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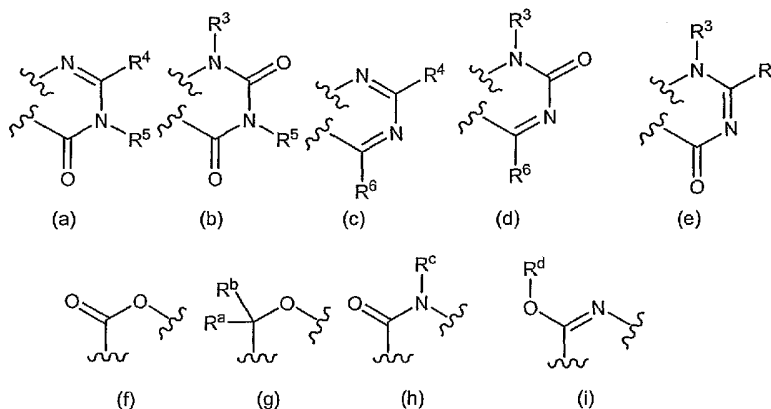
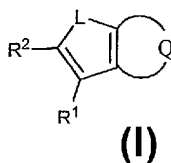
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[Continued on next page]

(54) Title: HETEROCYCLES AS NICOTINIC ACID RECEPTOR AGONISTS FOR THE TREATMENT OF DYSLIPIDEMIA



(57) Abstract: A compound having the general structure of Formula (I): Formula (I) or a pharmaceutically acceptable salt, solvate, ester, or tautomer thereof, wherein: Q is selected from the group consisting of: Formula (a), (b), (c), (d) and (e); and L is selected from the group consisting of: Formula (f), (g), (h), and (i); or a pharmaceutically acceptable salt, solvate, ester, or tautomer thereof, are useful in treating diseases, disorders, or conditions such as metabolic syndrome and dyslipidemia.



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HETEROCYCLES AS NICOTINIC ACID RECEPTOR AGONISTS FOR THE TREATMENT OF DYSLIPIDEMIA

Field of the Invention

The present invention relates to nicotinic acid receptor agonist compounds useful for treating metabolic syndrome, dyslipidemia, cardiovascular diseases, disorders of the peripheral and central nervous system, hematological diseases, cancer, inflammation, respiratory diseases, gastroenterological diseases, diabetes, and non-alcoholic fatty liver disease; pharmaceutical compositions comprising such compounds; pharmaceutical compositions comprising nicotinic acid receptor agonist compounds in combination with other therapeutic agents; and methods of treatment using the compounds and compositions to treat conditions such as metabolic syndrome, dyslipidemia, cardiovascular diseases, disorders of the peripheral and central nervous system, hematological diseases, cancer, inflammation, respiratory diseases, gastroenterological diseases, diabetes, hepatic steatosis and non-alcoholic fatty liver disease.

Background of the Invention

Nicotinic acid has been used to treat metabolic syndrome and dyslipidemia. However, nicotinic acid has undesirable side effects such as flushing and diarrhea. It is therefore desirable to provide improved nicotinic acid receptor agonists with improved efficacy at treating metabolic syndrome and dyslipidemia, yet without the undesirable side effects. The compounds of the present invention provide such improved nicotinic acid receptor agonists.

M. Ridi, Gazzetta Chim. Ital. (1950) vol. 80, p. 121 and M. Ridi, Gazzetta Chim. Ital. (1952) vol. 82, p. 23 disclose syntheses of barbituric acid derivatives. FR 2563223 discloses nucleoside analogs. T. Paterson et al., J. Chem. Soc., Perkins Trans. I (1972), vol. 8, pp. 1041-1050 discloses the synthesis of 8-substituted pyrido[2,3-d]pyrimidines. S. Rao, Indian J. Chem. (1974), 12(10), pp. 1028-1030 discloses the synthesis of pyrano[2,3-d]pyrimidines. M. Skof, Heterocycles, (1999), 51(5), pp. 1051-1058 discloses one step transformations of (S)-1-benzoyl-3-[(E)-dimethylaminomethylidene]-5-methoxycarbonyl-pyrrolidin-2-one into quinoliziny- and 2H-2-pyranonyl-

substituted alanine derivatives. R. Toplak J. Heterocyclic Chem. (1999), 36(1), pp. 225-235 discloses the synthesis of pyran-2-ones. However, the compounds of the above references differ from those of the present invention.

WO 2004/110368 describes combination therapies for the treatment of hypertension comprising the combination of an anti-obesity agent and an anti-hypertensive agent. However, WO 2004/110368 fails to describe nicotinic acid receptor agonists, or combinations of one or more nicotinic acid receptor agonists with a second therapeutic agent.

WO 2005/000217 describes combination therapies for the treatment of dyslipidemia comprising the administration of a combination of an anti-obesity agent and an anti-dyslipidemic agent. However, WO 2005/000217 fails to describe nicotinic acid receptor agonists, or combinations of one or more nicotinic acid receptor agonists with a second therapeutic agent.

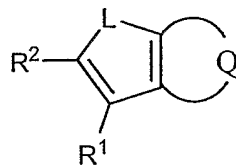
WO 2004/110375 describes combination therapies for the treatment of diabetes comprising the administration of a combination of an anti-obesity agent and an anti-diabetic agent. However, WO 2004/110375 fails to describe nicotinic acid receptor agonists, or combinations of one or more nicotinic acid receptor agonists with a second therapeutic agent.

US 2004/0122033 describes combination therapies for the treatment of obesity comprising the administration of a combination of an appetite suppressant and/or metabolic rate enhancers and/or nutrient absorption inhibitors. However, US 2004/0122033 fails to describe nicotinic acid receptor agonists, or combinations of one or more nicotinic acid receptor agonists with a second therapeutic agent. US 2004/0229844 describes combination therapies for treating atherosclerosis comprising the administration of a combination of nicotinic acid or another nicotinic acid receptor agonist and a DP receptor antagonist. However, the nicotinic acid agonists of US 2004/0229844 are quite different from those of the present invention.

WO2005/077950 describes xanthine derivatives which are agonists of the nicotinic acid receptor HM74A. However, the xanthine derivatives of WO2005/077950 are quite different from the compounds of the present invention.

Summary of the Invention

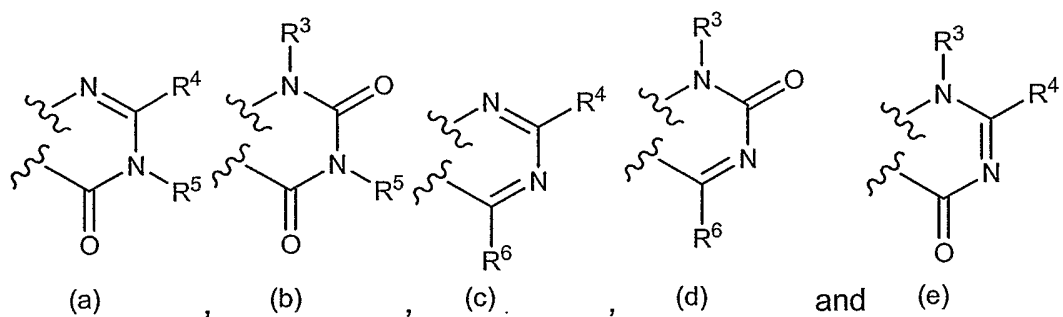
In one embodiment, the present invention is directed to a compound of Formula (I):



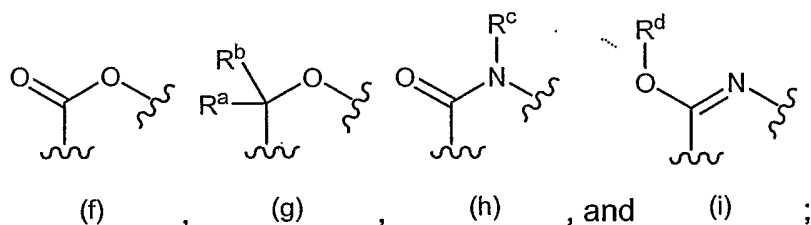
(I)

or a pharmaceutically acceptable salt, solvate, ester, or tautomer thereof, wherein:

Q is selected from the group consisting of:



L is selected from the group consisting of:



R¹ is selected from the group consisting of H, alkyl, alkenyl, alkynyl,

haloalkyl, alkyl substituted with one or more hydroxyl groups,

cycloalkyl, -C(O)-alkyl, -alkylene-C(O)-O-alkyl, -O-R¹⁰,

-alkylene-O-alkyl, aryl, -alkylene-aryl, heteroaryl, -alkylene-heteroaryl,

halogen, -(CH₂)_n-N(R⁷)₂, -alkylene-cycloalkyl, and

-alkylene-cycloalkenyl,

wherein said cycloalkyl or the cycloalkyl portion of said

-alkylene-cycloalkyl of R¹ is unsubstituted or substituted with one

or more X groups, said aryl or the aryl portion of said

-alkylene-aryl of R¹ is unsubstituted or substituted with one or

more Y groups, and said heteroaryl or the heteroaryl portion of

said -alkylene-heteroaryl of R^1 is unsubstituted or substituted with one or more Y groups;

R^2 is selected from the group consisting of H, halogen, alkyl, haloalkyl, alkyl substituted with one or more -OH, -C(O)-alkyl, -C(O)-O-alkyl, -C(O)-OH, -O- R^{10} , -alkylene-O-alkyl, unsubstituted aryl, aryl substituted with one or more Y groups, unsubstituted heteroaryl, heteroaryl substituted with one or more Y groups, and halogen; or

R^1 and R^2 together with the ring carbon atoms to which they are shown attached, form a 5- or 6-membered cycloalkenyl ring or a 5- or 6-membered heterocyclic ring having 1 or 2 heteroatoms;

R^3 is selected from the group consisting of H, alkyl, alkyl substituted with one or more hydroxyl groups, -alkylene-O-alkyl, cycloalkyl, -alkylene-cycloalkyl, -alkylene-C(O)-O-alkyl, -alkylene-O-C(O)-alkyl, alkenyl, aryl, and heteroaryl,

wherein said cycloalkyl or the cycloalkyl portion of said

-alkylene-cycloalkyl of R^3 is unsubstituted or substituted with one or more X groups, said aryl of R^3 is unsubstituted or substituted with one or more Y groups, and said heteroaryl of R^3 is unsubstituted or substituted with one or more Y groups;

R^4 is selected from the group consisting of H, halogen, alkyl, -O- R^{10} , -C(O)-O-alkyl, -S(O)_m- R^9 , -N(R^7)₂, -N(R^7)-NH-C(O)-alkyl, -N(R^7)-NH-C(O)-O-alkyl, -O-N=C(R^{12})₂, -N(R^7)-N=C(R^{12})₂, -C(O)-alkyl, unsubstituted heterocyclyl, heterocyclyl substituted with one or more X groups, -O-N(R^7)-C(O)-O-alkyl, -C(O)-N(R^7)₂, -CN, -N₃, and -O-C(O)-alkyl;

R^5 is selected from the group consisting of H, alkyl, -alkylene-C(O)- R^8 , -alkylene-C(O)-N(R^{11})₂, -alkylene-C(=N-O-alkyl)-aryl, cycloalkyl, -alkylene-cycloalkyl, -alkylene-C(O)-O-alkyl, -alkylene-O-C(O)-alkyl, -alkylene-C(O)-heterocyclyl, and alkenyl,

wherein said cycloalkyl or the cycloalkyl portion of said

-alkylene-cycloalkyl of R^5 is unsubstituted or substituted with one or more X groups, and the aryl portion of said -alkylene-C(=N-O-alkyl)-aryl of R^5 is unsubstituted or substituted with one or more Y groups;

R^6 is selected from the group consisting of H, alkyl, alkenyl, alkyl substituted with one or more hydroxyl groups, -alkylene-O-alkyl, -O- R^{10} , halogen, aryl, heteroaryl, and -N(R^7)₂,

5 wherein said aryl of R^6 is unsubstituted or substituted with one or more Y groups, and said heteroaryl of R^6 is unsubstituted or substituted with one or more Z groups;

each R^7 is independently selected from the group consisting of H, alkyl, cycloalkyl, aryl, -C(O)-alkyl, and -C(O)-aryl,

10 wherein said cycloalkyl of R^7 is unsubstituted or substituted with one or more X groups, and the aryl portion of said -C(O)-aryl or said aryl of R^7 is unsubstituted or substituted with one or more Y groups;

two R^7 groups, together with the N atom to which they are bonded form a heterocyclyl;

15 R^8 is selected from the group consisting of aryl, -OH, and heterocyclyl, wherein said heterocyclyl of R^8 is unsubstituted or substituted with one or more X groups, and said aryl of R^8 is unsubstituted or substituted with one or more Y groups;

20 R^9 is selected from the group consisting of alkyl, -alkylene-cycloalkyl, alkenyl, -N(R^{11})₂, and -alkylene-aryl,

wherein the cycloalkyl portion of said -alkylene-cycloalkyl of R^9 is unsubstituted or substituted with one or more X groups, and the aryl portion of said -alkylene-aryl of R^9 is unsubstituted or substituted with one or more Y groups, and

25 with the proviso that when R^9 is -N(R^{11})₂, m is 1 or 2;

R^{10} is selected from the group consisting of H, alkyl, -alkylene-aryl, -alkenylene-aryl, -alkylene-heteroaryl, alkenyl, -C(O)-alkyl, alkynyl, and -alkylene-cycloalkyl,

30 wherein the cycloalkyl portion of said -alkylene-cycloalkyl of R^{10} is unsubstituted or substituted with one or more X groups, the aryl portion of said -alkylene-aryl or -alkenylene-aryl of R^{10} is unsubstituted or substituted with one or more Y groups, and the heteroaryl portion of said -alkylene-heteroaryl of R^{10} is unsubstituted or substituted with one or more Z groups;

R^{11} is selected from the group consisting of H, alkyl, and aryl,
wherein said aryl of R^{11} is unsubstituted or substituted with one or
more Y groups; or
two R^{11} groups, together with the N atom to which they are attached, form
5 a heterocyclyl;
each R^{12} is independently selected from the group consisting of alkyl, aryl,
and heteroaryl,
wherein said aryl of R^{12} is unsubstituted or substituted with one or
more Y groups and said heteroaryl of R^{12} is unsubstituted or
10 substituted with one or more Z groups;
 R^a and R^b are each independently selected from the group consisting of H,
alkyl, aryl, and heteroaryl,
wherein said aryl of R^a and R^b is unsubstituted or substituted with
one or more Y groups, and said heteroaryl of R^a and R^b is
15 unsubstituted or substituted with one or more Z groups;
 R^c is selected from the group consisting of H, alkyl, alkylene-aryl, and
-C(O)-alkyl,
wherein the aryl portion of said alkylene-aryl of R^c is unsubstituted
or substituted with one or more Y groups;
20 R^d is selected from the group consisting of H, alkyl, and alkylene-aryl,
wherein the aryl portion of said alkylene-aryl of R^d is unsubstituted
or substituted with one or more Y groups;
each X is independently selected from the group consisting of halogen,
alkyl, haloalkyl, -O-alkyl, -O-haloalkyl, and -OH;
25 each Y is independently selected from the group consisting of halogen,
alkyl, haloalkyl, -O-alkyl, -O-haloalkyl, -CN, -NO₂, -OH, -S(O₂)-alkyl,
-S(O₂)-aryl, -S(O₂)-NH₂, -S(O₂)-NH-alkyl, -S(O₂)-NH-aryl,
-S(O₂)-N(alkyl)₂, -S(O₂)-N(aryl)₂, -S(O₂)-N(alkyl)(aryl), and aryl;
each Z is independently selected from the group consisting of alkyl,
30 haloalkyl, halogen, -O-alkyl, -O-haloalkyl, -CN, -OH, aryl, and N-oxide;
n is 0, 1, 2, or 3;
m is 0, 1, or 2; and
with the proviso that when L is (f), and R^2 , R^3 and R^5 are each H, then
 R^1 is not -CH₃.

In another embodiment, the present invention is directed to a pharmaceutical composition comprising a therapeutically effective amount of at least one compound of Formula (I), or a pharmaceutically acceptable salt, solvate, ester, or tautomer thereof, and at least one pharmaceutically acceptable carrier.

In another embodiment, the present invention is directed to a method of treating a disease or disorder in a patient, such as metabolic syndrome, dyslipidemia, cardiovascular diseases, disorders of the peripheral and central nervous system, hematological diseases, cancer, inflammation, respiratory diseases, gastroenterological diseases, diabetes, and non-alcoholic fatty liver disease. The method comprises administering to the patient an effective amount of at least one compound of Formula (I), or a pharmaceutically acceptable salt, solvate, ester, or tautomer thereof.

In another embodiment, the present invention is directed to a method of treating a disease or disorder in a patient, such as metabolic syndrome, dyslipidemia, cardiovascular diseases, disorders of the peripheral and central nervous system, hematological diseases, cancer, inflammation, respiratory diseases, gastroenterological diseases, diabetes, hepatic steatosis, and non-alcoholic fatty liver disease. The method comprises administering to the patient an effective amount of at least one compound of Formula (I), or a pharmaceutically acceptable salt, solvate, ester, or tautomer thereof, in combination with at least one additional active ingredient selected from the group consisting of hydroxy-substituted azetidinone compounds, substituted β -lactam compounds, HMG CoA reductase inhibitor compounds, HMG CoA synthetase inhibitors, squalene synthesis inhibitors, squalene epoxidase inhibitors, sterol biosynthesis inhibitors, nicotinic acid derivatives, bile acid sequestrants, inorganic cholesterol sequestrants, AcylCoA:Cholesterol O-acyltransferase inhibitors, cholesteryl ester transfer protein inhibitors, fish oils containing Omega 3 fatty acids, natural water soluble fibers, plant stanols and/or fatty acid esters of plant stanols (e.g., Omacor[®] from Pronova Biocare, Oslo, Norway), low-density lipoprotein receptor activators, anti-oxidants, PPAR α agonists, PPAR γ -agonists, FXR receptor modulators, LXR receptor agonists, lipoprotein synthesis inhibitors, renin angiotensin inhibitors,

- microsomal triglyceride transport protein inhibitors, bile acid reabsorption inhibitors, PPAR δ agonists, triglyceride synthesis inhibitors, squalene epoxidase inhibitors, low density lipoprotein receptor inducers, platelet aggregation inhibitors, 5-LO or FLAP inhibitors, PPAR δ partial agonists,
- 5 niacin or niacin receptor agonists, 5HT transporter inhibitors, NE transporter inhibitors, CB₁ antagonists/inverse agonists, ghrelin antagonists, H₃ antagonists/inverse agonists, MCH1R antagonists, MCH2R agonists/antagonists, NPY1 antagonists, NPY5 antagonists, NPY2 agonists, NPY4 agonists, mGluR5 antagonists, leptins, leptin agonists/modulators,
- 10 leptin derivatives, opioid antagonists, orexin receptor antagonists, BRS3 agonists, CCK-A agonists, CNTF, CNTF derivatives, CNTF agonists/modulators, 5HT_{2c} agonists, Mc4r agonists, monoamine reuptake inhibitors, serotonin reuptake inhibitors, GLP-1 agonists, phentermine, topiramate, phytopharm compound 57, ghrelin antibodies, Mc3r agonists,
- 15 ACC2 inhibitors, β 3 agonists, DGAT1 inhibitors, DGAT2 inhibitors, FAS inhibitors, PDE inhibitors, thyroid hormone β agonists, UCP-1 activators, UCP-2 activators, UCP-3 activators, acyl-estrogens, glucocorticoid agonists/antagonists, 11 β HSD-1 inhibitors, SCD-1 inhibitors, lipase inhibitors, fatty acid transporter inhibitors, dicarboxylate transporter inhibitors, glucose
- 20 transporter inhibitors, phosphate transporter inhibitors, antidiabetic agents, anti-hypertensive agents, anti-dyslipidemic agents, DP receptor antagonists, apolipoprotein-B secretion/microsomal triglyceride transfer protein (apo-B/MTP) inhibitors, sympathomimetic agonists, dopamine agonists, melanocyte-stimulating hormone receptor analogs, melanin concentrating
- 25 hormone antagonists, leptons, galanin receptor antagonists, bombesin agonists, neuropeptide-Y antagonists, thyromimetic agents, dehydroepiandrosterone, analogs of dehydroepiandrosterone, urocortin binding protein antagonists, glucagons-like peptide-1 receptor agonists, human agouti-related proteins (AGRP), neuromedin U receptor agonists,
- 30 noradrenergic anorectic agents, appetite suppressants, hormone sensitive lipase antagonists, MSH-receptor analogs, α -glucosidase inhibitors, apo A1 milano reverse cholesterol transport inhibitors, fatty acid binding protein inhibitors (FABP), and fatty acid transporter protein inhibitors (FATP).

DETAILED DESCRIPTION OF THE INVENTION

The nicotinic acid receptor agonist compounds of the present invention are useful for treating conditions such as metabolic syndrome, dyslipidemia, cardiovascular diseases, disorders of the peripheral and central nervous system, hematological diseases, cancer, inflammation, respiratory diseases, gastroenterological diseases, diabetes, hepatic steatosis, and non-alcoholic fatty liver disease and other diseases listed herein. One or more compounds of the present invention can be administered alone or in combination with one or more other therapeutic agents as described herein.

