-membered bicyclic heterocycle), -C(O)N((CH₂)_n-(3- to 7-membered monocyclic heterocycle)₂, -
- 5 C(O)N((CH₂)_n-7- to 10-membered bicyclic heterocycle)₂, or -SO₂NH₂;
- each n is an integer ranging from 0 to 10; and
- q is an integer ranging from 0 to 10.
14. The compound or the pharmaceutically acceptable salt of the compound of claim 13, wherein G₁ is -N-.
- 10 15. The compound or the pharmaceutically acceptable salt of the compound of claim 13, wherein: G₁ is -C-R₇; R₇ is H; and G₁ is -N-.
16. The compound or the pharmaceutically acceptable salt of the compound of claim 13, wherein G₁ and G₃ -N-.
17. The compound or the pharmaceutically acceptable salt or the hydrate of the
- 15 compound of claim 13 wherein R₅ is oxygen.
18. A composition comprising an effective amount of the compound or pharmaceutically acceptable salt or hydrate of the compound of claim 1 and a pharmaceutically acceptable carrier or vehicle.
19. A composition comprising an effective amount of the compound or pharmaceutically
- 20 acceptable salt or hydrate of the compound of claim 3 and a pharmaceutically acceptable carrier or vehicle.
20. A composition comprising an effective amount of the compound or pharmaceutically acceptable salt or hydrate of the compound of claim 4 and a pharmaceutically acceptable carrier or vehicle.
- 25 21. A composition comprising an effective amount of the compound or pharmaceutically acceptable salt or hydrate of the compound of claim 6 and a pharmaceutically acceptable carrier or vehicle.

22. A composition comprising an effective amount of the compound or pharmaceutically acceptable salt or hydrate of the compound of claim 10 and a pharmaceutically acceptable carrier or vehicle.
23. A composition comprising an effective amount of the compound or pharmaceutically acceptable salt or hydrate of the compound of claim 11 and a pharmaceutically acceptable carrier or vehicle.
24. A composition comprising an effective amount of the compound or pharmaceutically acceptable salt or hydrate of the compound of claim 12 and a pharmaceutically acceptable carrier or vehicle.
25. A composition comprising an effective amount of the compound or pharmaceutically acceptable salt or hydrate of the compound of claim 13 and a pharmaceutically acceptable carrier or vehicle.
26. A method for treating an inflammatory disease, comprising administering to a subject in need thereof the compound or a pharmaceutically acceptable salt or hydrate of a compound of claim 1 in an amount effective to treat the inflammatory disease.
27. A method for treating an inflammatory disease, comprising administering to a subject in need thereof the compound or a pharmaceutically acceptable salt or hydrate of a compound of claim 3 in an amount effective to treat the inflammatory disease.
28. A method for treating an inflammatory disease, comprising administering to a subject in need thereof the compound or a pharmaceutically acceptable salt or hydrate of a compound of claim 4 in an amount effective to treat the inflammatory disease.
29. A method for treating an inflammatory disease, comprising administering to a subject in need thereof the compound or a pharmaceutically acceptable salt or hydrate of a compound of claim 6 in an amount effective to treat the inflammatory disease.
30. A method for treating an inflammatory disease, comprising administering to a subject in need thereof the compound or a pharmaceutically acceptable salt or hydrate of a compound of claim 10 in an amount effective to treat the inflammatory disease.

31. A method for treating an inflammatory disease, comprising administering to a subject in need thereof the compound or a pharmaceutically acceptable salt or hydrate of a compound of claim 11 in an amount effective to treat the inflammatory disease.
32. A method for treating an inflammatory disease, comprising administering to a subject
5 in need thereof the compound or a pharmaceutically acceptable salt or hydrate of a compound of claim 12 in an amount effective to treat the inflammatory disease.
33. A method for treating an inflammatory disease, comprising administering to a subject in need thereof the compound or a pharmaceutically acceptable salt or hydrate of a compound of claim 13 in an amount effective to treat the inflammatory disease.
- 10 34. A method for treating an reperfusion disease, comprising administering to a subject in need thereof the compound or a pharmaceutically acceptable salt or hydrate of a compound of claim 1 in an amount effective to treat the reperfusion disease.
35. A method for treating an reperfusion disease, comprising administering to a subject in need thereof the compound or a pharmaceutically acceptable salt or hydrate of a
15 compound of claim 3 in an amount effective to treat the reperfusion disease.
36. A method for treating an reperfusion disease, comprising administering to a subject in need thereof the compound or a pharmaceutically acceptable salt or hydrate of a compound of claim 4 in an amount effective to treat the reperfusion disease.
37. A method for treating an reperfusion disease, comprising administering to a subject
20 in need thereof the compound or a pharmaceutically acceptable salt or hydrate of a compound of claim 6 in an amount effective to treat the reperfusion disease.
38. A method for treating an reperfusion disease, comprising administering to a subject in need thereof the compound or a pharmaceutically acceptable salt or hydrate of a compound of claim 10 in an amount effective to treat the reperfusion disease.
- 25 39. A method for treating an reperfusion disease, comprising administering to a subject in need thereof the compound or a pharmaceutically acceptable salt or hydrate of a compound of claim 11 in an amount effective to treat the reperfusion disease.

40. A method for treating an reperfusion disease, comprising administering to a subject in need thereof the compound or a pharmaceutically acceptable salt or hydrate of a compound of claim 12 in an amount effective to treat the reperfusion disease.

41. A method for treating an reperfusion disease, comprising administering to a subject in need thereof the compound or a pharmaceutically acceptable salt or hydrate of a compound of claim 13 in an amount effective to treat the reperfusion disease.

42. A method for treating diabetes or a diabetic complication, comprising administering to a subject in need thereof the compound or a pharmaceutically acceptable salt or hydrate of a compound of claim 1 in an amount effective to treat the diabetes or a diabetic complication.

43. A method for treating diabetes or a diabetic complication, comprising administering to a subject in need thereof the compound or a pharmaceutically acceptable salt or hydrate of a compound of claim 3 in an amount effective to treat the diabetes or a diabetic complication.

44. A method for treating diabetes or a diabetic complication, comprising administering to a subject in need thereof the compound or a pharmaceutically acceptable salt or hydrate of a compound of claim 4 in an amount effective to treat the diabetes or a diabetic complication.

45. A method for treating diabetes or a diabetic complication, comprising administering to a subject in need thereof the compound or a pharmaceutically acceptable salt or hydrate of a compound of claim 6 in an amount effective to treat the diabetes or a diabetic complication.

46. A method for treating diabetes or a diabetic complication, comprising administering to a subject in need thereof the compound or a pharmaceutically acceptable salt or hydrate of a compound of claim 10 in an amount effective to treat the diabetes or a diabetic complication.

47. A method for treating diabetes or a diabetic complication, comprising administering to a subject in need thereof the compound or a pharmaceutically acceptable salt or hydrate of a compound of claim 11 in an amount effective to treat the diabetes or a diabetic complication.

48. A method for treating diabetes or a diabetic complication, comprising administering to a subject in need thereof the compound or a pharmaceutically acceptable salt or hydrate of a compound of claim 12 in an amount effective to treat the diabetes or a diabetic complication.
- 5 49. A method for treating diabetes or a diabetic complication, comprising administering to a subject in need thereof the compound or a pharmaceutically acceptable salt or hydrate of a compound of claim 13 in an amount effective to treat the diabetes or a diabetic complication.
- 10 50. A method for treating cancer, comprising administering to a subject in need thereof the compound or a pharmaceutically acceptable salt or hydrate of a compound of claim 1 in an amount effective to treat the cancer.
51. A method for treating cancer, comprising administering to a subject in need thereof the compound or a pharmaceutically acceptable salt or hydrate of a compound of claim 3 in an amount effective to treat the cancer.
- 15 52. A method for treating cancer, comprising administering to a subject in need thereof the compound or a pharmaceutically acceptable salt or hydrate of a compound of claim 4 in an amount effective to treat the cancer.
53. A method for treating cancer, comprising administering to a subject in need thereof the compound or a pharmaceutically acceptable salt or hydrate of a compound of claim 6 in an amount effective to treat the cancer.
- 20 54. A method for treating cancer, comprising administering to a subject in need thereof the compound or a pharmaceutically acceptable salt or hydrate of a compound of claim 10 in an amount effective to treat the cancer.
55. A method for treating cancer, comprising administering to a subject in need thereof the compound or a pharmaceutically acceptable salt or hydrate of a compound of claim 11 in an amount effective to treat the cancer.
- 25 56. A method for treating cancer, comprising administering to a subject in need thereof the compound or a pharmaceutically acceptable salt or hydrate of a compound of claim 12 in an amount effective to treat the cancer.