10 In a first embodiment, the present invention is directed to a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, ester, or tautomer thereof, as described herein.

In another embodiment of the compounds of Formula (I),
R¹ is selected from the group consisting of -(C₁-C₆)alkyl, -(C₁-C₆)alkenyl, -(C₁-
15 C₆)alkynyl, -(C₁-C₆)haloalkyl, -(C₁-C₆)alkyl substituted with one hydroxyl group, -(C₃-C₇)cycloalkyl, -(C₁-C₆)alkylene-O-(C₁-C₆)alkyl, -(C₁-C₆)alkylene-(C₆-C₁₀)aryl, -(C₁-C₆)alkylene-(C₂-C₁₀)heteroaryl, -(C₁-C₆)alkylene-C(O)-O-(C₁-C₆)alkyl, -(CH₂)_n-N(R⁷)₂, -(C₁-C₆)alkylene-(C₃-C₇)cycloalkyl, and
20 -(C₁-C₆)alkylene-(C₃-C₇)cycloalkenyl

wherein said -(C₃-C₇)cycloalkyl or the (C₃-C₇)cycloalkyl portion of said -(C₁-C₆)alkylene-(C₃-C₇)cycloalkyl is unsubstituted or substituted with one or more X groups, the (C₆-C₁₀)aryl portion of said -(C₁-C₆)alkylene-(C₆-C₁₀)aryl is unsubstituted or substituted with one or more Y groups, and the
25 (C₂-C₁₀)heteroaryl portion of said -(C₁-C₆)alkylene-(C₂-C₁₀)heteroaryl is unsubstituted or substituted with one or more Z groups;

R² is H, halogen, unsubstituted aryl, aryl substituted with one or more
30 independently selected Y groups, unsubstituted heteroaryl, heteroaryl substituted with one or more independently selected Y groups; or R¹ and R² together with the ring carbon atoms to which they are shown attached, form a 5- or 6-membered cycloalkenyl ring;

R^3 is selected from the group consisting of H, (C₁-C₆)alkyl,
-(C₃-C₆)alkylene-O-(C₁-C₆)alkyl, (C₃-C₇)cycloalkyl,
-(C₁-C₆)alkylene-(C₃-C₇)cycloalkyl, -(C₁-C₆)alkylene-C(O)-O-alkyl, and
(C₁-C₆)alkenyl,

5 wherein said (C₃-C₇)cycloalkyl or the (C₃-C₇)cycloalkyl portion of
 said -(C₃-C₆)alkylene-(C₃-C₇)cycloalkyl of R^3 is unsubstituted or
 substituted with one or more X groups;

R^4 is selected from the group consisting of halogen, -O- R^{10} ,
-C(O)-O-(C₁-C₆)alkyl, -S(O)_m- R^9 , -N(R^7)₂, -O-N=C(R^{12})₂,
10 -N(R^7)-NH-C(O)-O-(C₁-C₆)alkyl and -C(O)-(C₁-C₆)alkyl;

R^5 is selected from the group consisting of H, -(C₁-C₆)alkyl,
-(C₁-C₆)alkylene-C(O)- R^8 ,
-(C₁-C₆)alkylene-C(=N-O-(C₁-C₆)alkyl)-(C₆-C₁₀)aryl, (C₃-C₇)cycloalkyl,
-(C₁-C₆)alkylene-(C₃-C₇)cycloalkyl,
15 -(C₁-C₆)alkylene-C(O)-O-(C₁-C₆)alkyl, and (C₂-C₆)alkenyl
 wherein said (C₃-C₇)cycloalkyl or the (C₃-C₇)cycloalkyl portion of
 said -(C₁-C₆)alkylene-(C₃-C₇)cycloalkyl of R^5 is unsubstituted or
 substituted with one or more X groups, and the (C₆-C₁₀)aryl
 portion of said
20 -(C₁-C₆)alkylene-C(=N-O-(C₁-C₆)alkyl)-(C₆-C₁₀)aryl of R^5 is
 unsubstituted or substituted with one or more Y groups;

R^6 is selected from the group consisting of -O- R^{10} , halogen, and -N(R^7)₂;
each R^7 is independently selected from the group consisting of H,

(C₁-C₆)alkyl, (C₃-C₇)cycloalkyl, and (C₆-C₁₀)aryl,
25 wherein said (C₃-C₇)cycloalkyl of R^7 is unsubstituted or substituted
 with one or more X groups, and said (C₆-C₁₀)aryl of R^7 is
 unsubstituted or substituted with one or more Y groups;

R^8 is selected from the group consisting of unsubstituted (C₆-C₁₀)aryl,
(C₆-C₁₀)aryl substituted with one or more Y groups, -OH, unsubstituted
30 (C₂-C₁₀)heterocyclyl, and (C₂-C₁₀)heterocyclyl substituted with one or
 more X groups;

R^9 is selected from the group consisting of (C₁-C₆)alkyl,
-(C₁-C₆)alkylene-(C₃-C₇)cycloalkyl, (C₂-C₆)alkenyl, and
-(C₁-C₆)alkylene-(C₆-C₁₀)aryl,

wherein the (C₃-C₇)cycloalkyl portion of said

-(C₁-C₆)alkylene-(C₃-C₇)cycloalkyl of R⁹ is unsubstituted or substituted with one or more X groups, and the (C₆-C₁₀)aryl portion of said -(C₁-C₆)alkylene-(C₆-C₁₀)aryl of R⁹ is

5 unsubstituted or substituted with one or more groups Y;

R¹⁰ is selected from the group consisting of H, (C₁-C₆)alkyl,

-(C₁-C₆)alkylene-(C₆-C₁₀)aryl, -(C₂-C₆)alkenylene-(C₆-C₁₀)aryl,

-(C₁-C₆)alkylene-(C₂-C₁₀)heteroaryl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, and

-(C₁-C₆)alkylene-(C₃-C₇)cycloalkyl,

10 wherein the (C₃-C₇)cycloalkyl portion of said

-(C₁-C₆)alkylene-(C₃-C₇)cycloalkyl of R¹⁰ is unsubstituted or substituted with one or more X groups, and the (C₆-C₁₀)aryl portion of said -(C₁-C₆)alkylene-(C₆-C₁₀)aryl or

15 -(C₂-C₆)alkenylene-(C₆-C₁₀)aryl of R¹⁰ is unsubstituted or substituted with one or more Y groups, and the (C₂-C₁₀)heteroaryl portion of said

-(C₁-C₆)alkylene-(C₂-C₁₀)heteroaryl of R¹⁰ is unsubstituted or substituted with one or more Z groups;

each R¹² is independently a (C₁-C₆)alkyl;

20 R^a and R^b are each independently a (C₁-C₆)alkyl;

R^c is H;

R^d is selected from the group consisting of H, (C₁-C₆)alkyl, and

-(C₁-C₆)alkylene-(C₆-C₁₀)aryl,

wherein the (C₆-C₁₀)aryl portion of said

25 -(C₁-C₆)alkylene-(C₆-C₁₀)aryl of R^d is unsubstituted or substituted with one or more Y groups;

each X is independently selected from the group consisting of F, Cl, Br,

(C₁-C₆)alkyl, (C₁-C₆)haloalkyl, -O-(C₁-C₆)alkyl, -O-(C₁-C₆)haloalkyl, and -OH;

30 each Y is independently selected from the group consisting of F, Br, Cl,

(C₁-C₆)alkyl, (C₁-C₆)haloalkyl, -O-(C₁-C₆)alkyl, -O-(C₁-C₆)haloalkyl, -CN, -NO₂, -OH, , -S(O₂)-(C₁-C₆)alkyl, -S(O₂)-(C₆-C₁₀)aryl, -S(O₂)-NH₂, -S(O₂)-NH-(C₁-C₆)alkyl, -S(O₂)-NH-(C₆-C₁₀)aryl,

-S(O₂)-N((C₁-C₆)alkyl)₂, -S(O₂)-N((C₆-C₁₀)aryl)₂,
 -S(O₂)-N((C₁-C₆)alkyl)((C₆-C₁₀)aryl), and (C₆-C₁₀)aryl; and

each Z is independently selected from the group consisting of (C₁-C₆)alkyl,
 (C₁-C₆)haloalkyl, F, Br, and Cl, -O-(C₁-C₆)alkyl, -CN, -OH, (C₆-C₁₀)aryl,
 5 and N-oxide.

In another embodiment of the compounds of Formula (I),

R¹ is selected from the group consisting of -CH₃, -CH₂CH₃, -CH₂CH₂CH₃,
 -CH₂CH₂CH₂CH₃, -CH₂CH₂CH₂CH₂CH₃, -CH₂CH₂CH₂CH₂CH₂CH₃,
 -CH₂CH₂CH(CH₃)₂, -CH₂CH₂CH₂CH(CH₃)₂, -CH(CH₃)₂,
 10 -CH₂CH₂CH=CH₂, -CH₂CH₂CH=CHCH₃, -CH₂CH₂CH₂CH₂CH=CH₂,
 -CH₂CH₂CH₂CH=CH₂, -CH₂-OH, -CH(CH₃)-OH, cyclobutyl,
 -CH₂-C(O)-O-CH₂CH₃, -CH₂CH₂CH₂-O-CH₃, -CH₂CF₃, -CHBrCH₃,
 -CH₂CH₂CF₃, -CH₂CH₂CH₂CF₃, -CH₂CH₂CH₂CH₂CF₃, -CH₂CH₂CH₂Cl,
 , -CH₂-(2-thiophenyl), -CH₂CH₂CH₂-(2-thiophenyl), -CH₂-cyclopropyl,
 15 -CH₂CH₂-cyclopropyl, -CH₂CH₂CH₂-cyclopropyl,
 -CH₂CH₂CH₂CH₂-cyclopropyl, -CH₂-cyclobutyl, -CH₂CH₂-cyclobutyl,
 -CH₂CH₂CH₂-cyclobutyl, -CH₂CH₂CH₂CH₂-cyclobutyl,
 -CH₂-cyclopentyl, -CH₂CH₂-cyclopentyl, -CH₂CH₂CH₂-cyclopentyl,
 -CH₂CH₂CH₂CH₂-cyclopentyl, -CH₂-cyclohexyl, -CH₂-(4-
 20 methylcyclohexyl), -CH₂CH₂-cyclohexyl, -CH₂-cycloheptyl, -CH₂-(2-
 cyclopentenyl, -CH₂CH₂C≡CH, -CH₂CH₂CH₂C≡CH, -CH₂-phenyl,
 -CH₂-(2-fluorophenyl), -CH₂-(3-fluorophenyl), and -CH₂-NH(3-
 methoxyphenyl);

R² is selected from the group consisting of H, F, Cl, Br, unsubstituted aryl,
 25 aryl substituted with one or more Y groups, unsubstituted heteroaryl,
 heteroaryl substituted with one or more Y groups; or

R¹ and R² together with the ring carbon atoms to which they are shown
 attached, form a cyclopentenyl or cyclohexenyl ring;

R³ is selected from the group consisting of H, -CH₂-cyclopropyl,
 30 -CH₂-C(O)-O-CH₃, cyclopropyl, cyclobutyl, cyclopentyl, cyclopentyl,
 -CH₃, -CH₂CH₃, -CH₂CH₂CH₃, -CH₂CH=CH₂, and -CH₂-O-CH₃;

R⁴ is selected from the group consisting of Cl, -O-R¹⁰, -C(O)-O-CH₃,
 -S(O)₂-CH₃, -S(O)-CH₃, -S(O)-CH₂CH₃, -S(O)-CH(CH₃)₂,
 -S(O)-C(CH₃)₃, -S(O)-CH₂-cyclopropyl, -S(O)-CH₂-phenyl,

-S(O)-CH(CH₃)-phenyl, -S-CH₂-CH=CH₂, -N(R⁷)₂, -O-N=C(CH₃)₂,
-NH-NH-C(O)-O-CH₃, and -C(O)-CH₃,

wherein the phenyl portion of said -S(O)-CH₂-phenyl, or
-S(O)-CH(CH₃)-phenyl of R⁴ is unsubstituted or substituted with
one or more groups Y;

R⁵ is selected from the group consisting of H, -CH₃, -CH₂CH₃,
-CH₂CH₂CH₃, -CH₂-C(O)-phenyl, -CH₂-C(O)-OH,
-CH₂-C(=N-O-CH₃)-phenyl, cyclopropyl, cyclobutyl, cyclopentyl,
-CH₂-C(O)-piperidyl, -CH₂-cyclopropyl, -CH₂-C(O)-O-CH₃, and
-CH₂-CH=CH₃,

wherein the phenyl portion of said -CH₂-C(O)-phenyl is
unsubstituted or substituted with one or more Y groups;

R⁶ is selected from the group consisting of -OR¹⁰, Cl, and -N(R⁷)₂;

each R⁷ is independently selected from the group consisting of H,
cyclobutyl, unsubstituted phenyl, and phenyl substituted with one or
more Y groups;

R¹⁰ is selected from the group consisting of H, -CH₃, -CH₂-cyclopropyl,
-CH₂-CH=CH₃, -CH₂C≡C-CH₃, -CH₂-phenyl, -CH(CH₃)-phenyl,
-CH(CH₂CH₃)-phenyl, -CH(CH₂CH₂CH₃)-phenyl,
-CH(CH(CH₃)₂)-phenyl, -CH(CH₂CH=CH₂)-phenyl, -CH₂-pyridyl,
-CH(CH₃)-thiazolyl, and -CH₂-pyrimidinyl,

wherein the phenyl portion of said -CH₂-phenyl, -CH(CH₃)-phenyl,
-CH(CH₂CH₃)-phenyl, -CH(CH₂CH₂CH₃)-phenyl,
-CH(CH(CH₃)₂)-phenyl, or -CH(CH₂CH=CH₂)-phenyl of R¹⁰ is
unsubstituted or substituted with one or more groups Y, and the
pyridyl, thiazolyl, or pyrimidinyl portion of said -CH₂-pyridyl,
-CH₂-thiazolyl, or -CH₂-pyrimidinyl of R¹⁰ is unsubstituted or
substituted with one or more groups Z;

R^a and R^b are each -CH₃;

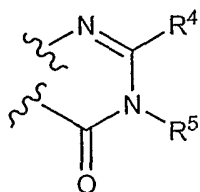
R^c is H;

R^d is selected from the group consisting of H, -CH₃, and -CH₂-phenyl,

wherein the phenyl portion of said -CH₂-phenyl of R^d is
unsubstituted or substituted with one or more Y groups;

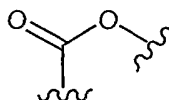
each Y is independently selected from the group consisting of F, Cl, Br,
 $-\text{CH}_3$, $-\text{CF}_3$, $-\text{O}-\text{CH}_3$, $-\text{O}-\text{CF}_3$, $-\text{CN}$, $-\text{OH}$, and phenyl; and
 each Z is independently selected from the group consisting of $-\text{CH}_3$, $-\text{CF}_3$,
 F, Br, and Cl, $-\text{O}-\text{CH}_3$, $-\text{CN}$, $-\text{OH}$, phenyl, and N-oxide.

5 In another embodiment of the compounds of Formula (I),
 Q is:



(a) ;

L is:



(f) ;

10 R^1 is selected from the group consisting of $-(\text{C}_1-\text{C}_6)\text{alkyl}$,
 $-(\text{C}_1-\text{C}_6)\text{alkylene}-\text{O}-(\text{C}_1-\text{C}_6)\text{alkyl}$, unsubstituted $(\text{C}_6-\text{C}_{10})\text{aryl}$, and
 $(\text{C}_6-\text{C}_{10})\text{aryl}$ substituted with one or more substituents Y;

R^2 is H or halogen;

15 R^4 is selected from the group consisting of halogen, $-\text{O}-\text{R}^{10}$,
 $-\text{C}(\text{O})-\text{O}-(\text{C}_1-\text{C}_6)\text{alkyl}$, $-\text{S}(\text{O})_m-\text{R}^9$, $-\text{N}(\text{R}^7)_2$, $-\text{O}-\text{N}=\text{C}(\text{R}^{12})_2$,
 $-\text{N}(\text{R}^7)-\text{NH}-\text{C}(\text{O})-\text{O}-(\text{C}_1-\text{C}_6)\text{alkyl}$, and $-\text{C}(\text{O})-(\text{C}_1-\text{C}_6)\text{alkyl}$;

R^5 is H or $(\text{C}_1-\text{C}_6)\text{alkyl}$;

20 each R^7 is independently selected from the group consisting of H,
 $(\text{C}_1-\text{C}_6)\text{alkyl}$, $(\text{C}_3-\text{C}_6)\text{cycloalkyl}$, unsubstituted $(\text{C}_6-\text{C}_{10})\text{aryl}$, and
 $(\text{C}_6-\text{C}_{10})\text{aryl}$ substituted with one or more Y groups;

R^9 is selected from the group consisting of $(\text{C}_1-\text{C}_6)\text{alkyl}$,
 $-(\text{C}_1-\text{C}_6)\text{alkylene}-(\text{C}_3-\text{C}_6)\text{cycloalkyl}$, $(\text{C}_2-\text{C}_6)\text{alkenyl}$, and
 $-(\text{C}_1-\text{C}_6)\text{alkylene}-(\text{C}_6-\text{C}_{10})\text{aryl}$,

25 wherein the $(\text{C}_6-\text{C}_{10})\text{aryl}$ of said $-(\text{C}_1-\text{C}_6)\text{alkylene}-(\text{C}_6-\text{C}_{10})\text{aryl}$ of R^9
 is unsubstituted or substituted with one or more groups Y;

R^{10} is selected from the group consisting of H, $(\text{C}_1-\text{C}_6)\text{alkyl}$,
 $-(\text{C}_1-\text{C}_6)\text{alkylene}-(\text{C}_6-\text{C}_{10})\text{aryl}$, $-(\text{C}_1-\text{C}_6)\text{alkenylene}-(\text{C}_6-\text{C}_{10})\text{aryl}$,

-(C₁-C₆)alkylene-(C₂-C₁₀)heteroaryl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, and
 -(C₁-C₆)alkylene-(C₃-C₆)cycloalkyl

wherein the aryl of said -(C₁-C₆)alkylene-(C₆-C₁₀)aryl or

-(C₁-C₆)alkenylene-(C₆-C₁₀)aryl of R¹⁰ is unsubstituted or
 substituted with one or more groups Y, and the

(C₂-C₁₀)heteroaryl of said -(C₁-C₆)alkylene-(C₂-C₁₀)heteroaryl of
 R¹⁰ is unsubstituted or substituted with one or more groups Z;

each R¹² is independently selected from the group consisting of

(C₁-C₆)alkyl, (C₆-C₁₀)aryl, and (C₂-C₁₀)heteroaryl,

wherein said (C₆-C₁₀)aryl is unsubstituted or substituted with one or
 more Y group, and said (C₂-C₁₀)heteroaryl is unsubstituted or
 substituted with one or more Z group;

each Y is independently selected from the group consisting of halogen,

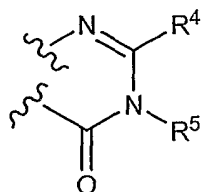
(C₁-C₆)alkyl, (C₁-C₆)haloalkyl, -O-(C₁-C₆)haloalkyl, -O-(C₁-C₆)alkyl,
 -CN, -NO₂, -OH, -S(O₂)-(C₁-C₆)alkyl, -S(O₂)-(C₆-C₁₀)aryl, -S(O₂)-NH₂,
 -S(O₂)-NH-(C₁-C₆)alkyl, -S(O₂)-NH-(C₆-C₁₀)aryl,
 -S(O₂)-N((C₁-C₆)alkyl)₂, -S(O₂)-N((C₆-C₁₀)aryl)₂,
 -S(O₂)-N((C₁-C₆)alkyl)((C₆-C₁₀)aryl), and (C₆-C₁₀)aryl; and

each Z is independently selected from the group consisting of (C₁-C₆)alkyl,

(C₁-C₆)haloalkyl, halogen, -O-alkyl, -O-(C₁-C₆)haloalkyl, -CN, -OH,
 (C₆-C₁₀)aryl, and, and N-oxide.

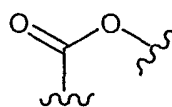
In another embodiment of the compounds of Formula (I),

Q is:



(a) ;

L is:



(f) ;

R¹ is -CH₂CH₃, butyl, pentyl, -CH₂-CH₂-CH₂-cyclopropyl;

R^2 is H, Br, unsubstituted aryl, aryl substituted with one or more Y groups, unsubstituted heteroaryl, heteroaryl substituted with one or more Y groups;

5 R^4 is selected from the group consisting of Cl, $-O-R^{10}$, $-C(O)-O-CH_3$, $-S(O)-CH_3$, $-S(O)-CH_2CH_3$, $-S(O)-CH(CH_3)_2$, $-S(O)-C(CH_3)_3$, $-S(O)-CH_2$ -cyclopropyl, $-S-CH_2-CH=CH_2$, $-S(O)-CH_2$ -phenyl, $-S(O)-CH(CH_3)$ -phenyl, $-N(R^7)_2$, $-O-N=C(CH_3)_2$, $-NH-NH-C(O)-O-CH_3$, and $-C(O)-CH_3$,

10 wherein the phenyl portion of said $-S(O)-CH_2$ -phenyl, or $-S(O)-CH(CH_3)$ -phenyl of R^4 is unsubstituted or substituted with one or more groups Y;

R^5 is H or $-CH_2CH_3$;

each R^7 is independently selected from the group consisting of H and cyclobutyl;

15 R^{10} is selected from the group consisting of H, $-CH_3$, $-CH_2$ -cyclopropyl, $-CH_2-CH=CH_2$, $-CH_2C \equiv C-CH_3$, $-CH_2$ -phenyl, $-CH(CH_3)$ -phenyl, $-CH(CH_2CH_3)$ -phenyl, $-CH(CH(CH_3)_2)$ -phenyl, $-CH(CH_2CH_2CH_3)$ -phenyl, $-CH(CH_2CH=CH_2)$ -phenyl, $-CH_2$ -pyridyl, $-CH(CH_3)$ -thiazolyl, $-CH_2$ -pyrimidinyl,

20 wherein the phenyl portion of said $-CH_2$ -phenyl, $-CH(CH_3)$ -phenyl, $-CH(CH_2CH_3)$ -phenyl, $-CH(CH(CH_3)_2)$ -phenyl, $-CH(CH_2CH=CH_2)$ -phenyl, or $-CH(CH_2CH_2CH_3)$ -phenyl, of R^{10} is unsubstituted or substituted with one or more groups Y, and the pyridyl, thiazolyl, or pyrimidinyl portion of said $-CH_2$ -pyridyl, $-CH(CH_3)$ -thiazolyl, or $-CH_2$ -pyrimidinyl of R^{10} is

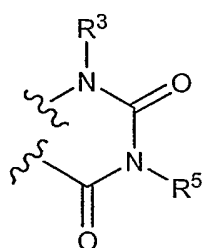
25 unsubstituted or substituted with one or more groups Z;

each Y is independently selected from the group consisting of F, Cl, Br, $-CH_3$, $-CF_3$, $-O-CH_3$, $-O-CF_3$, and phenyl; and

30 each Z is independently selected from the group consisting of $-CH_3$, phenyl, and N-oxide.

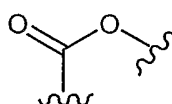
In another embodiment of the compounds of Formula (I),

Q is:



(b) ;

L is:



(f) ;

is selected from the group consisting of $-(C_1-C_6)alkyl$, $-(C_1-C_6)alkenyl$, $-(C_1-C_6)alkynyl$, $-(C_1-C_6)alkylene-C(O)-O-(C_1-C_6)alkyl$, $-(C_3-C_7)cycloalkyl$, $-(C_1-C_6)alkylene-O-(C_1-C_6)alkyl$, $-(C_1-C_6)alkylene-(C_6-C_{10})aryl$, $-(C_1-C_6)alkylene-(C_2-C_{10})heteroaryl$, $-(C_1-C_6)alkylene-(C_3-C_7)cycloalkyl$, $-(C_1-C_6)alkylene-(C_3-C_7)cycloalkenyl$, $(C_1-C_6)alkyl$ substituted with one or more hydroxyl groups, $-(CH_2)_n-N(R^7)_2$, and $-(C_1-C_6)haloalkyl$ wherein said $-(C_3-C_7)cycloalkyl$ or the $(C_3-C_7)cycloalkyl$ portion of said $-(C_1-C_6)alkylene-(C_3-C_7)cycloalkyl$ is unsubstituted or substituted with one or more X groups, the $(C_6-C_{10})aryl$ portion of said $-(C_1-C_6)alkylene-(C_6-C_{10})aryl$ is unsubstituted or substituted with one or more Y groups, and the $(C_2-C_{10})heteroaryl$ portion of said $-(C_1-C_6)alkylene-(C_2-C_{10})heteroaryl$ is unsubstituted or substituted with one or more Z groups;

 R^2 is H; R^3 is selected from the group consisting of H, $(C_1-C_6)alkyl$, $(C_3-C_6)cycloalkyl$, $-(C_1-C_6)alkylene-(C_3-C_6)cycloalkyl$, $-(C_1-C_6)alkylene-C(O)-O-(C_1-C_6)alkyl$, $(C_2-C_6)alkenyl$, and $-(C_1-C_6)alkylene-O-(C_1-C_6)alkyl$; R^5 is selected from the group consisting of H, $-(C_1-C_6)alkyl$, $(C_2-C_6)alkenyl$, $-(C_1-C_6)alkylene-C(O)-R^8$, $-(C_1-C_6)alkylene-C(=N-O-(C_1-C_6)alkyl)-(C_6-C_{10})aryl$, $(C_3-C_6)cycloalkyl$,

-(C₁-C₆)alkylene-(C₃-C₆)cycloalkyl, and

-(C₁-C₆)alkylene-C(O)-O-(C₁-C₆)alkyl;

each R⁷ is independently selected from the group consisting of H and aryl,
wherein said aryl of R⁷ is unsubstituted or substituted with one or more

5 Y groups;

R⁸ is selected from the group consisting of unsubstituted (C₆-C₁₀)aryl,
(C₆-C₁₀)aryl substituted with one or more Y groups, -OH, unsubstituted
(C₂-C₁₀)heterocyclyl and (C₂-C₁₀)heterocyclyl substituted with one or
more X groups;

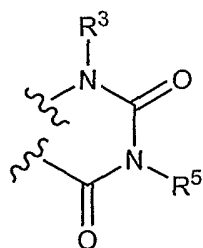
10 each X is independently selected from the group consisting of halogen,
(C₁-C₆)alkyl, (C₁-C₆)haloalkyl, -O-(C₁-C₆)alkyl, -O-(C₁-C₆)haloalkyl, and
-OH;

each Y is independently selected from the group consisting of halogen,
(C₁-C₆)alkyl, (C₁-C₆)haloalkyl, -O-(C₁-C₆)haloalkyl, -O-(C₁-C₆)alkyl,
15 -CN, -NO₂, -OH, -S(O₂)-(C₁-C₆)alkyl, -S(O₂)-(C₆-C₁₀)aryl, -S(O₂)-NH₂,
-S(O₂)-NH-(C₁-C₆)alkyl, -S(O₂)-NH-(C₆-C₁₀)aryl,
-S(O₂)-N((C₁-C₆)alkyl)₂, -S(O₂)-N((C₆-C₁₀)aryl)₂,
-S(O₂)-N((C₁-C₆)alkyl)((C₆-C₁₀)aryl), and (C₆-C₁₀)aryl; and

each Z is independently selected from the group consisting of (C₁-C₆)alkyl,
20 (C₁-C₆)haloalkyl, F, Br, and Cl, -O-(C₁-C₆)alkyl, -CN, -OH, (C₆-C₁₀)aryl,
and N-oxide.

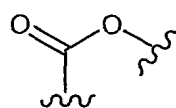
In another embodiment of the compounds of Formula (I),

Q is:



(b) ;

25 L is:

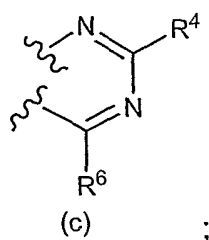


(f) ;

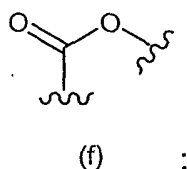
- R^1 is selected from the group consisting of $-\text{CH}_3$, $-\text{CH}_2\text{CH}_3$, $-\text{CH}_2\text{CH}_2\text{CH}_3$,
 $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$,
 $-\text{CH}_2\text{CH}_2\text{CH}(\text{CH}_3)_2$, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}(\text{CH}_3)_2$, $-\text{CH}(\text{CH}_3)_2$,
 $-\text{CH}_2-\text{C}(\text{O})-\text{O}-\text{CH}_2\text{CH}_3$, $-\text{CH}_2\text{CF}_3$, $-\text{CH}_2\text{CH}_2\text{CH}=\text{CH}_2$,
5 $-\text{CH}_2\text{CH}_2\text{CH}=\text{CHCH}_3$, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}=\text{CH}_2$,
 $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}=\text{CH}_2$, $-\text{CH}_2\text{OH}$, $-\text{CH}(\text{CH}_3)\text{OH}$, $-\text{CH}_2\text{N}(\text{R}^7)_2$, cyclobutyl,
 $-\text{CH}_2\text{CH}_2\text{CH}_2-\text{O}-\text{CH}_3$, $-\text{CH}_2\text{CH}_2\text{CF}_3$, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CF}_3$,
 $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CF}_3$, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{Cl}$, $-\text{CH}_2-(2\text{-thiophenyl})$,
 $-\text{CH}_2\text{CH}_2\text{CH}_2-(2\text{-thiophenyl})$, $-\text{CH}_2\text{-cyclopropyl}$, $-\text{CH}_2\text{CH}_2\text{-cyclopropyl}$,
10 $-\text{CH}_2\text{CH}_2\text{CH}_2\text{-cyclopropyl}$, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{-cyclopropyl}$,
 $-\text{CH}_2\text{-cyclopentyl}$, $-\text{CH}_2\text{CH}_2\text{-cyclopentyl}$, $-\text{CH}_2\text{-cyclohexyl}$, $-\text{CH}_2-(4\text{-methylcyclohexyl})$,
 $-\text{CH}_2\text{CH}_2\text{-cyclohexyl}$, $-\text{CH}_2\text{-cycloheptyl}$, $-\text{CH}_2-(2\text{-cyclopentenyl})$, $-\text{CH}_2\text{CH}_2\text{C}\equiv\text{CH}$, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{C}\equiv\text{CH}$, $-\text{CH}_2\text{-phenyl}$,
 $-\text{CH}_2-(2\text{-fluorophenyl})$, $-\text{CH}_2-(3\text{-fluorophenyl})$, and $-\text{CHBrCH}_3$;
- 15 R^2 is H; or
 R^1 and R^2 together with the ring carbon atoms to which they are shown attached, form a cyclopentenyl or cyclohexenyl ring;
- R^3 is selected from the group consisting of H, $-\text{CH}_2\text{-cyclopropyl}$,
 $-\text{CH}_2-\text{C}(\text{O})-\text{O}-\text{CH}_3$, $-\text{cyclopropyl}$, cyclobutyl, cyclopentyl, $-\text{CH}_3$,
20 $-\text{CH}_2\text{CH}_3$, $-\text{CH}_2\text{CH}_2\text{CH}_3$, $-\text{CH}_2\text{CH}=\text{CH}_2$, and $-\text{CH}_2-\text{O}-\text{CH}_3$;
- R^5 is selected from the group consisting of H, $-\text{CH}_2\text{-cyclopropyl}$,
 $-\text{CH}_2-\text{C}(\text{O})-\text{O}-\text{CH}_3$, $-\text{CH}_2-\text{C}(\text{O})-\text{R}^8$, $-\text{CH}_2-\text{C}(=\text{N}-\text{O}-\text{CH}_3)\text{-phenyl}$,
cyclopropyl, cyclobutyl, cyclopentyl, $-\text{CH}_3$, $-\text{CH}_2\text{CH}_3$, $-\text{CH}_2\text{CH}_2\text{CH}_3$, and
 $-\text{CH}_2\text{CH}=\text{CH}_2$;
- 25 each R^7 is independently H or phenyl,
wherein said phenyl of R^7 is unsubstituted or substituted with one or more Y groups;
- R^8 is selected from the group consisting of unsubstituted phenyl, phenyl substituted with one or more Y groups, $-\text{OH}$, and piperidyl; and
30 each Y is independently selected from the group consisting of F, $-\text{CF}_3$,
 $-\text{OCH}_3$, $-\text{CN}$, and $-\text{OH}$.

In another embodiment of the compounds of Formula (I),

Q is:



L is:



5 R^1 is selected from the group consisting of $-(C_1-C_6)$ alkyl, $-(C_1-C_6)$ alkenyl,
 $-(C_1-C_6)$ alkynyl, $-(C_1-C_6)$ alkylene- $C(O)-O-(C_1-C_6)$ alkyl,
 $-(C_3-C_7)$ cycloalkyl, $-(C_1-C_6)$ alkylene- $O-(C_1-C_6)$ alkyl,
 $-(C_1-C_6)$ alkylene- (C_6-C_{10}) aryl, $-(C_1-C_6)$ alkylene- (C_2-C_{10}) heteroaryl,
 $-(C_1-C_6)$ alkylene- (C_3-C_7) cycloalkyl,
 $-(C_1-C_6)$ alkylene- (C_3-C_7) cycloalkenyl, $-(C_1-C_6)$ alkyl substituted with one
 10 or more hydroxyl groups, $-(CH_2)_n-N(R^7)_2$, and $-(C_1-C_6)$ haloalkyl
 wherein said $-(C_3-C_7)$ cycloalkyl or the (C_3-C_7) cycloalkyl portion of
 said $-(C_1-C_6)$ alkylene- (C_3-C_7) cycloalkyl is unsubstituted or
 substituted with one or more X groups, the (C_6-C_{10}) aryl portion
 of said $-(C_1-C_6)$ alkylene- (C_6-C_{10}) aryl is unsubstituted or
 15 substituted with one or more Y groups, and the
 (C_2-C_{10}) heteroaryl portion of said $-(C_1-C_6)$ alkylene-
 (C_2-C_{10}) heteroaryl is unsubstituted or substituted with one or
 more Z groups;

R^2 is H; or

20 R^1 and R^2 together with the ring carbon atoms to which they are shown
 attached, form a 5- or 6-membered cycloalkenyl ring;

R^4 is selected from the group consisting of halogen, $-O-R^{10}$,
 $-C(O)-O-(C_1-C_6)$ alkyl, $-S(O)_m-R^9$, $-N(R^7)_2$, $-O-N=C(R^{12})_2$,
 $-N(R^7)-NH-C(O)-O-(C_1-C_6)$ alkyl, and $-C(O)-(C_1-C_6)$ alkyl;

25 R^6 is selected from the group consisting of $-O-R^{10}$, halogen, and $-N(R^7)_2$;
 each R^7 is independently selected from the group consisting of H,
 (C_1-C_6) alkyl, (C_3-C_6) cycloalkyl, unsubstituted (C_6-C_{10}) aryl, and
 (C_6-C_{10}) aryl substituted with one or more Y groups;

R^9 is selected from the group consisting of (C_1-C_6) alkyl,

$-(C_1-C_6)$ alkylene- (C_3-C_6) cycloalkyl, (C_2-C_6) alkenyl, and

$-(C_1-C_6)$ alkylene- (C_6-C_{10}) aryl,

wherein the (C_6-C_{10}) aryl portion of said $-(C_1-C_6)$ alkylene-

5 (C_6-C_{10}) aryl of R^9 is unsubstituted or substituted with one or more groups Y;

R^{10} is selected from the group consisting of H, (C_1-C_6) alkyl,

$-(C_1-C_6)$ alkylene- (C_6-C_{10}) aryl, $-(C_1-C_6)$ alkenylene- (C_6-C_{10}) aryl,

$-(C_1-C_6)$ alkylene- (C_2-C_{10}) heteroaryl, (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, and

10 $-(C_1-C_6)$ alkylene- (C_3-C_6) cycloalkyl,

wherein the (C_6-C_{10}) aryl portion of said

$-(C_1-C_6)$ alkylene- (C_6-C_{10}) aryl or $-(C_1-C_6)$ alkenylene- (C_6-C_{10}) aryl

of R^{10} is unsubstituted or substituted with one or more groups Y,

and the (C_2-C_{10}) heteroaryl portion of said

15 $-(C_1-C_6)$ alkylene- (C_2-C_{10}) heteroaryl of R^{10} is unsubstituted or substituted with one or more groups Z;

each Y is independently selected from the group consisting of F, Br, Cl,

(C_1-C_6) alkyl, (C_1-C_6) haloalkyl, $-O-(C_1-C_6)$ alkyl, $-O-(C_1-C_6)$ haloalkyl,

$-CN$, $-NO_2$, $-OH$, $-S(O_2)-(C_1-C_6)$ alkyl, $-S(O_2)-(C_6-C_{10})$ aryl, $-S(O_2)-NH_2$,

20 $-S(O_2)-NH-(C_1-C_6)$ alkyl, $-S(O_2)-NH-(C_6-C_{10})$ aryl,

$-S(O_2)-N((C_1-C_6)alkyl)_2$, $-S(O_2)-N((C_6-C_{10})aryl)_2$,

$-S(O_2)-N((C_1-C_6)alkyl)((C_6-C_{10})aryl)$, and (C_6-C_{10}) aryl; and

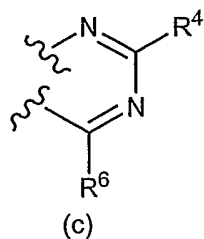
each Z is independently selected from the group consisting of (C_1-C_6) alkyl,

(C_1-C_6) haloalkyl, F, Br, and Cl, $-O-(C_1-C_6)$ alkyl, $-CN$, $-OH$, (C_6-C_{10}) aryl,

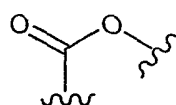
25 and N-oxide.

In another embodiment of the compounds of Formula (I),

Q is:



L is:



(f) ;

R^1 is selected from the group consisting of $-\text{CH}_3$, $-\text{CH}_2\text{CH}_3$, $-\text{CH}_2\text{CH}_2\text{CH}_3$,
 $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$,
 $-\text{CH}_2\text{CH}_2\text{CH}(\text{CH}_3)_2$, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}(\text{CH}_3)_2$, $-\text{CH}(\text{CH}_3)_2$, -
 5 $\text{CH}_2-\text{C}(\text{O})-\text{O}-\text{CH}_2\text{CH}_3$, $-\text{CH}_2-\text{OH}$, $-\text{CH}(\text{CH}_3)-\text{OH}$, $-\text{CH}_2\text{CH}_2\text{CH}=\text{CH}_2$,
 $-\text{CH}_2\text{CH}_2\text{CH}=\text{CHCH}_3$, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}=\text{CH}_2$,
 $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}=\text{CH}_2$, cyclobutyl, $-\text{CH}_2\text{CH}_2\text{CH}_2-\text{O}-\text{CH}_3$, $-\text{CH}_2\text{CH}_2\text{CF}_3$,
 $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CF}_3$, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CF}_3$, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{Cl}$, , $-\text{CH}_2-(2-$
 thiophenyl), $-\text{CH}_2\text{CH}_2\text{CH}_2-(2-\text{thiophenyl})$, $-\text{CH}_2-\text{cyclopropyl}$,
 10 $-\text{CH}_2\text{CH}_2-\text{cyclopropyl}$, $-\text{CH}_2\text{CH}_2\text{CH}_2-\text{cyclopropyl}$,
 $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-\text{cyclopropyl}$, $-\text{CH}_2-\text{cyclopentyl}$, $-\text{CH}_2\text{CH}_2-\text{cyclopentyl}$,
 $-\text{CH}_2-\text{cyclohexyl}$, $-\text{CH}_2-(4-\text{methylcyclohexyl})$, $-\text{CH}_2\text{CH}_2-\text{cyclohexyl}$,
 $-\text{CH}_2-\text{cycloheptyl}$, $-\text{CH}_2-(2-\text{cyclopentenyl})$, $-\text{CH}_2\text{CH}_2\text{C}\equiv\text{CH}$,
 $-\text{CH}_2\text{CH}_2\text{CH}_2\text{C}\equiv\text{CH}$, $-\text{CH}_2-\text{phenyl}$, $-\text{CH}_2-(2-\text{fluorophenyl})$,
 15 $-\text{CH}_2-(3-\text{fluorophenyl})$, $-\text{CHBrCH}_3$ and $-\text{CH}_2\text{CF}_3$;

R^2 is H; or

R^1 and R^2 together with the ring carbon atoms to which they are shown attached, form a cyclopentenyl or cyclohexenyl ring

R^4 is selected from the group consisting of Cl , $-\text{O}-R^{10}$, $-\text{C}(\text{O})-\text{O}-\text{CH}_3$,
 20 $-\text{S}(\text{O})_2-\text{CH}_3$, $-\text{S}(\text{O})-\text{CH}_3$, $-\text{S}(\text{O})-\text{CH}_2\text{CH}_3$, $-\text{S}(\text{O})-\text{CH}(\text{CH}_3)_2$,
 $-\text{S}(\text{O})-\text{C}(\text{CH}_3)_3$, $-\text{S}(\text{O})-\text{CH}_2-\text{cyclopropyl}$, $-\text{S}-\text{CH}_2-\text{CH}=\text{CH}_2$,
 $-\text{S}(\text{O})-\text{CH}_2-\text{phenyl}$, $-\text{S}(\text{O})-\text{CH}(\text{CH}_3)-\text{phenyl}$, $-\text{N}(\text{R}^7)_2$, $-\text{O}-\text{N}=\text{C}(\text{CH}_3)_2$,
 $-\text{NH}-\text{NH}-\text{C}(\text{O})-\text{O}-\text{CH}_3$, and $-\text{C}(\text{O})-\text{CH}_3$,

wherein the phenyl portion of said $-\text{S}(\text{O})-\text{CH}_2-\text{phenyl}$, or
 25 $-\text{S}(\text{O})-\text{CH}(\text{CH}_3)-\text{phenyl}$ of R^4 is unsubstituted or substituted with
 one or more groups Y;

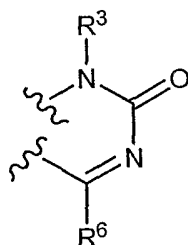
R^6 is selected from the group consisting of $-\text{O}-R^{10}$, $-\text{N}(\text{R}^7)_2$, and Cl ;
 each R^7 is independently selected from the group consisting of H,
 unsubstituted phenyl, phenyl substituted with one or more Y groups,
 30 and cyclobutyl;

R^{10} is selected from the group consisting of H, CH_3 , $-CH_2$ -cyclopropyl,
 $-CH_2-C \equiv C-CH_3$, $-CH_2-CH=CH_2$, $-CH_2$ -phenyl, $-CH(CH_3)$ -phenyl,
 $-CH(CH_2CH_3)$ -phenyl, $-CH(CH(CH_3)_2)$ -phenyl,
 $-CH(CH_2CH_2CH_3)$ -phenyl, $-CH(CH_2CH=CH_2)$ -phenyl, $-CH_2$ -pyridyl,
 5 $-CH(CH_3)$ -thiazolyl, $-CH_2$ -pyrimidinyl,
 wherein the phenyl portion of said $-CH_2$ -phenyl, $-CH(CH_3)$ -phenyl,
 $-CH(CH_2CH_3)$ -phenyl, $-CH(CH_2CH=CH_2)$ -phenyl, or
 $-CH(CH_2CH_2CH_3)$ -phenyl of R^{10} is unsubstituted or substituted
 with one or more groups Y, and the pyridyl, thiazolyl, or
 10 pyrimidinyl portion of said $-CH_2$ -pyridyl, $-CH(CH_3)$ -thiazolyl, or
 $-CH_2$ -pyrimidinyl of R^{10} is unsubstituted or substituted with one
 or more groups Z;

each Y is independently selected from the group consisting of F, Cl, Br,
 $-CH_3$, $-CF_3$, $-O-CH_3$, $-O-CF_3$, $-CN$, $-OH$, and phenyl; and
 15 each Z is independently selected from the group consisting of $-CH_3$, F, Br,
 and Cl, $-O-CH_3$, $-CN$, $-OH$, phenyl, and N-oxide.