57. A method for treating cancer, comprising administering to a subject in need thereof the compound or a pharmaceutically acceptable salt or hydrate of a compound of claim 13 in an amount effective to treat the cancer.
58. A method for treating renal failure, comprising administering to a subject in need thereof the compound or a pharmaceutically acceptable salt or hydrate of a compound of claim 1 in an amount effective to treat the chronic renal failure.
59. A method for treating renal failure, comprising administering to a subject in need thereof the compound or a pharmaceutically acceptable salt or hydrate of a compound of claim 3 in an amount effective to treat the chronic renal failure.
60. A method for treating renal failure, comprising administering to a subject in need thereof the compound or a pharmaceutically acceptable salt or hydrate of a compound of claim 4 in an amount effective to treat the chronic renal failure.
61. A method for treating renal failure, comprising administering to a subject in need thereof the compound or a pharmaceutically acceptable salt or hydrate of a compound of claim 6 in an amount effective to treat the chronic renal failure.
62. A method for treating renal failure, comprising administering to a subject in need thereof the compound or a pharmaceutically acceptable salt or hydrate of a compound of claim 10 in an amount effective to treat the chronic renal failure.
63. A method for treating renal failure, comprising administering to a subject in need thereof the compound or a pharmaceutically acceptable salt or hydrate of a compound of claim 11 in an amount effective to treat the chronic renal failure.
64. A method for treating renal failure, comprising administering to a subject in need thereof the compound or a pharmaceutically acceptable salt or hydrate of a compound of claim 12 in an amount effective to treat the chronic renal failure.
65. A method for treating renal failure, comprising administering to a subject in need thereof the compound or a pharmaceutically acceptable salt or hydrate of a compound of claim 13 in an amount effective to treat the chronic renal failure.

66. A method for treating a vascular disease, comprising administering to a subject in need thereof the compound or a pharmaceutically acceptable salt or hydrate of a compound of claim 1 in an amount effective to treat the vascular disease.
67. A method for treating a vascular disease, comprising administering to a subject in
5 need thereof the compound or a pharmaceutically acceptable salt or hydrate of a compound of claim 3 in an amount effective to treat the vascular disease.
68. A method for treating a vascular disease, comprising administering to a subject in need thereof the compound or a pharmaceutically acceptable salt or hydrate of a compound of claim 4 in an amount effective to treat the vascular disease.
- 10 69. A method for treating a vascular disease, comprising administering to a subject in need thereof the compound or a pharmaceutically acceptable salt or hydrate of a compound of claim 6 in an amount effective to treat the vascular disease.
70. A method for treating a vascular disease, comprising administering to a subject in need thereof the compound or a pharmaceutically acceptable salt or hydrate of a
15 compound of claim 10 in an amount effective to treat the vascular disease.
71. A method for treating a vascular disease, comprising administering to a subject in need thereof the compound or a pharmaceutically acceptable salt or hydrate of a compound of claim 11 in an amount effective to treat the vascular disease.
72. A method for treating a vascular disease, comprising administering to a subject in
20 need thereof the compound or a pharmaceutically acceptable salt or hydrate of a compound of claim 12 in an amount effective to treat the vascular disease.
73. A method for treating a vascular disease, comprising administering to a subject in need thereof the compound or a pharmaceutically acceptable salt or hydrate of a compound of claim 13 in an amount effective to treat the vascular disease.
- 25 74. A method for treating an ischemic condition, comprising administering to a subject in need thereof the compound or a pharmaceutically acceptable salt or hydrate of a compound of claim 1 in an amount effective to treat the ischemic condition.

75. A method for treating an ischemic condition, comprising administering to a subject in need thereof the compound or a pharmaceutically acceptable salt or hydrate of a compound of claim 3 in an amount effective to treat the ischemic condition.
76. A method for treating an ischemic condition, comprising administering to a subject in need thereof the compound or a pharmaceutically acceptable salt or hydrate of a compound of claim 4 in an amount effective to treat the ischemic condition.
77. A method for treating an ischemic condition, comprising administering to a subject in need thereof the compound or a pharmaceutically acceptable salt or hydrate of a compound of claim 6 in an amount effective to treat the ischemic condition.
78. A method for treating an ischemic condition, comprising administering to a subject in need thereof the compound or a pharmaceutically acceptable salt or hydrate of a compound of claim 10 in an amount effective to treat the ischemic condition.
79. A method for treating an ischemic condition, comprising administering to a subject in need thereof the compound or a pharmaceutically acceptable salt or hydrate of a compound of claim 11 in an amount effective to treat the ischemic condition.
80. A method for treating an ischemic condition, comprising administering to a subject in need thereof the compound or a pharmaceutically acceptable salt or hydrate of a compound of claim 12 in an amount effective to treat the ischemic condition.
81. A method for treating an ischemic condition, comprising administering to a subject in need thereof the compound or a pharmaceutically acceptable salt or hydrate of a compound of claim 13 in an amount effective to treat the ischemic condition.