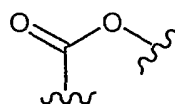
In another embodiment of the compounds of Formula (I),

Q is:



(d) ;

20 L is:



(f) ;

R^1 is $-(C_1-C_6)$ alkyl;

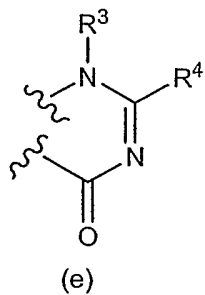
R^2 is H;

R^3 is H or $-(C_2-C_6)$ alkenyl; and

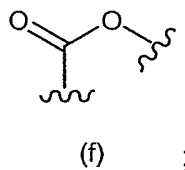
25 R^6 is $-OH$ or $-O-(C_1-C_6)$ alkylene- (C_1-C_6) cycloalkyl.

In another embodiment of the compounds of Formula (I),

Q is:



L is:



5 R^1 is $-(C_1-C_6)$ alkyl or $-(C_1-C_6)$ haloalkyl;

R^2 is H;

R^3 is selected from the group consisting of H,

$-(C_1-C_6)$ alkylene- (C_1-C_6) cycloalkyl,

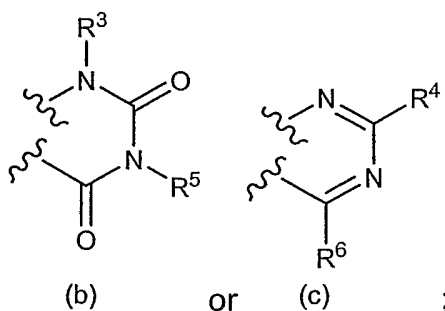
$-(C_1-C_6)$ alkylene-C(O)-O- (C_1-C_6) alkyl, $-(C_1-C_6)$ cycloalkyl, (C_1-C_6) alkyl,

10 (C_2-C_6) alkenyl, and $-(C_1-C_6)$ alkylene-O- (C_1-C_6) alkyl; and

R^4 is $-O-N=C((C_1-C_6)alkyl)_2$.

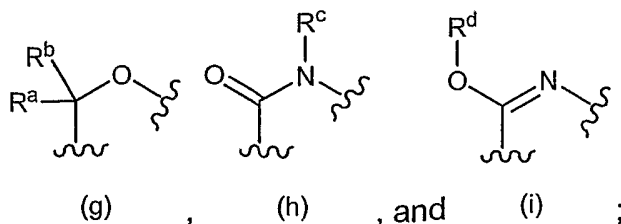
In another embodiment of the compounds of Formula (I),

Q is:



15

L is selected from the group consisting of:



R^a and R^b are each independently selected from the group consisting of H, (C₁-C₆)alkyl, (C₆-C₁₀)aryl, and (C₂-C₁₀)heteroaryl,

wherein said (C₆-C₁₀)aryl of R^a and R^b is unsubstituted or substituted with one or more Y groups, and said

5 (C₂-C₁₀)heteroaryl of R^a and R^b is unsubstituted or substituted with one or more Z groups;

R^c is selected from the group consisting of H, (C₁-C₆)alkyl, -(C₁-C₆)alkylene-(C₆-C₁₀)aryl, and -C(O)-(C₁-C₆)alkyl,

10 wherein the (C₆-C₁₀)aryl portion of said -(C₁-C₆)alkylene-(C₆-C₁₀)aryl of R^c is unsubstituted or substituted with one or more Y groups;

R^d is selected from the group consisting of H, (C₁-C₆)alkyl, and -(C₁-C₆)alkylene-(C₆-C₁₀)aryl,

15 wherein the (C₆-C₁₀)aryl portion of said -(C₁-C₆)alkylene-(C₆-C₁₀)aryl of R^d is unsubstituted or substituted with one or more Y groups;

R¹ is (C₁-C₆)alkyl or -(C₁-C₆)haloalkyl;

R² is H;

R³ is H;

20 R⁴ is -O-R¹⁰;

R⁵ is H or -(C₁-C₆)alkylene-(C₃-C₆)cycloalkyl;

R⁶ is -O-R¹⁰;

R¹⁰ is H, (C₁-C₆)alkyl, or -(C₁-C₆)alkylene-(C₆-C₁₀)aryl; and

each Y is independently selected from the group consisting of F, Br, Cl,

25 (C₁-C₆)alkyl, (C₁-C₆)haloalkyl, -O-(C₁-C₆)alkyl, -O-(C₁-C₆)haloalkyl, -CN, -NO₂, -OH, , -S(O₂)-(C₁-C₆)alkyl, -S(O₂)-(C₆-C₁₀)aryl, -S(O₂)-NH₂, -S(O₂)-NH-(C₁-C₆)alkyl, -S(O₂)-NH-(C₆-C₁₀)aryl, -S(O₂)-N((C₁-C₆)alkyl)₂, -S(O₂)-N((C₆-C₁₀)aryl)₂, -S(O₂)-N((C₁-C₆)alkyl)((C₆-C₁₀)aryl), and (C₆-C₁₀)aryl; and

30 each Z is independently selected from the group consisting of (C₁-C₆)alkyl, (C₁-C₆)haloalkyl, F, Br, and Cl, -O-(C₁-C₆)alkyl, -CN, -OH, (C₆-C₁₀)aryl, and N-oxide.

In another embodiment of the Formula (I), R¹ is -CH₃, -CH₂CH₃, -CH₂CH₂CH₃, -CH₂CH₂CH₂CH₃, -CH(CH₃)₂, -CH₂-C(O)-O-CH₂CH₃, -CH₂CF₃,

- CH₂-OH, -CH(CH₃)OH, -CH₂-N(R⁷)₂, -CH₂-NH(3-methoxyphenyl),
 -CH₂CH₂CH₂CH₂CH₃, -CH₂CH₂CH₂CH₂CH₂CH₃, -CH₂CH₂CH(CH₃)₂,
 -CH₂CH₂CH₂CH(CH₃)₂, -CH₂CH₂CH=CH₂, -CH₂CH₂CH=CHCH₃,
 -CH₂CH₂CH₂CH₂CH=CH₂, -CH₂CH₂CH₂CH=CH₂, cyclobutyl,
 5 -CH₂CH₂CH₂-O-CH₃, -CH₂CF₃, -CHBrCH₃, -CH₂CH₂CF₃, -CH₂CH₂CH₂CF₃,
 -CH₂CH₂CH₂CH₂CF₃, -CH₂CH₂CH₂Cl, , -CH₂-(2-thiophenyl), -CH₂CH₂CH₂-(2-
 thiophenyl), -CH₂-cyclopropyl, -CH₂CH₂-cyclopropyl,
 -CH₂CH₂CH₂-cyclopropyl, -CH₂CH₂CH₂CH₂-cyclopropyl, -CH₂-cyclopentyl,
 -CH₂CH₂-cyclopentyl, -CH₂-cyclohexyl, -CH₂-(4-methylcyclohexyl), -CH₂CH₂-
 10 cyclohexyl, -CH₂-cycloheptyl, -CH₂-(2-cyclopentenyl), -CH₂CH₂C≡CH,
 -CH₂CH₂CH₂C≡CH, -CH₂-phenyl, -CH₂-(2-fluorophenyl),
 -CH₂-(3-fluorophenyl), or -CHBrCH₃.

In another embodiment of the Formula (I), R² is H.

In another embodiment of the Formula (I), R² is Br.

- 15 In another embodiment, R¹ and R² together with the ring carbon atoms
 to which they are shown attached in Formula (I), form a cyclopentenyl or
 cyclohexenyl ring.

- In another embodiment of the Formula (I), R³ is H, -CH₂-cyclopropyl,
 -CH₂-C(O)-O-CH₃, -cyclopropyl, cyclobutyl, cyclopentyl, -CH₃, -CH₂CH₃,
 20 -CH₂-CH₂CH₃, -CH₂CH=CH₂, or -CH₂-O-CH₃.

- In another embodiment of the Formula (I), R⁴ is Cl, -OH, -O-CH₃,
 -O-CH₂-cyclopropyl, -CH₂-C≡C-CH₃, -O-CH₂-phenyl, -O-CH(CH₃)-phenyl,
 -O-CH(CH₂CH₃)-phenyl, -O-CH(CH₂CH₂CH₃)-phenyl,
 -O-CH(CH(CH₃)₂)-phenyl, -O-CH(CH₂CH=CH₂)-phenyl, -O-CH₂-pyridyl,
 25 -O-CH₂-thiazolyl, -O-CH(CH₃)-thiazolyl, -O-CH₂-pyrimidinyl, -C(O)-O-CH₃,
 -S(O₂)-CH₃, -S(O)-CH₃, -S(O)-CH₂CH₃, -S(O)-CH(CH₃)₂, -S(O)-C(CH₃)₃,
 -S(O)-CH₂-cyclopropyl, -S(O)-CH₂-phenyl, -S(O)-CH(CH₃)-phenyl,
 -S(O)-N(R¹¹)₂, -S(O₂)-N(R¹¹)₂, -S-CH₂-CH=CH₂, -N(H)cyclobutyl, -N(H)phenyl,
 -NH-NH-C(O)-O-CH₃, -O-CH₂-CH=CH₂, -O-N=C(CH₃)₂, or -C(O)-CH₃, wherein
 30 the phenyl portions of any of these groups can be unsubstituted or substituted
 with one or more Y groups as defined herein, the cyclobutyl portions of any of
 these groups may be unsubstituted or substituted with one or more X groups
 as defined herein, and the pyridyl, thiazolyl, or pyrimidinyl portions of any of

these groups can be unsubstituted or substituted with one or more Z groups as defined herein.

In another embodiment of the compound of Formula (I), R⁵ is H, -CH₃, -CH₂CH₃, -CH₂CH₂CH₃, -CH₂-C(O)-phenyl, -CH₂-C(O)-OH,
5 -CH₂-C(=N-O-CH₃)-phenyl, cyclopropyl, cyclobutyl, cyclopentyl, -CH₂-C(O)-piperidyl, -CH₂-cyclopropyl, -CH₂-C(O)-O-CH₃, or -CH₂-CH=CH₃, wherein the phenyl of said -CH₂-C(O)-phenyl of R⁵ is unsubstituted or substituted with one or more Y groups as defined herein, said cyclopropyl, the cyclopropyl of said -CH₂-cyclopropyl, cyclobutyl, cyclopentyl, or the piperidyl
10 of said -CH₂-C(O)-piperidyl of R⁵ are unsubstituted or substituted with one or more X groups as defined herein.

In another embodiment of the compound of Formula (I), R⁶ is -OH, Cl, -O-CH₃, -O-CH₂-cyclopropyl, -O-CH₂-CH=CH₃, -O-CH₂-phenyl, -O-CH(CH₃)-phenyl, -O-CH(CH₂CH₃)-phenyl, -O-CH(CH₂CH₂CH₃)-phenyl,
15 -O-CH(CH(CH₃)₂)-phenyl, -O-CH(CH₂CH=CH₂)-phenyl, -O-CH₂-pyridyl, -O-CH₂-thiazolyl, -O-CH₂-pyrimidinyl, and -N(H)cyclobutyl, -N(H)phenyl, -NH-NH-C(O)-O-CH₃, wherein the phenyl of said -O-CH₂-phenyl, -O-CH(CH₃)-phenyl, -O-CH(CH₂CH₃)-phenyl, -O-CH(CH₂CH₂CH₃)-phenyl, -O-CH(CH(CH₃)₂)-phenyl, or -O-CH(CH₂CH=CH₂)-phenyl of R⁶ is
20 unsubstituted or substituted with one or more groups Y as defined herein, and the pyridyl, thiazolyl, or pyrimidinyl of said -O-CH₂-pyridyl, -O-CH₂-thiazolyl, or -O-CH₂-pyrimidinyl of R⁶ is unsubstituted or substituted with one or more groups Z as defined herein.

In another embodiment of the compound of Formula (I), each R⁷ is
25 independently H, -CH₃, -CH₂CH₃, -CH₂CH₂CH₃, unsubstituted phenyl, phenyl substituted with one or more Y groups, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, -C(O)-CH₃, and -C(O)-phenyl. Alternatively, two groups R⁷, together with the N atom to which they are attached, form an azetidyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, pyrrolidinonyl, triazolyl, or
30 pyrrolyl ring.

In another embodiment of the compound of Formula (I), R⁸ is -CH₃, unsubstituted phenyl, phenyl substituted with one or more Y groups, piperidyl, and -OH.

In another embodiment of the compound of Formula (I), R^9 is $-\text{CH}_3$, $-\text{CH}_2\text{CH}_3$, $-\text{CH}(\text{CH}_3)_2$, $-\text{C}(\text{CH}_3)_3$, $-\text{CH}_2$ -cyclopropyl, $-\text{CH}_2\text{-CH=CH}_2$ (allyl), $-\text{CH}_2$ -phenyl, and $-\text{CH}(\text{CH}_3)$ -phenyl.

In another embodiment of the compound of Formula (I), R^{10} is H,
5 $-\text{CH}_2\text{C}\equiv\text{CH}_3$, $-\text{CH}_2$ -cyclopropyl, $-\text{CH}_2\text{CH=CH}_2$, $-\text{CH}_2$ -phenyl,
 $-\text{CH}(\text{CH}_3)$ -phenyl, $-\text{CH}(\text{CH}_2\text{CH}_3)$ -phenyl, $-\text{CH}(\text{CH}(\text{CH}_3)_2)$ -phenyl, $-\text{CH}_2$ -pyridyl,
 $-\text{CH}_2$ -thiazolyl, $-\text{CH}(\text{CH}_3)$ -thiazolyl, $-\text{CH}_2$ -pyrimidyl, $-\text{CH}(\text{CH}_2\text{CH=CH}_2)$ -phenyl,
 $-\text{CH}(\text{CH}_2\text{CH}_2\text{CH}_3)$ -phenyl, wherein the phenyl portion of $-\text{CH}_2$ -phenyl,
 $-\text{CH}(\text{CH}_3)$ -phenyl, $-\text{CH}(\text{CH}_2\text{CH}_3)$ -phenyl, $-\text{CH}(\text{CH}(\text{CH}_3)_2)$ -phenyl,
10 $-\text{CH}(\text{CH}_2\text{CH=CH}_2)$ -phenyl, and $-\text{CH}(\text{CH}_2\text{CH}_2\text{CH}_3)$ -phenyl of R^{10} are
unsubstituted or substituted with one or more Y groups, and the pyridyl,
thiazolyl, and pyrimidyl portion of said $-\text{CH}_2$ -pyridyl, $-\text{CH}_2$ -thiazolyl, $-\text{CH}(\text{CH}_3)$ -
thiazolyl, $-\text{CH}_2$ -pyrimidyl are unsubstituted or substituted with one or more Z
groups.

15 In another embodiment of the compound of Formula (I), R^{11} is H, $-\text{CH}_3$,
or phenyl, wherein said phenyl is unsubstituted or substituted with one or
more Y groups. Alternatively, two groups R^{11} , together with the N atom to
which they are attached, form an azetidyl, pyrrolidinyl, piperidinyl,
piperazinyl, morpholinyl, pyrrolidinonyl, triazolyl, or pyrrolyl ring.

20 In another embodiment of the compound of Formula (I), R^{12} is H, $-\text{CH}_3$,
 $-\text{CH}_2\text{CH}_3$, or unsubstituted pyridyl or pyridyl substituted with one or more Z
groups.

In another embodiment of the compound of Formula (I), R^a is H or
 $-\text{CH}_3$.

25 In another embodiment of the compound of Formula (I), R^b is H or
 $-\text{CH}_3$.

In another embodiment of the compound of Formula (I), R^a and R^b are
both $-\text{CH}_3$.

In another embodiment of the compound of Formula (I), R^c is H or
30 $-\text{CH}_3$.

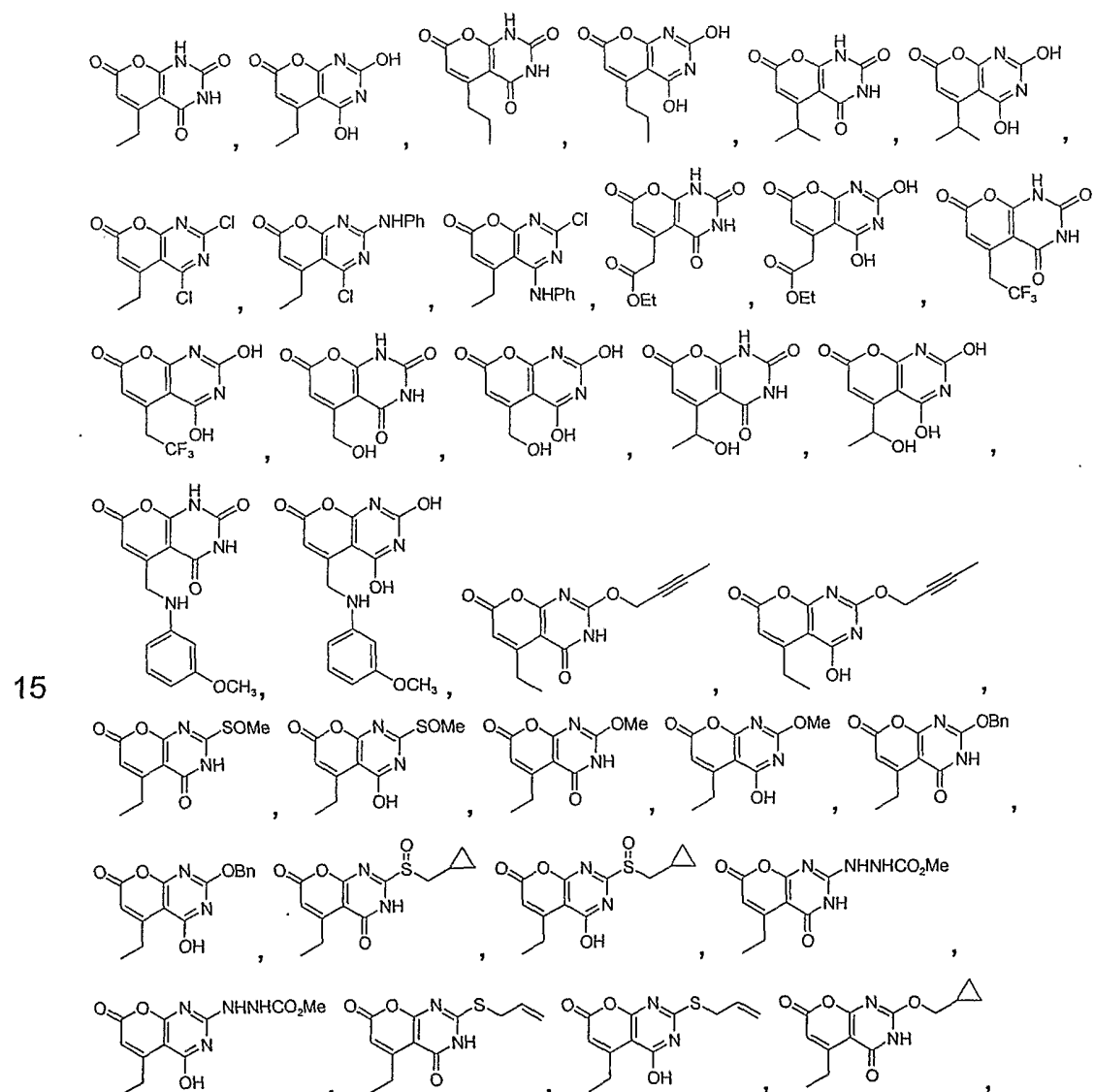
In another embodiment of the compound of Formula (I), R^d is H, $-\text{CH}_3$,
or $-\text{CH}_2$ -phenyl, wherein the phenyl portion of said $-\text{CH}_2$ -phenyl of R^d is
unsubstituted or substituted with one or more Y groups as defined herein.

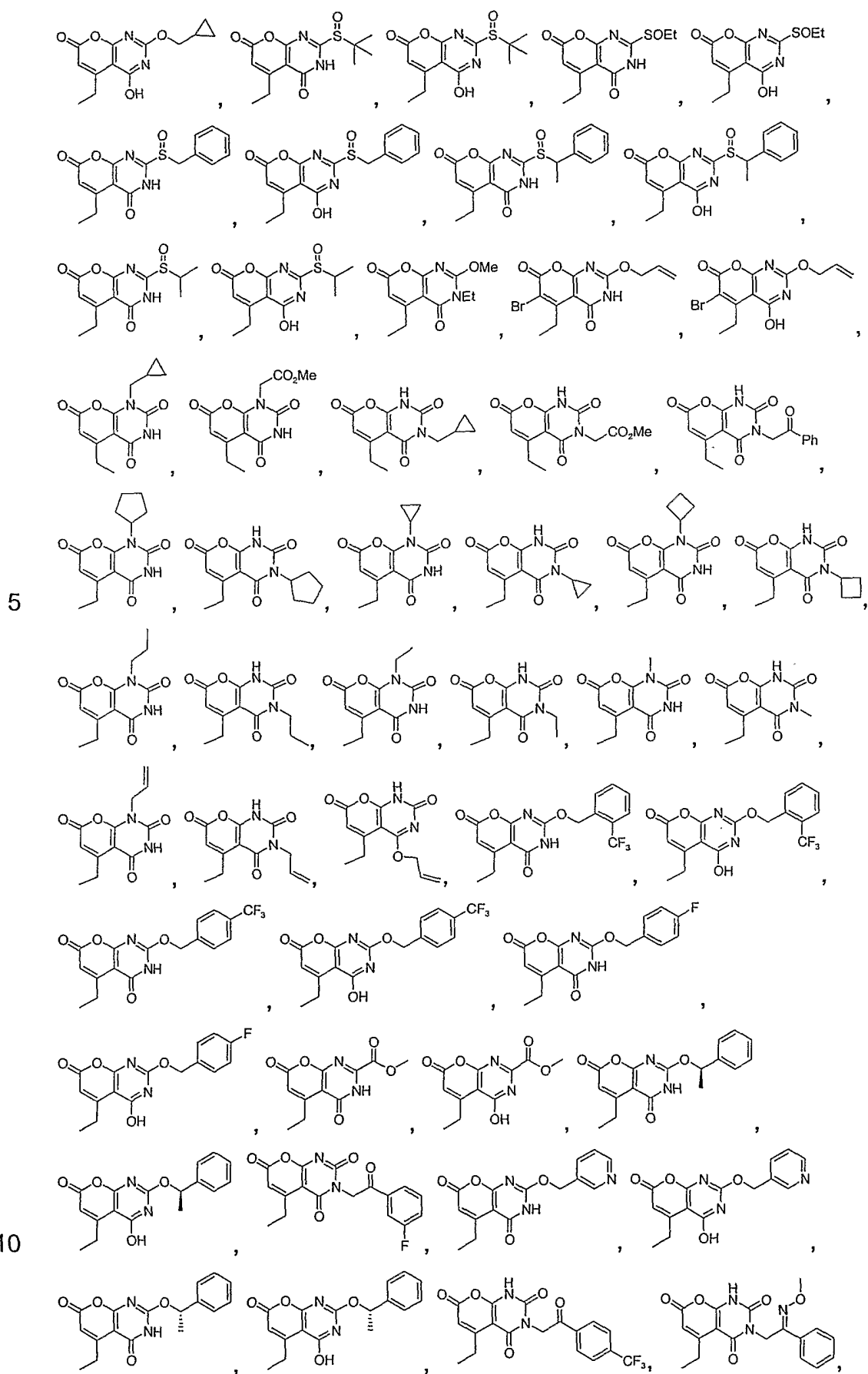
In another embodiment of the compound of Formula (I), each X is independently selected from the group consisting of $-\text{CH}_3$, $-\text{CF}_3$, F, Br, and Cl, $-\text{O}-\text{CH}_3$, $-\text{O}-\text{CF}_3$, $-\text{CN}$, $-\text{OH}$, phenyl, and N-oxide;

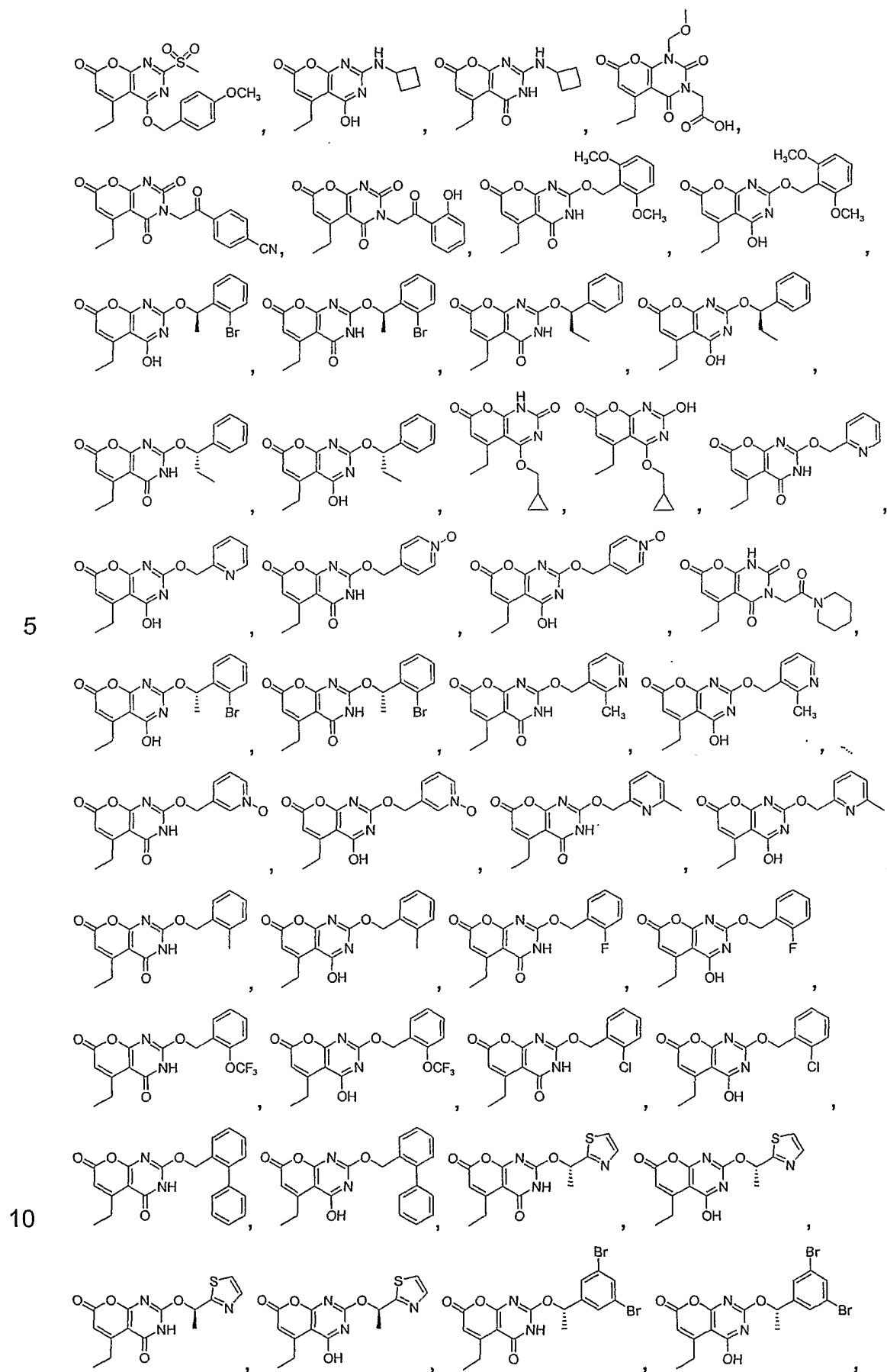
In another embodiment of the compound of Formula (I), each Y is
5 independently selected from the group consisting of F, Cl, Br, $-\text{CH}_3$, $-\text{CF}_3$, $-\text{O}-\text{CH}_3$, $-\text{O}-\text{CF}_3$, $-\text{CN}$, $-\text{OH}$, and phenyl; and

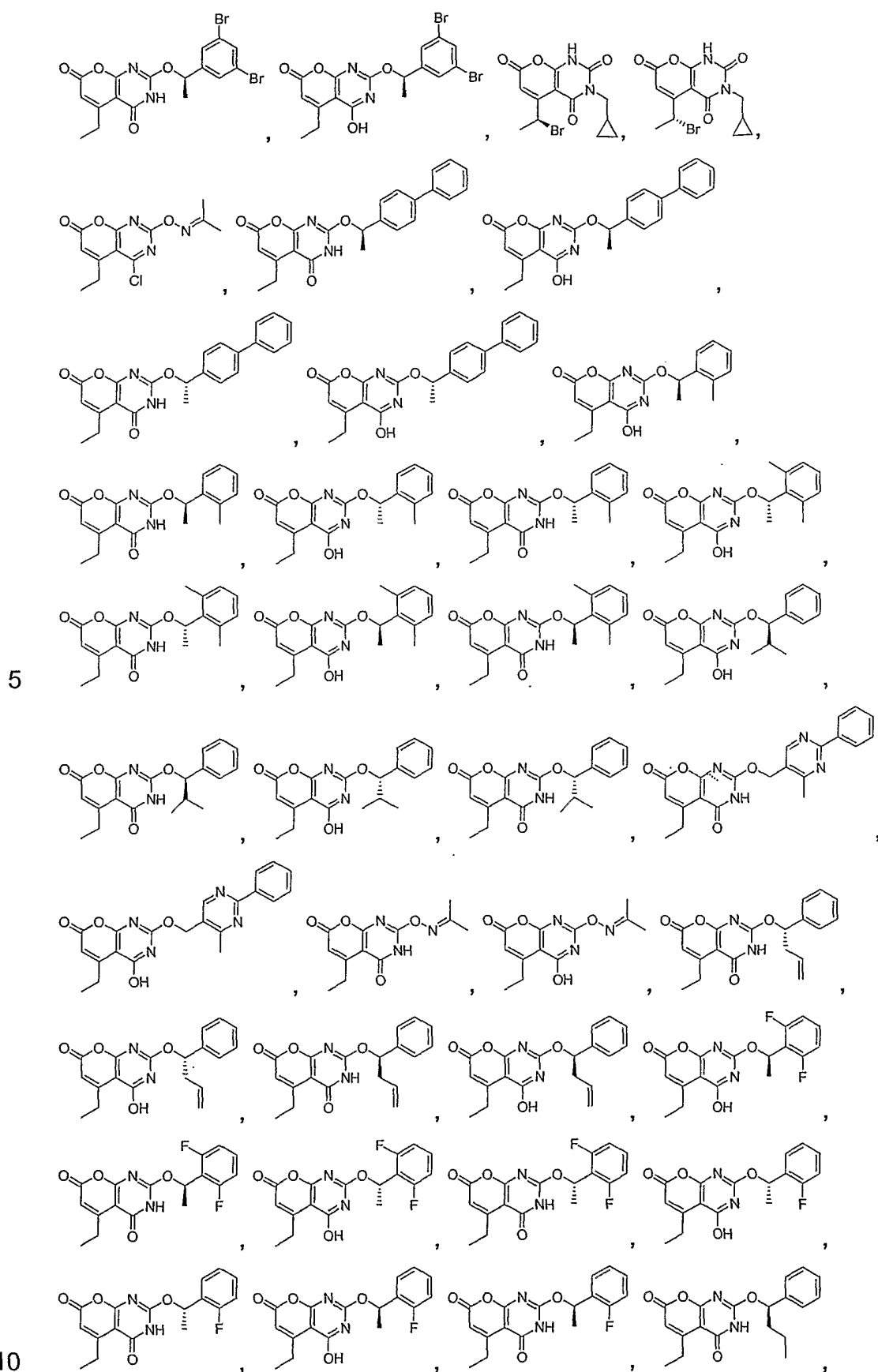
In another embodiment of the compound of Formula (I), each Z is independently selected from the group consisting of $-\text{CH}_3$, $-\text{CF}_3$, F, Br, and Cl, $-\text{O}-\text{CH}_3$, $-\text{O}-\text{CF}_3$, $-\text{CN}$, $-\text{OH}$, phenyl, and N-oxide.

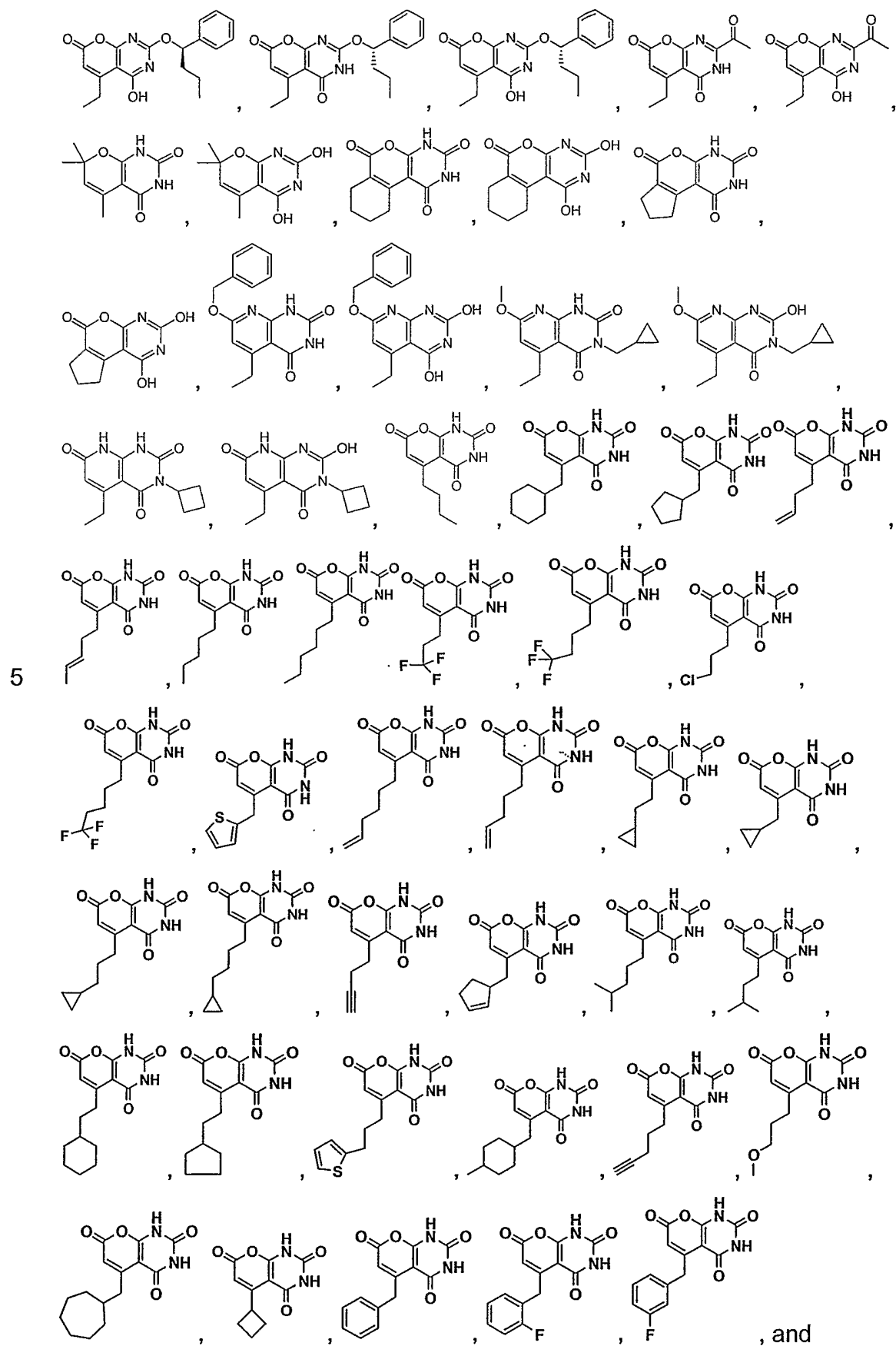
10 In yet another embodiment, the compounds of the present invention are selected from the following:







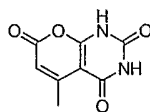




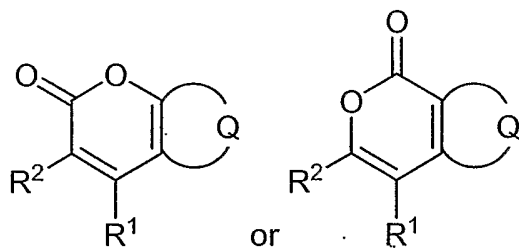


or pharmaceutically acceptable salts, solvates, esters, or tautomers thereof.

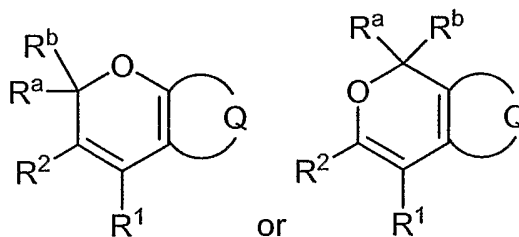
- In all embodiments of the present invention, when L is (f), and R^2 , R^3 and R^5 are each H, then R^1 is not $-CH_3$. One of skill in the art will recognize that the present invention does not include the following compound, or tautomeric forms thereof:



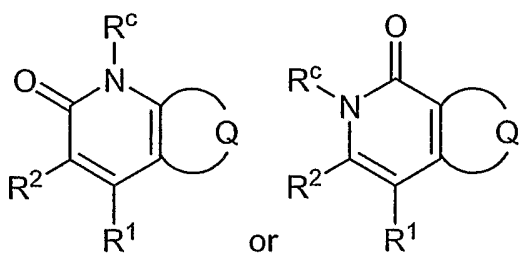
- The moiety L of Formula (I) of the present invention can have any chemically stable orientation. That is, when L is (f), the compounds of Formula (I) of the present invention can include the following:



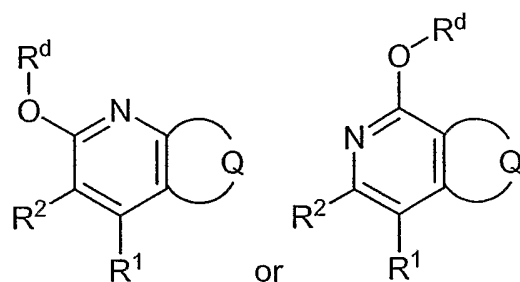
, or salts, solvates, esters, or tautomers thereof. When L is (g), the compounds of Formula (I) of the present invention can include the following:



- , or salts, solvates, esters, or tautomers thereof. When L is (h), the compounds of Formula (I) of the present invention can include the following:



, or salts, solvates, esters, or tautomers thereof. When L is (i), the compounds of Formula (I) of the present invention can include the following:

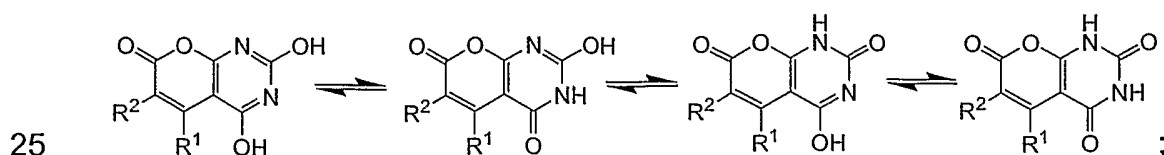


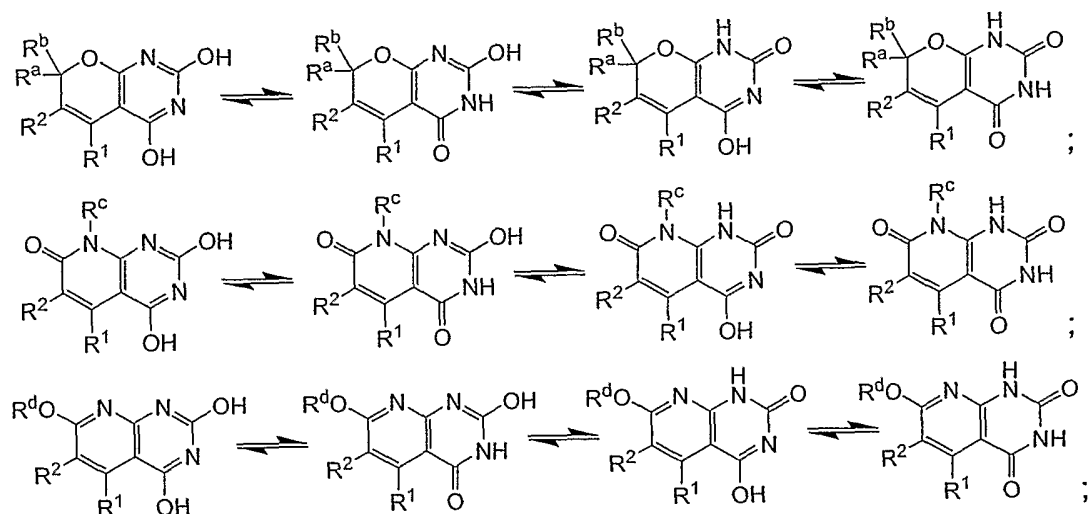
, or salts, solvates, esters, or tautomers thereof.

The compounds of Formula (I) can be purified to a degree suitable for use as a pharmaceutically active substance. That is, the compounds of Formula (I) can have a purity of 95 wt% or more (excluding adjuvants such as pharmaceutically acceptable carriers, solvents, etc., which are used in formulating the compound of Formula (I) into a conventional form, such as a pill, capsule, IV solution, etc. suitable for administration into a patient). The purity can be 97 wt% or more, or, 99 wt% or more. A purified compound of Formula (I) includes a single isomer having a purity, as discussed above, of 95 wt% or more, 97 wt% or more, or 99 wt% or more, as discussed above.

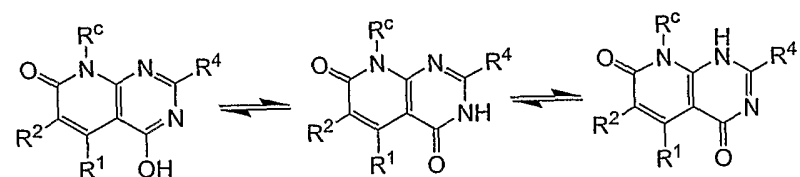
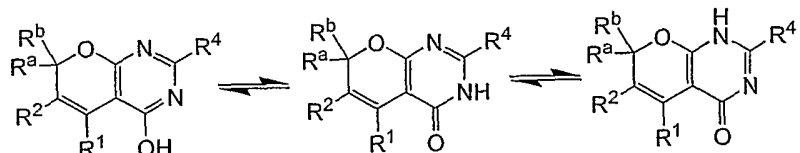
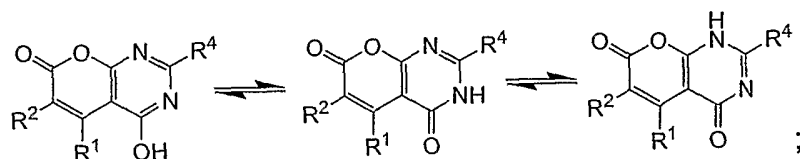
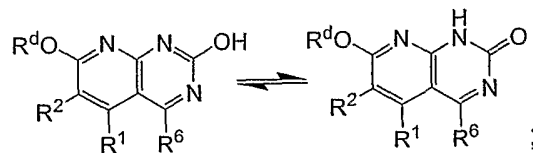
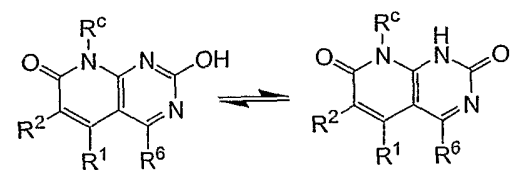
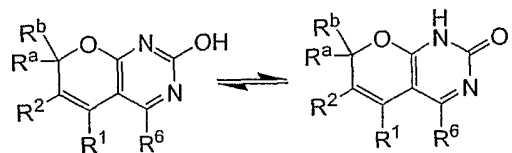
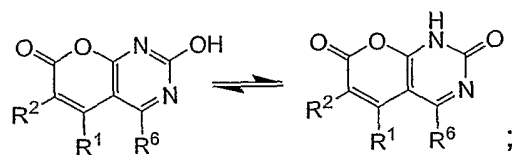
Alternatively, the purified compound of Formula (I) can include a mixture of isomers, each having a structure according to Formula (I), where the amount of impurity (i.e., compounds or other contaminants, exclusive of adjuvants as discussed above) is 5 wt% or less, 3 wt% or less, or 1 wt% or less. For example, the purified compound of Formula (I) can be an isomeric mixture of compounds of Structure (I), where the ratio of the amounts of the two isomers is approximately 1:1, and the combined amount of the two isomers is 95 wt% or more, 97 wt% or more, or 99 wt% or more.

Compounds of Formula (I), and salts, solvates, esters and prodrugs thereof, may exist in their tautomeric form (for example, as an amide or imino ether). All such tautomeric forms are contemplated herein as part of the present invention. For example, the compounds of the present invention include tautomeric forms as shown below:

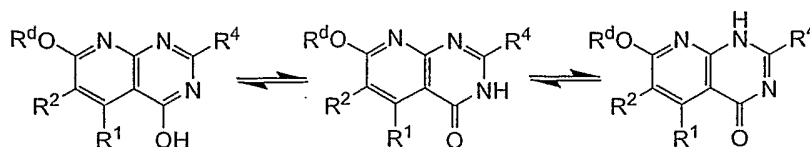




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Such tautomeric forms are considered equivalent.

As used above, and throughout this disclosure, the following terms, unless otherwise indicated, shall be understood to have the following

5 meanings:

"Bn" means benzyl.

"BnBr" means benzyl bromide.

"BnOH" means benzyl alcohol.

"DCM" means dichloromethane (CH₂Cl₂).

10 "DIAD" means diisopropyl azodicarboxylate.

"DIEA" means N,N-diisopropylethylamine.

"DMF" means dimethylformamide.

"Et" means ethyl.

"EtO₂" means diethyl ether.

15 "EtOAc" means ethylacetate.

"HATU" means O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethylammonium hexafluorophosphate.

"HOAc" means acetic acid.

"IBMX" means 3-isobutyl-1-methylxanthine.

20 "*m*-CPBA" means *m*-chloroperoxybenzoic acid.

"Me" means methyl.

"MeOH" means methanol.

"NBS" means N-bromosuccinimide.

"NEt₃" means triethylamine.

25 "*t*-Bu" means tertiary-butyl.

"*t*-BuOK" means potassium tertiary-butoxide.

"TFA" means trifluoroacetic acid.

"THF" means tetrahydrofuran.

"TLC" means thin layer chromatography.

30 "PMBOH" means 4-methoxybenzyl alcohol.

"Prep TLC" means preparative thin layer chromatography.

"Patient" includes both human and animals.

"Mammal" means humans and other mammalian animals.

"Alkyl" means an aliphatic hydrocarbon group which may be straight or branched and comprising about 1 to about 20 carbon atoms in the chain.

- 5 Preferred alkyl groups contain about 1 to about 12 carbon atoms in the chain. More preferred alkyl groups contain about 1 to about 6 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl, are attached to a linear alkyl chain. "Lower alkyl" means a group having about 1 to about 6 carbon atoms in the chain which may be
- 10 straight or branched. "Alkyl" may be unsubstituted or optionally substituted by one or more substituents which may be the same or different, each substituent being independently selected from the group consisting of halo, alkyl, aryl, cycloalkyl, cyano, hydroxy, alkoxy, alkylthio, amino, -NH(alkyl), -NH(cycloalkyl), -N(alkyl)₂, carboxy and -C(O)O-alkyl. Non-limiting examples
- 15 of suitable alkyl groups include methyl, ethyl, n-propyl, isopropyl and t-butyl.

- "Alkenyl" means an aliphatic hydrocarbon group containing at least one carbon-carbon double bond and which may be straight or branched and comprising about 2 to about 15 carbon atoms in the chain. Preferred alkenyl groups have about 2 to about 12 carbon atoms in the chain; and more
- 20 preferably about 2 to about 6 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl, are attached to a linear alkenyl chain. "Lower alkenyl" means about 2 to about 6 carbon atoms in the chain which may be straight or branched. "Alkenyl" may be unsubstituted or optionally substituted by one or more substituents which may
- 25 be the same or different, each substituent being independently selected from the group consisting of halo, alkyl, aryl, cycloalkyl, cyano, alkoxy and -S(alkyl). Non-limiting examples of suitable alkenyl groups include ethenyl, propenyl, n-butenyl, 3-methylbut-2-enyl, n-pentenyl, octenyl and decenyl.

- "Alkylene" means a difunctional group obtained by removal of a
- 30 hydrogen atom from an alkyl group that is defined above. Non-limiting examples of alkylene include methylene, ethylene and propylene.

"Alkenylene" means a difunctional group obtained by removal of a hydrogen from an alkenyl group that is defined above. Non-limiting examples of alkenylene include -CH=CH-, -C(CH₃)=CH-, and -CH=CHCH₂-.

"Alkylene-aryl" (or aryl-alkylene-) means a group in which the aryl and alkylene are as previously described. The bond to the parent moiety is through the alkylene. The alkylene moiety can be bonded to one or more aryl moieties. Alkylene-aryls can comprise a lower alkylene group. Non-limiting
5 examples of suitable alkylene-aryl groups include benzyl, 2-phenethyl, 2,2-diphenylethylene and naphthalenylmethyl.

"Alkynyl" means an aliphatic hydrocarbon group containing at least one carbon-carbon triple bond and which may be straight or branched and comprising about 2 to about 15 carbon atoms in the chain. Preferred alkynyl
10 groups have about 2 to about 12 carbon atoms in the chain; and more preferably about 2 to about 4 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl, are attached to a linear alkynyl chain. "Lower alkynyl" means about 2 to about 6 carbon atoms in the chain which may be straight or branched. Non-limiting examples
15 of suitable alkynyl groups include ethynyl, propynyl, 2-butylnyl and 3-methylbutynyl. "Alkynyl" may be unsubstituted or optionally substituted by one or more substituents which may be the same or different, each substituent being independently selected from the group consisting of alkyl, aryl and cycloalkyl.

20 "Aryl" means an aromatic monocyclic or multicyclic ring system comprising about 6 to about 14 carbon atoms, preferably about 6 to about 10 carbon atoms. The aryl group can be optionally substituted with one or more "ring system substituents" which may be the same or different, and are as defined herein. Non-limiting examples of suitable aryl groups include phenyl
25 and naphthyl.

"Heteroaryl" means an aromatic monocyclic or multicyclic ring system comprising about 5 to about 14 ring atoms, preferably about 5 to about 10 ring atoms, in which one or more of the ring atoms is an element other than carbon, for example nitrogen, oxygen or sulfur, alone or in combination.
30 Preferred heteroaryls contain about 5 to about 6 ring atoms. The "heteroaryl" can be optionally substituted by one or more "ring system substituents" which may be the same or different, and are as defined herein. The prefix aza, oxa or thia before the heteroaryl root name means that at least a nitrogen, oxygen or sulfur atom respectively, is present as a ring atom. A nitrogen atom of a

heteroaryl can be optionally oxidized to the corresponding N-oxide.

"Heteroaryl" may also include a heteroaryl as defined above fused to an aryl as defined above. Non-limiting examples of suitable heteroaryls include pyridyl, pyrazinyl, furanyl, thienyl, pyrimidinyl, pyridone (including N-

5 substituted pyridones), isoxazolyl, isothiazolyl, oxazolyl, thiazolyl, pyrazolyl, furazanyl, pyrrolyl, pyrazolyl, triazolyl, 1,2,4-thiadiazolyl, pyrazinyl, pyridazinyl, quinoxaliny, phthalazinyl, oxindolyl, imidazo[1,2-a]pyridinyl, imidazo[2,1-b]thiazolyl, benzofurazanyl, indolyl, azaindolyl, benzimidazolyl, benzothienyl, quinolinyl, imidazolyl, thienopyridyl, quinazolinyl, thienopyrimidyl,

10 pyrrolopyridyl, imidazopyridyl, isoquinolinyl, benzoazaindolyl, 1,2,4-triazinyl, benzothiazolyl and the like. The term "heteroaryl" also refers to partially saturated heteroaryl moieties such as, for example, tetrahydroisoquinolyl, tetrahydroquinolyl and the like.

"Aralkyl" or "arylalkyl" means an aryl-alkyl- group in which the aryl and

15 alkyl are as previously described. Preferred aralkyls comprise a lower alkyl group. Non-limiting examples of suitable aralkyl groups include benzyl, 2-phenethyl and naphthalenylmethyl. The bond to the parent moiety is through the alkyl.

"Alkylaryl" means an alkyl-aryl- group in which the alkyl and aryl are as

20 previously described. Preferred alkylaryls comprise a lower alkyl group. Non-limiting example of a suitable alkylaryl group is tolyl. The bond to the parent moiety is through the aryl.

"Cycloalkyl" means a non-aromatic mono- or multicyclic ring system comprising about 3 to about 10 carbon atoms, preferably about 5 to about 10

25 carbon atoms. Preferred cycloalkyl rings contain about 5 to about 7 ring atoms. The cycloalkyl can be optionally substituted with one or more "ring system substituents" which may be the same or different, and are as defined above. Non-limiting examples of suitable monocyclic cycloalkyls include cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl and the like. Non-limiting

30 examples of suitable multicyclic cycloalkyls include 1-decalinyl, norbornyl, adamantyl and the like.

"Cycloalkylalkyl" means a cycloalkyl moiety as defined above linked via an alkyl moiety (defined above) to a parent core. Non-limiting examples of

suitable cycloalkylalkyls include cyclohexylmethyl, adamantylmethyl and the like.

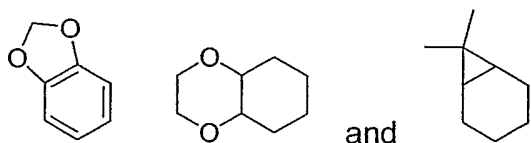
"Cycloalkenyl" means a non-aromatic mono or multicyclic ring system comprising about 3 to about 10 carbon atoms, preferably about 5 to about 10 carbon atoms which contains at least one carbon-carbon double bond. Preferred cycloalkenyl rings contain about 5 to about 7 ring atoms. The cycloalkenyl can be optionally substituted with one or more "ring system substituents" which may be the same or different, and are as defined above. Non-limiting examples of suitable monocyclic cycloalkenyls include cyclopentenyl, cyclohexenyl, cyclohepta-1,3-dienyl, and the like. Non-limiting example of a suitable multicyclic cycloalkenyl is norbornenyl.

"Cycloalkenylalkyl" means a cycloalkenyl moiety as defined above linked via an alkyl moiety (defined above) to a parent core. Non-limiting examples of suitable cycloalkenylalkyls include cyclopentenylmethyl, cyclohexenylmethyl and the like.

"Halogen" means fluorine, chlorine, bromine, or iodine. Preferred are fluorine, chlorine and bromine.

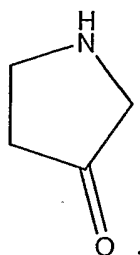
"Ring system substituent" means a substituent attached to an aromatic or non-aromatic ring system which, for example, replaces an available hydrogen on the ring system. Ring system substituents may be the same or different, each being independently selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, heteroaryl, aralkyl, alkylaryl, heteroaralkyl, heteroarylalkenyl, heteroarylalkynyl, alkylheteroaryl, hydroxy, hydroxyalkyl, alkoxy, aryloxy, aralkoxy, acyl, aroyl, halo, nitro, cyano, carboxy, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylthio, arylthio, heteroarylthio, aralkylthio, heteroaralkylthio, cycloalkyl, heterocyclyl, $-C(=N-CN)-NH_2$, $-C(=NH)-NH_2$, $-C(=NH)-NH(alkyl)$, Y_1Y_2N- , $Y_1Y_2N-alkyl-$, $Y_1Y_2NC(O)-$, $Y_1Y_2NSO_2-$ and $-SO_2NY_1Y_2$, wherein Y_1 and Y_2 can be the same or different and are independently selected from the group consisting of hydrogen, alkyl, aryl, cycloalkyl, and aralkyl. "Ring system substituent" may also mean a single moiety which simultaneously replaces two available hydrogens on two adjacent carbon atoms (one H on each carbon) on a ring system. Examples of

such moiety are methylene dioxy, ethylenedioxy, $-\text{C}(\text{CH}_3)_2-$ and the like which form moieties such as, for example:



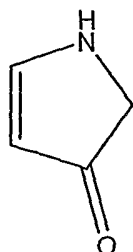
“Heteroarylalkyl” means a heteroaryl moiety as defined above linked
5 via an alkyl moiety (defined above) to a parent core. Non-limiting examples of suitable heteroaryls include 2-pyridinylmethyl, quinolinylmethyl and the like.

“Heterocyclyl” means a non-aromatic saturated monocyclic or
multicyclic ring system comprising about 3 to about 10 ring atoms, preferably
about 5 to about 10 ring atoms, in which one or more of the atoms in the ring
10 system is an element other than carbon, for example nitrogen, oxygen or sulfur, alone or in combination. There are no adjacent oxygen and/or sulfur atoms present in the ring system. Preferred heterocyclyls contain about 5 to about 6 ring atoms. The prefix aza, oxa or thia before the heterocyclyl root name means that at least a nitrogen, oxygen or sulfur atom respectively is
15 present as a ring atom. Any $-\text{NH}$ in a heterocyclyl ring may exist protected such as, for example, as an $-\text{N}(\text{Boc})$, $-\text{N}(\text{CBz})$, $-\text{N}(\text{Tos})$ group and the like; such protections are also considered part of this invention. The heterocyclyl can be optionally substituted by one or more “ring system substituents” which may be the same or different, and are as defined herein. The nitrogen or
20 sulfur atom of the heterocyclyl can be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Non-limiting examples of suitable monocyclic heterocyclyl rings include piperidyl, pyrrolidinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, 1,4-dioxanyl, tetrahydrofuranyl, tetrahydrothiophenyl, lactam, lactone, and the like. “Heterocyclyl” may also
25 mean a single moiety (e.g., carbonyl) which simultaneously replaces two available hydrogens on the same carbon atom on a ring system. Example of such moiety is pyrrolidone:



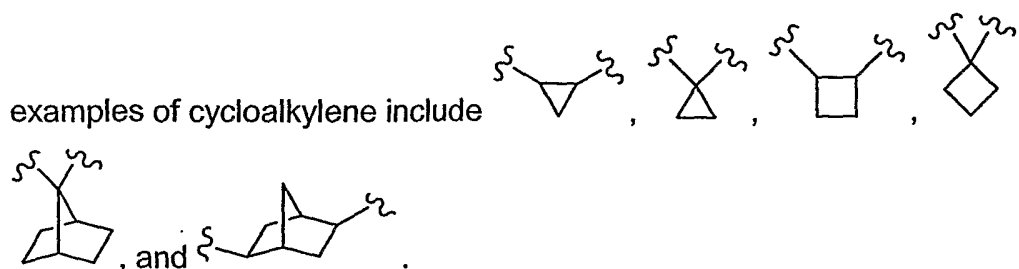
"Heterocyclalkyl" means a heterocycl moiety as defined above linked via an alkyl moiety (defined above) to a parent core. Non-limiting examples of suitable heterocyclalkyls include piperidinylmethyl, piperazinylmethyl and the like.

- 5 "Heterocyclenyl" means a non-aromatic monocyclic or multicyclic ring system comprising about 3 to about 10 ring atoms, preferably about 5 to about 10 ring atoms, in which one or more of the atoms in the ring system is an element other than carbon, for example nitrogen, oxygen or sulfur atom, alone or in combination, and which contains at least one carbon-carbon
10 double bond or carbon-nitrogen double bond. There are no adjacent oxygen and/or sulfur atoms present in the ring system. Preferred heterocyclenyl rings contain about 5 to about 6 ring atoms. The prefix aza, oxa or thia before the heterocyclenyl root name means that at least a nitrogen, oxygen or sulfur atom respectively is present as a ring atom. The heterocyclenyl can be
15 optionally substituted by one or more ring system substituents, wherein "ring system substituent" is as defined above. The nitrogen or sulfur atom of the heterocyclenyl can be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Non-limiting examples of suitable heterocyclenyl groups include 1,2,3,4- tetrahydropyridinyl, 1,2-dihydropyridinyl, 1,4-dihydropyridinyl,
20 1,2,3,6-tetrahydropyridinyl, 1,4,5,6-tetrahydropyrimidinyl, 2-pyrrolinyl, 3-pyrrolinyl, 2-imidazolinyl, 2-pyrazolinyl, dihydroimidazolyl, dihydrooxazolyl, dihydrooxadiazolyl, dihydrothiazolyl, 3,4-dihydro-2H-pyranyl, dihydrofuranyl, fluorodihydrofuranyl, 7-oxabicyclo[2.2.1]heptenyl, dihydrothiophenyl, dihydrothiopyranyl, and the like. "Heterocyclenyl" may also mean a single
25 moiety (e.g., carbonyl) which simultaneously replaces two available hydrogens on the same carbon atom on a ring system. Example of such moiety is pyrrolidinone:

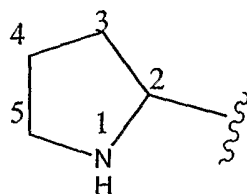


- "Heterocyclenylalkyl" means a heterocyclenyl moiety as defined above
30 linked via an alkyl moiety (defined above) to a parent core.

"Cycloalkylene" means a difunctional group obtained by removal of a hydrogen atom from a cycloalkyl group that is defined above. Non-limiting

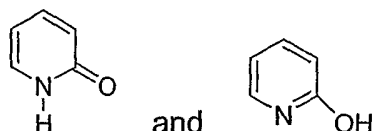


- 5 It should be noted that in hetero-atom containing ring systems of this invention, there are no hydroxyl groups on carbon atoms adjacent to a N, O or S, as well as there are no N or S groups on carbon adjacent to another heteroatom. Thus, for example, in the ring:



- 10 there is no -OH attached directly to carbons marked 2 and 5.

It should also be noted that tautomeric forms such as, for example, the moieties:



are considered equivalent in certain embodiments of this invention.

- 15 "Alkynylalkyl" means an alkynyl-alkyl- group in which the alkynyl and alkyl are as previously described. Alkynylalkyls can contain a lower alkynyl and a lower alkyl group. The bond to the parent moiety is through the alkyl. Non-limiting examples of suitable alkynylalkyl groups include propargylmethyl.

- "Heteroaralkyl" means a heteroaryl-alkyl- group in which the heteroaryl
20 and alkyl are as previously described. Preferred heteroaralkyls contain a lower alkyl group. Non-limiting examples of suitable aralkyl groups include pyridylmethyl, and quinolin-3-ylmethyl. The bond to the parent moiety is through the alkyl.

- "Hydroxyalkyl" means a HO-alkyl- group in which alkyl is as previously
25 defined. Preferred hydroxyalkyls contain lower alkyl. Non-limiting examples of suitable hydroxyalkyl groups include hydroxymethyl and 2-hydroxyethyl.

"Acyl" means an H-C(O)-, alkyl-C(O)- or cycloalkyl-C(O)-, group in which the various groups are as previously described. The bond to the parent moiety is through the carbonyl. Preferred acyls contain a lower alkyl. Non-limiting examples of suitable acyl groups include formyl, acetyl and propanoyl.

5 "Aroyl" means an aryl-C(O)- group in which the aryl group is as previously described. The bond to the parent moiety is through the carbonyl. Non-limiting examples of suitable groups include benzoyl and 1-naphthoyl.

 "Alkoxy" means an alkyl-O- group in which the alkyl group is as previously described. Non-limiting examples of suitable alkoxy groups include
10 methoxy, ethoxy, n-propoxy, isopropoxy and n-butoxy. The bond to the parent moiety is through the ether oxygen.

 "Aryloxy" means an aryl-O- group in which the aryl group is as previously described. Non-limiting examples of suitable aryloxy groups include phenoxy and naphthoxy. The bond to the parent moiety is through the ether
15 oxygen.

 "Aralkyloxy" means an aralkyl-O- group in which the aralkyl group is as previously described. Non-limiting examples of suitable aralkyloxy groups include benzyloxy and 1- or 2-naphthalenemethoxy. The bond to the parent moiety is through the ether oxygen.

20 "Alkylthio" means an alkyl-S- group in which the alkyl group is as previously described. Non-limiting examples of suitable alkylthio groups include methylthio and ethylthio. The bond to the parent moiety is through the sulfur.

 "Arylthio" means an aryl-S- group in which the aryl group is as previously described. Non-limiting examples of suitable arylthio groups
25 include phenylthio and naphthylthio. The bond to the parent moiety is through the sulfur.

 "Aralkylthio" means an aralkyl-S- group in which the aralkyl group is as previously described. Non-limiting example of a suitable aralkylthio group is
30 benzylthio. The bond to the parent moiety is through the sulfur.

 "Alkoxy carbonyl" means an alkyl-O-CO- group. Non-limiting examples of suitable alkoxy carbonyl groups include methoxy carbonyl and ethoxy carbonyl. The bond to the parent moiety is through the carbonyl.

"Aryloxycarbonyl" means an aryl-O-C(O)- group. Non-limiting examples of suitable aryloxycarbonyl groups include phenoxycarbonyl and naphthoxycarbonyl. The bond to the parent moiety is through the carbonyl.

"Aralkoxycarbonyl" means an aralkyl-O-C(O)- group. Non-limiting
5 example of a suitable aralkoxycarbonyl group is benzyloxycarbonyl. The bond to the parent moiety is through the carbonyl.

"Alkylsulfonyl" means an alkyl-S(O₂)- group. Preferred groups are those in which the alkyl group is lower alkyl. The bond to the parent moiety is through the sulfonyl.

10 "Arylsulfonyl" means an aryl-S(O₂)- group. The bond to the parent moiety is through the sulfonyl.

The term "substituted" means that one or more hydrogens on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valency under the existing
15 circumstances is not exceeded, and that the substitution results in a stable compound. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds. By "stable compound" or "stable structure" is meant a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation
20 into an efficacious therapeutic agent.

The term "optionally substituted" means optional substitution with the specified groups, radicals or moieties.

The term "purified", "in purified form" or "in isolated and purified form" for a compound refers to the physical state of said compound after being
25 isolated from a synthetic process (e.g. from a reaction mixture), or natural source or combination thereof. Thus, the term "purified", "in purified form" or "in isolated and purified form" for a compound refers to the physical state of said compound after being obtained from a purification process or processes described herein or well known to the skilled artisan (e.g., chromatography,
30 recrystallization and the like), in sufficient purity to be characterizable by standard analytical techniques described herein or well known to the skilled artisan.

It should also be noted that any carbon as well as heteroatom with unsatisfied valences in the text, schemes, examples and Tables herein is

assumed to have the sufficient number of hydrogen atom(s) to satisfy the valences.

When a functional group in a compound is termed "protected", this means that the group is in modified form to preclude undesired side reactions at the protected site when the compound is subjected to a reaction. Suitable protecting groups will be recognized by those with ordinary skill in the art as well as by reference to standard textbooks such as, for example, T. W. Greene *et al*, *Protective Groups in organic Synthesis* (1991), Wiley, New York.

When any variable (e.g., aryl, heterocycle, R^2 , etc.) occurs more than one time in any constituent or in Formula I, its definition on each occurrence is independent of its definition at every other occurrence.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

Prodrugs and solvates of the compounds of the invention are also contemplated herein. A discussion of prodrugs is provided in T. Higuchi and V. Stella, *Pro-drugs as Novel Delivery Systems* (1987) 14 of the A.C.S. Symposium Series, and in *Bioreversible Carriers in Drug Design*, (1987) Edward B. Roche, ed., American Pharmaceutical Association and Pergamon Press. The term "prodrug" means a compound (e.g, a drug precursor) that is transformed *in vivo* to yield a compound of Formula (I) or a pharmaceutically acceptable salt, hydrate or solvate of the compound. The transformation may occur by various mechanisms (e.g., by metabolic or chemical processes), such as, for example, through hydrolysis in blood. A discussion of the use of prodrugs is provided by T. Higuchi and W. Stella, "Pro-drugs as Novel Delivery Systems," Vol. 14 of the A.C.S. Symposium Series, and in *Bioreversible Carriers in Drug Design*, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987.

For example, if a compound of Formula (I) or a pharmaceutically acceptable salt, hydrate or solvate of the compound contains a carboxylic acid functional group, a prodrug can comprise an ester formed by the replacement of the hydrogen atom of the acid group with a group such as, for example,

(C₁–C₈)alkyl, (C₂–C₁₂)alkanoyloxymethyl, 1-(alkanoyloxy)ethyl having from 4 to 9 carbon atoms, 1-methyl-1-(alkanoyloxy)-ethyl having from 5 to 10 carbon atoms, alkoxycarbonyloxymethyl having from 3 to 6 carbon atoms, 1-(alkoxycarbonyloxy)ethyl having from 4 to 7 carbon atoms, 1-methyl-1-(alkoxycarbonyloxy)ethyl having from 5 to 8 carbon atoms, N-(alkoxycarbonyl)aminomethyl having from 3 to 9 carbon atoms, 1-(N-(alkoxycarbonyl)amino)ethyl having from 4 to 10 carbon atoms, 3-phthalidyl, 4-crotonolactonyl, gamma-butyrolacton-4-yl, di-N,N-(C₁–C₂)alkylamino(C₂–C₃)alkyl (such as β -dimethylaminoethyl), carbamoyl-(C₁–C₂)alkyl, N,N-di (C₁–C₂)alkylcarbamoyl-(C₁–C₂)alkyl and piperidino-, pyrrolidino- or morpholino(C₂–C₃)alkyl, and the like.

Similarly, if a compound of Formula (I) contains an alcohol functional group, a prodrug can be formed by the replacement of the hydrogen atom of the alcohol group with a group such as, for example, (C₁–C₆)alkanoyloxymethyl, 1-((C₁–C₆)alkanoyloxy)ethyl, 1-methyl-1-((C₁–C₆)alkanoyloxy)ethyl, (C₁–C₆)alkoxycarbonyloxymethyl, N-(C₁–C₆)alkoxycarbonylaminomethyl, succinoyl, (C₁–C₆)alkanoyl, α -amino(C₁–C₄)alkanyl, arylacyl and α -aminoacyl, or α -aminoacyl- α -aminoacyl, where each α -aminoacyl group is independently selected from the naturally occurring L-amino acids, P(O)(OH)₂, -P(O)(O(C₁–C₆)alkyl)₂ or glycosyl (the radical resulting from the removal of a hydroxyl group of the hemiacetal form of a carbohydrate), and the like.

If a compound of Formula (I) incorporates an amine functional group, a prodrug can be formed by the replacement of a hydrogen atom in the amine group with a group such as, for example, R-carbonyl, RO-carbonyl, NRR'-carbonyl where R and R' are each independently (C₁–C₁₀)alkyl, (C₃–C₇)cycloalkyl, benzyl, or R-carbonyl is a natural α -aminoacyl or natural α -aminoacyl, —C(OH)C(O)OY¹ wherein Y¹ is H, (C₁–C₆)alkyl or benzyl, —C(OY²)Y³ wherein Y² is (C₁–C₄) alkyl and Y³ is (C₁–C₆)alkyl, carboxy (C₁–C₆)alkyl, amino(C₁–C₄)alkyl or mono-N— or di-N,N-(C₁–C₆)alkylaminoalkyl, —C(Y⁴)Y⁵ wherein Y⁴ is H or methyl and Y⁵ is mono-N— or di-N,N-(C₁–C₆)alkylamino morpholino, piperidin-1-yl or pyrrolidin-1-yl, and the like.

One or more compounds of the invention may exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like, and it is intended that the invention embrace both solvated and unsolvated forms. "Solvate" means a physical association of a compound of this invention with one or more solvent molecules. This physical association involves varying degrees of ionic and covalent bonding, including hydrogen bonding. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. "Solvate" encompasses both solution-phase and isolatable solvates. Non-limiting examples of suitable solvates include ethanlates, methanlates, and the like. "Hydrate" is a solvate wherein the solvent molecule is H₂O.

One or more compounds of the invention may optionally be converted to a solvate. Preparation of solvates is generally known. Thus, for example, M. Caira *et al*, *J. Pharmaceutical Sci.*, 93(3), 601-611 (2004) describe the preparation of the solvates of the antifungal fluconazole in ethyl acetate as well as from water. Similar preparations of solvates, hemisolvate, hydrates and the like are described by E. C. van Tonder *et al*, *AAPS PharmSciTech.*, 5(1), article 12 (2004); and A. L. Bingham *et al*, *Chem. Commun.*, 603-604 (2001). A typical, non-limiting, process involves dissolving the inventive compound in desired amounts of the desired solvent (organic or water or mixtures thereof) at a higher than ambient temperature, and cooling the solution at a rate sufficient to form crystals which are then isolated by standard methods. Analytical techniques such as, for example I. R. spectroscopy, show the presence of the solvent (or water) in the crystals as a solvate (or hydrate).

"Effective amount" or "therapeutically effective amount" is meant to describe an amount of compound or a composition of the present invention effective in inhibiting the above-noted diseases and thus producing the desired therapeutic, ameliorative, inhibitory or preventative effect.

The compounds of Formula I can form salts which are also within the scope of this invention. Reference to a compound of Formula I herein is understood to include reference to salts thereof, unless otherwise indicated. The term "salt(s)", as employed herein, denotes acidic salts formed with

inorganic and/or organic acids, as well as basic salts formed with inorganic and/or organic bases. In addition, when a compound of Formula I contains both a basic moiety, such as, but not limited to a pyridine or imidazole, and an acidic moiety, such as, but not limited to a carboxylic acid, zwitterions ("inner salts") may be formed and are included within the term "salt(s)" as used
5 herein. Pharmaceutically acceptable (i.e., non-toxic, physiologically acceptable) salts are preferred, although other salts are also useful. Salts of the compounds of the Formula I may be formed, for example, by reacting a compound of Formula I with an amount of acid or base, such as an equivalent
10 amount, in a medium such as one in which the salt precipitates or in an aqueous medium followed by lyophilization.

Exemplary acid addition salts include acetates, ascorbates, benzoates, benzenesulfonates, bisulfates, borates, butyrates, citrates, camphorates, camphorsulfonates, fumarates, hydrochlorides, hydrobromides, hydroiodides,
15 lactates, maleates, methanesulfonates, naphthalenesulfonates, nitrates, oxalates, phosphates, propionates, salicylates, succinates, sulfates, tartarates, thiocyanates, toluenesulfonates (also known as tosylates,) and the like. Additionally, acids which are generally considered suitable for the formation of pharmaceutically useful salts from basic pharmaceutical
20 compounds are discussed, for example, by P. Stahl *et al*, Camille G. (eds.) *Handbook of Pharmaceutical Salts. Properties, Selection and Use*. (2002) Zurich: Wiley-VCH; S. Berge *et al*, *Journal of Pharmaceutical Sciences* (1977) 66(1) 1-19; P. Gould, *International J. of Pharmaceutics* (1986) 33 201-217; Anderson *et al*, *The Practice of Medicinal Chemistry* (1996), Academic Press,
25 New York; and in *The Orange Book* (Food & Drug Administration, Washington, D.C. on their website). These disclosures are incorporated herein by reference thereto.

Exemplary basic salts include ammonium salts, alkali metal salts such as sodium, lithium, and potassium salts, alkaline earth metal salts such as
30 calcium and magnesium salts, salts with organic bases (for example, organic amines) such as dicyclohexylamines, t-butyl amines, and salts with amino acids such as arginine, lysine and the like. Basic nitrogen-containing groups may be quarternized with agents such as lower alkyl halides (e.g. methyl, ethyl, and butyl chlorides, bromides and iodides), dialkyl sulfates (e.g.

dimethyl, diethyl, and dibutyl sulfates), long chain halides (e.g. decyl, lauryl, and stearyl chlorides, bromides and iodides), aralkyl halides (e.g. benzyl and phenethyl bromides), and others.

5 All such acid salts and base salts are intended to be pharmaceutically acceptable salts within the scope of the invention and all acid and base salts are considered equivalent to the free forms of the corresponding compounds for purposes of the invention.

Pharmaceutically acceptable esters of the present compounds include the following groups: (1) carboxylic acid esters obtained by esterification of
10 the hydroxy groups, in which the non-carbonyl moiety of the carboxylic acid portion of the ester grouping is selected from straight or branched chain alkyl (for example, acetyl, n-propyl, t-butyl, or n-butyl), alkoxyalkyl (for example, methoxymethyl), aralkyl (for example, benzyl), aryloxyalkyl (for example, phenoxymethyl), aryl (for example, phenyl optionally substituted with, for
15 example, halogen, C₁₋₄alkyl, or C₁₋₄alkoxy or amino); (2) sulfonate esters, such as alkyl- or aralkylsulfonyl (for example, methanesulfonyl); (3) amino acid esters (for example, L-valyl or L-isoleucyl); (4) phosphonate esters and (5) mono-, di- or triphosphate esters. The phosphate esters may be further esterified by, for example, a C₁₋₂₀ alcohol or reactive derivative thereof, or by a
20 2,3-di (C₆₋₂₄)acyl glycerol.

Compounds of Formula I, and salts, solvates, esters and prodrugs thereof, may exist in their tautomeric form (for example, as an amide or imino ether). All such tautomeric forms are contemplated herein as part of the present invention.

25 The compounds of Formula (I) may contain asymmetric or chiral centers, and, therefore, exist in different stereoisomeric forms. It is intended that all stereoisomeric forms of the compounds of Formula (I) as well as mixtures thereof, including racemic mixtures, form part of the present invention. In addition, the present invention embraces all geometric and
30 positional isomers. For example, if a compound of Formula (I) incorporates a double bond or a fused ring, both the cis- and trans-forms, as well as mixtures, are embraced within the scope of the invention.

Diastereomeric mixtures can be separated into their individual diastereomers on the basis of their physical chemical differences by methods

well known to those skilled in the art, such as, for example, by chromatography and/or fractional crystallization. Enantiomers can be separated by converting the enantiomeric mixture into a diastereomeric mixture by reaction with an appropriate optically active compound (e.g., chiral auxiliary such as a chiral alcohol or Mosher's acid chloride), separating the diastereomers and converting (e.g., hydrolyzing) the individual diastereomers to the corresponding pure enantiomers. Also, some of the compounds of Formula (I) may be atropisomers (e.g., substituted biaryls) and are considered as part of this invention. Enantiomers can also be separated by use of chiral HPLC column.

It is also possible that the compounds of Formula (I) may exist in different tautomeric forms, and all such forms are embraced within the scope of the invention. Also, for example, all keto-enol and imine-enamine forms of the compounds are included in the invention.

All stereoisomers (for example, geometric isomers, optical isomers and the like) of the present compounds (including those of the salts, solvates, esters and prodrugs of the compounds as well as the salts, solvates and esters of the prodrugs), such as those which may exist due to asymmetric carbons on various substituents, including enantiomeric forms (which may exist even in the absence of asymmetric carbons), rotameric forms, atropisomers, and diastereomeric forms, are contemplated within the scope of this invention, as are positional isomers (such as, for example, 4-pyridyl and 3-pyridyl). (For example, if a compound of Formula (I) incorporates a double bond or a fused ring, both the cis- and trans-forms, as well as mixtures, are embraced within the scope of the invention. Also, for example, all keto-enol and imine-enamine forms of the compounds are included in the invention.).

Individual stereoisomers of the compounds of the invention may, for example, be substantially free of other isomers, or may be admixed, for example, as racemates or with all other, or other selected, stereoisomers. The chiral centers of the present invention can have the S or R configuration as defined by the *IUPAC* 1974 Recommendations. The use of the terms "salt", "solvate", "ester", "prodrug" and the like, is intended to equally apply to the salt, solvate, ester and prodrug of enantiomers, stereoisomers, rotamers,

tautomers, positional isomers, racemates or prodrugs of the inventive compounds.

The present invention also embraces isotopically-labelled compounds of the present invention which are identical to those recited herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, fluorine and chlorine, such as ^2H , ^3H , ^{13}C , ^{14}C , ^{15}N , ^{18}O , ^{17}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F , and ^{36}Cl , respectively.

Certain isotopically-labelled compounds of Formula (I) (e.g., those labeled with ^3H and ^{14}C) are useful in compound and/or substrate tissue distribution assays. Tritiated (i.e., ^3H) and carbon-14 (i.e., ^{14}C) isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium (i.e., ^2H) may afford certain therapeutic advantages resulting from greater metabolic stability (e.g., increased in vivo half-life or reduced dosage requirements) and hence may be preferred in some circumstances. Isotopically labelled compounds of Formula (I) can generally be prepared by following procedures analogous to those disclosed in the Schemes and/or in the Examples hereinbelow, by substituting an appropriate isotopically labelled reagent for a non-isotopically labelled reagent.

Polymorphic forms of the compounds of Formula I, and of the salts, solvates, esters and prodrugs of the compounds of Formula I, are intended to be included in the present invention.

The term "pharmaceutical composition" is also intended to encompass both the bulk composition and individual dosage units comprised of more than one (e.g., two) pharmaceutically active agents such as, for example, a compound of the present invention and an additional agent selected from the lists of the additional agents described herein, along with any pharmaceutically inactive excipients. The bulk composition and each individual dosage unit can contain fixed amounts of the afore-said "more than one pharmaceutically active agents". The bulk composition is material that has not yet been formed into individual dosage units. An illustrative dosage

unit is an oral dosage unit such as tablets, pills and the like. Similarly, the herein-described method of treating a patient by administering a pharmaceutical composition of the present invention is also intended to encompass the administration of the afore-said bulk composition and
5 individual dosage units.

The compounds of Formula (I), or pharmaceutically acceptable salts, solvates, or esters thereof according to the invention have pharmacological properties; in particular, the compounds of Formula (I) can be nicotinic acid receptor agonists.

10 The compounds of Formula (I) of the present invention, or pharmaceutically acceptable salts, solvates, or esters thereof are useful in treating diseases or conditions including dyslipidemia and metabolic syndrome.

The compounds of Formula (I), or pharmaceutically acceptable salts,
15 solvates, or esters thereof, can be administered in any suitable form, e.g., alone, or in combination with a pharmaceutically acceptable carrier, excipient or diluent in a pharmaceutical composition, according to standard pharmaceutical practice. The compounds of Formula (I), or pharmaceutically acceptable salts, solvates, or esters thereof, can be administered orally or
20 parenterally, including intravenous, intramuscular, interperitoneal, subcutaneous, rectal, or topical routes of administration, or if so selected, by a combination of one or more of the above-shown methods.

Pharmaceutical compositions comprising at least one compound of Formula (I), or a pharmaceutically acceptable salt, solvate, ester, or tautomer
25 thereof can be in a form suitable for oral administration, e.g., as tablets, troches, capsules, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, syrups, or elixirs. Oral compositions may be prepared by any conventional pharmaceutical method, and may also contain sweetening agents, flavoring agents, coloring agents, and preserving agents.

30 The amount of compound of Formula (I), or a pharmaceutically acceptable salt, solvate, ester, or tautomer thereof, administered to a patient can be determined by a physician based on the age, weight, and response of the patient, as well as by the severity of the condition treated. For example, the amount of compound of Formula I, or a pharmaceutically acceptable salt,

solvate, ester, or tautomer thereof, administered to the patient can range from about 0.1 mg/kg body weight per day to about 60 mg/kg/d, preferably about 0.5 mg/kg/d to about 40 mg/kg/d.

The compounds of Formula (I), or pharmaceutically acceptable salts, solvates, or esters thereof, can also be administered in combination with other therapeutic agents. For example one or more compounds of Formula (I) or pharmaceutically acceptable salts, solvates, or esters thereof, can be administered with one or more additional active ingredients selected from the group consisting of hydroxy-substituted azetidinone compounds, substituted β -lactam compounds, HMG CoA reductase inhibitor compounds, HMG CoA synthetase inhibitors, squalene synthesis inhibitors, squalene epoxidase inhibitors, sterol biosynthesis inhibitors, nicotinic acid derivatives, bile acid sequestrants, inorganic cholesterol sequestrants, AcylCoA:Cholesterol O-acyltransferase inhibitors, cholesteryl ester transfer protein inhibitors, fish oils containing Omega 3 fatty acids, natural water soluble fibers, plant stanols and/or fatty acid esters of plant stanols, anti-oxidants, PPAR α agonists, PPAR γ -agonists, FXR receptor modulators, LXR receptor agonists, lipoprotein synthesis inhibitors, renin angiotensin inhibitors, microsomal triglyceride transport protein inhibitors, bile acid reabsorption inhibitors, PPAR δ agonists, triglyceride synthesis inhibitors, squalene epoxidase inhibitors, low density lipoprotein receptor inducers or activators, platelet aggregation inhibitors, 5-LO or FLAP inhibitors, PPAR δ partial agonists, niacin or niacin receptor agonists, 5HT transporter inhibitors, NE transporter inhibitors, CB₁ antagonists/inverse agonists, ghrelin antagonists, H₃ antagonists/inverse agonists, MCH1R antagonists, MCH2R agonists/antagonists, NPY1 antagonists, NPY5 antagonists, NPY2 agonists, NPY4 agonists, mGluR5 antagonists, leptins, leptin agonists/modulators, leptin derivatives, opioid antagonists, orexin receptor antagonists, BRS3 agonists, CCK-A agonists, CNTF, CNTF derivatives, CNTF agonists/modulators, 5HT_{2c} agonists, Mc4r agonists, monoamine reuptake inhibitors, serotonin reuptake inhibitors, GLP-1 agonists, phentermine, topiramate, phytopharm compound 57, ghrelin antibodies, Mc3r agonists, ACC inhibitors, β 3 agonists, DGAT1 inhibitors, DGAT2 inhibitors, FAS inhibitors, PDE inhibitors, thyroid hormone β agonists,

UCP-1 activators, UCP-2 activators, UCP-3 activators, acyl-estrogens, glucocorticoid agonists/antagonists, 11 β HSD-1 inhibitors, SCD-1 inhibitors, lipase inhibitors, fatty acid transporter inhibitors, dicarboxylate transporter inhibitors, glucose transporter inhibitors, phosphate transporter inhibitors, anti-
5 diabetic agents, anti-hypertensive agents, anti-dyslipidemic agents, DP receptor antagonists, apolipoprotein-B secretion/microsomal triglyceride transfer protein (apo-B/MTP) inhibitors, sympathomimetic agonists, dopamine agonists, melanocyte-stimulating hormone receptor analogs, melanin concentrating hormone antagonists, leptons, galanin receptor antagonists,
10 bombesin agonists, neuropeptide-Y antagonists, thyromimetic agents, dehydroepiandrosterone, analogs of dehydroepiandrosterone, urocortin binding protein antagonists, glucagons-like peptide-1 receptor agonists, human agouti-related proteins (AGRP), neuromedin U receptor agonists, noradrenergic anorectic agents, appetite suppressants, hormone sensitive
15 lipase antagonists, MSH-receptor analogs, α -glucosidase inhibitors, apo A1 milano reverse cholesterol transport inhibitors, fatty acid binding protein inhibitors (FABP), and fatty acid transporter protein inhibitors (FATP).

Non-limiting examples of hydroxy-substituted azetidinone compounds and substituted β -lactam compounds useful in combination with the nicotinic
20 acid receptor agonists of the present invention are those disclosed in U.S. Patents Nos. 5,767,115, 5,624,920, 5,668,990, 5,656,624 and 5,688,787, 5,756,470, U.S. Patent Application Nos. 2002/0137690 and 2002/0137689 and PCT Patent Application No. WO 2002/066464, each of which is incorporated herein by reference in their entirety. A preferred azetidinone
25 compound is ezetimibe (for example, ZETIA[®] which is available from Schering-Plough Corporation).

Non-limiting examples of HMG CoA reductase inhibitor compounds useful in combination with the nicotinic acid receptor agonists of the present invention are lovastatin (for example MEVACOR[®] which is available from
30 Merck & Co.), simvastatin (for example ZOCOR[®] which is available from Merck & Co.), pravastatin (for example PRAVACHOL[®] which is available from Bristol Meyers Squibb), atorvastatin, fluvastatin, cerivastatin, CI-981, rivastatin (sodium 7-(4-fluorophenyl)-2,6-diisopropyl-5-methoxymethylpyridin-3-yl)-3,5-

dihydroxy-6-heptanoate), rosuvastatin calcium (CRESTOR® from AstraZeneca Pharmaceuticals), pitavastatin (such as NK-104 of Negma Kowa of Japan).

5 A non-limiting example of a HMG CoA synthetase inhibitor useful in combination with the nicotinic acid receptor agonists of the present invention is, for example, L-659,699 ((E,E)-11-[3'R-(hydroxy-methyl)-4'-oxo-2'R-oxetanyl]-3,5,7R-trimethyl-2,4-undecadienoic acid).

10 A non-limiting example of a squalene synthesis inhibitor useful in combination with the nicotinic acid receptor agonists of the present invention is, for example, squalestatin 1.

A non-limiting example of a squalene epoxidase inhibitor useful in combination with the nicotinic acid receptor agonists of the present invention is, for example, NB-598 ((E)-N-ethyl-N-(6,6-dimethyl-2-hepten-4-ynyl)-3-[(3,3'-bithiophen-5-yl)methoxy]benzene-methanamine hydrochloride).

15 A non-limiting example of a sterol biosynthesis inhibitor useful in combination with the nicotinic acid receptor agonists of the present invention is, for example, DMP-565.

20 Non-limiting examples of nicotinic acid derivatives (e.g., compounds comprising a pyridine-3-carboxylate structure or a pyrazine-2-carboxylate structure, including acid forms, salts, esters, zwitterions and tautomers) useful in combination with the nicotinic acid receptor agonists of the present invention are niceritrol, nicofuranose and acipimox (5-methyl pyrazine-2-carboxylic acid 4-oxide).

25 Non-limiting examples of bile acid sequestrants useful in combination with the nicotinic acid receptor agonists of the present invention are cholestyramine (a styrene-divinylbenzene copolymer containing quaternary ammonium cationic groups capable of binding bile acids, such as QUESTRAN® or QUESTRAN LIGHT® cholestyramine which are available from Bristol-Myers Squibb), colestipol (a copolymer of diethylenetriamine and 1-chloro-2,3-epoxypropane, such as COLESTID® tablets which are available 30 from Pharmacia), colesvelam hydrochloride (such as WelChol® Tablets (poly(allylamine hydrochloride) cross-linked with epichlorohydrin and alkylated with 1-bromodecane and (6-bromohexyl)-trimethylammonium bromide) which

are available from Sankyo), water soluble derivatives such as 3,3-ioene, N-(cycloalkyl) alkylamines and poliglusam, insoluble quaternized polystyrenes, saponins and mixtures thereof.

Non-limiting examples of inorganic cholesterol sequestrants useful in combination with the nicotinic acid receptor agonists of the present invention are bismuth salicylate plus montmorillonite clay, aluminum hydroxide and calcium carbonate antacids.

Non-limiting examples of AcylCoA:Cholesterol O-acyltransferase ("ACAT") inhibitors useful in combination with the nicotinic acid receptor agonists of the present invention are avasimibe ([2,4,6-tris(1-methylethyl)phenyl]acetyl)sulfamic acid, 2,6-bis(1-methylethyl)phenyl ester, formerly known as CI-1011), HL-004, lecimibide (DuP-128) and CL-277082 (N-(2,4-difluorophenyl)-N-[[4-(2,2-dimethylpropyl)phenyl]methyl]-N-heptylurea), and the compounds described in P. Chang et al., "Current, New and Future Treatments in Dyslipidaemia and Atherosclerosis", Drugs 2000 Jul; 60(1); 55-93, which is incorporated by reference herein.

Non-limiting examples of cholesteryl ester transfer protein ("CETP") inhibitors useful in combination with the nicotinic acid receptor agonists of the present invention are those disclosed in PCT Patent Application No. WO 00/38721, U.S. Patent Nos. 6,147,090, 6,958,346, 6,924,313 6,906,082, 6,861,561, 6,803,388, 6,794,396, 6,787,570, 6,753,346, 6,723,752, 6,723,753, 6,710,089, 6,699,898, 6,696,472, 6,696,435, 6,683,113, 5,519,001, 5,512,548, 6,410,022, 6,426,365, 6,448,295, 6,387,929, 6,683,099, 6,677,382, 6,677,380, 6,677,379, 6,677,375, 6,677,353, 6,677,341, 6,605,624, 6,586,433, 6,451,830, 6,451,823, 6,462,092, 6,458,849, 6,458,803, 6,455,519, 6,583,183, 6,562,976, 6,555,113, 6,544,974, 6,521,607, 6,489,366, 6,482,862, 6,479,552, 6,476,075, 6,476,057, and 6,897,317, each of which are incorporated herein by reference; compounds described in Yan Xia et al., "Substituted 1,3,5-Triazines As Cholesterol Ester Transfer Protein Inhibitors", Bioorganic & Medicinal Chemistry Letters, vol. 6, No. 7, 1996, pp. 919-922, herein incorporated by reference; natural products described in S. Coval et al., "Wiedendiol-A and-B, Cholesteryl Ester Transfer Protein Inhibitors From The Marine Sponge Xestosponga Wiedenmayeri", Bioorganic & Medicinal

Chemistry Letter, vol. 5, No. 6, pp. 605-610, 1995, herein incorporated by reference; the compounds described in Barrett et al. *J. Am. Chem. Soc.*, 118, 7863-63 (1996), herein incorporated by reference; the compounds described in Kuo et al. *J. Am. Chem. Soc.*, 117, 10629-34 (1995), herein incorporated by reference; the compounds described in Pietzonka et al. *Bioorg. Med. Chem. Lett.*, 6, 1951-54 (1996), herein incorporated by reference; the compounds described in Lee et al. *J. Antibiotics*, 49, 693-96 (1996), herein incorporated by reference; the compounds described by Busch et al. *Lipids*, 25, 216-220, (1990), herein incorporated by reference; the compounds described in Morton and Zilversmit *J. Lipid Res.*, 35, 836-47 (1982), herein incorporated by reference; the compounds described in Connolly et al. *Biochem. Biophys. Res. Comm.*, 223, 42-47 (1996), herein incorporated by reference; the compounds described in Bisgaier et al. *Lipids*, 29, 811-8 (1994), herein incorporated by reference; the compounds described in EP 818448, herein incorporated by reference; the compounds described in JP 10287662, herein incorporated by reference; the compounds described in PCT applications WO 98/35937, WO 9914174, WO 9839299, and WO 9914215, each of which is herein incorporated by reference; the compounds of EP applications EP 796846, EP 801060, 818448, and 818197, each of which is herein incorporated by reference; probucol or derivatives thereof, such as AGI-1067 and other derivatives disclosed in U.S. Patents Nos. 6,121,319 and 6,147,250, herein incorporated by reference; low-density lipoprotein (LDL) receptor activators such as HOE-402, an imidazolidinyl-pyrimidine derivative that directly stimulates LDL receptor activity, described in M. Huettinger et al., "Hypolipidemic activity of HOE-402 is Mediated by Stimulation of the LDL Receptor Pathway", *Arterioscler. Thromb.* 1993; 13:1005-12, herein incorporated by reference; 4-carboxyamino-2-substituted-1,2,3,4-tetrahydroquinolines, e.g., torcetrapib, described in WO 00/017164, WO 00/017166, WO 00/140190, WO 00/213797, and WO 2005/033082 (each of which is herein incorporated by reference). Torcetrapib can be combined with HMG-CoA reductase inhibitors such as atorvastatin (WO 00/213797, WO 2004/056358, WO 2004/056359, and WO2005/011634).

A non-limiting example of a fish oil containing Omega 3 fatty acids useful in combination with the nicotinic acid receptor agonists of the present invention is 3-PUFA.

5 Non-limiting examples of natural water soluble fibers useful in combination with the nicotinic acid receptor agonists of the present invention are psyllium, guar, oat and pectin.

A non-limiting example of a plant stanol and/or fatty acid ester of plant stanols useful in combination with the nicotinic acid receptor agonists of the present invention is the sitostanol ester used in BENECOL[®] margarine.

10 A non-limiting example of an anti-oxidant useful in combination with the nicotinic acid receptor agonists of the present invention includes probucol.

Non-limiting examples of PPAR α agonists useful in combination with the nicotinic acid receptor agonists of the present invention include beclofibrate, benzaifibrate, ciprofibrate, clofibrate, etofibrate, fenofibrate, and
15 gemfibrozil.

Non-limiting examples of lipoprotein synthesis inhibitors useful in combination with the nicotinic acid receptor agonists of the present invention include niacin or nicotinic acid.

Non-limiting examples of 5HT (serotonin) transport inhibitors useful in
20 combination with the nicotinic acid receptor agonists of the present invention include paroxetine, fluoxetine, fenfluramine, fluvoxamine, sertraline, and imipramine.

Non-limiting examples of NE (norepinephrine) transport inhibitors useful in combination with the nicotinic acid receptor agonists of the present
25 invention include GW 320659, despiramine, talsupram, and nomifensine.

Non-limiting examples of CB₁ antagonists/inverse agonists useful in combination with the nicotinic acid receptor agonists of the present invention include rimonabant, SR-147778 (Sanofi Aventis), and the compounds described in US 5,532,237, US 4,973,587, US 5,013,837, US 5,081,122, US
30 5,112,820, US 5,292,736, US 5,624,941, US 6,028,084, WO 96/33159, WO 98/33765, WO 98/43636, WO 98/43635, WO 01/09120, WO 98/31227, WO 98/41519, WO 98/37061, WO 00/10967, WO 00/10968, WO 97/29079, WO

99/02499, WO 01/58869, WO 02/076949, and EP-658546 (each of the preceding references is herein incorporated by reference).

Non-limiting examples of ghrelin antagonists useful in combination with the nicotinic acid receptor agonists of the present invention include those
5 described in WO 01/87335 and WO 02/08250 (each of the preceding references is herein incorporated by reference). Ghrelin antagonists are also known as GHS (growth hormone secretagogue receptor) antagonists. The pharmaceutical combinations and methods of the present invention therefore comprehend the use GHS antagonists in place of ghrelin antagonists (in
10 combination with the nicotinic acid receptor agonists of the present invention).

Non-limiting examples of H₃ antagonists/inverse agonists useful in combination with the nicotinic acid receptor agonists of the present invention include thioperamide, 3-(1H-imidazol-4-yl)propyl N-(4-pentenyl)carbamate, clobenpropit, iodophenpropit, imoproxifan, and GT2394 (Gliatech), those
15 described in WO 02/15905 (herein incorporated by reference); O-[3-(1H-imidazol-4-yl)propanol]carbamates described in Kiec-Kononowicz, K. et al., Pharmazie, 55:349-55 (2000) (herein incorporated by reference), piperidine-containing histamine H₃-receptor antagonists described in Lazewska, D. et al., Pharmazie, 56:927-32 (2001) (herein incorporated by reference),
20 benzophenone derivatives and related compounds described in Sasse, A. et al., Arch. Pharm.(Weinheim) 334:45-52 (2001)(herein incorporated by reference), substituted N-phenylcarbamates described in Reidemeister, S. et al., Pharmazie, 55:83-6 (2000)(herein incorporated by reference), and proxifan derivatives described in Sasse, A. et al., J. Med. Chem. 43:3335-43
25 (2000)(each of the preceding references is herein incorporated by reference).

Non-limiting examples of MCH1R (melanin-concentrating hormone 1 receptor) antagonists and MCH2R (melanin-concentrating hormone 2 receptor) agonists/antagonists useful in combination with the nicotinic acid receptor agonists of the present invention include those described in WO
30 01/82925, WO 01/87834, WO 02/06245, WO 02/04433, WO 02/51809, and JP 13226269 (each of the preceding references is herein incorporated by reference), and T-226296 (Takeda).

Non-limiting examples of NPY1 antagonists useful in combination with the nicotinic acid receptor agonists of the present invention include those

described in US 6,001,836, WO 96/14307, WO 01/23387, WO 99/51600, WO 01/85690, WO 01/85098, WO 01/85173, and WO 01/89528 (each of the preceding references is herein incorporated by reference); and BIBP3226, J-115814, BIBO 3304, LY-357897, CP-671906, and GI-264879A.

5 Non-limiting examples of NPY5 antagonists useful in combination with the nicotinic acid receptor agonists of the present invention include those described in US 6,140,354, US 6,191,160, US 6,258,837, US 6,313,298, US 6,337,332, US 6,329,395, US 6,340,683, US 6,326,375, US 6,335,345, EP-01010691, EP-01044970, WO 97/19682, WO 97/20820, WO 97/20821, WO
10 97/20822, WO 97/20823, WO 98/27063, WO 00/64880, WO 00/68197, WO 00/69849, WO 01/09120, WO 01/85714, WO 01/85730, WO 01/07409, WO 01/02379, WO 01/02379, WO 01/23388, WO 01/23389, WO 01/44201, WO 01/62737, WO 01/62738, WO 01/09120, WO 02/22592, WO 02/48152, WO 02/49648, WO 01/14376, WO 04/110375, WO 05/000217 and Norman et al.,
15 J. Med. Chem. 43:4288-4312 (2000) (each of the preceding references is herein incorporated by reference); and 152,804, GW-569180A, GW-594884A, GW-587081X, GW-548118X; FR226928, FR 240662, FR252384; 1229U91, GI-264879A, CGP71683A, LY-377897, PD-160170, SR-120562A, SR-120819A and JCF-104.

20 Non-limiting examples of NPY2 agonists useful in combination with the nicotinic acid receptor agonists of the present invention include PYY3-36 as described in Batterham, et al., Nature. 418:650-654 (2003), NPY3-36, and other Y2 agonists such as N acetyl [Leu(28,31)] NPY 24-36 (White-Smith and Potter, Neuropeptides 33:526-33 (1999)), TASP-V (Malis et al., Br. J.
25 Pharmacol. 126:989-96 (1999)), cyclo-(28/32)-Ac-[Lys28-Glu32]-(25-36)-pNPY (Cabrele and Beck-Sickinger J-Pept-Sci. 6:97-122 (2000)) (each of the preceding references is herein incorporated by reference).

 Non-limiting examples of NPY4 agonists useful in combination with the nicotinic acid receptor agonists of the present invention include pancreatic
30 peptide (PP) as described in Batterham et al., J. Clin. Endocrinol. Metab. 88:3989-3992 (2003), and other Y4 agonists such as 1229U91 (Raposinho et al., Neuroendocrinology. 71:2-7(2000) (both references are herein incorporated by reference).

Non-limiting examples of mGluR5 (Metabotropic glutamate subtype 5 receptor) antagonists useful in combination with the nicotinic acid receptor agonists of the present invention include 2-methyl-6-(phenylethynyl)-pyridine (MPEP) and (3-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine) (MTEP) and those
5 compounds described in Anderson J. et al., J, Eur J Pharmacol. Jul. 18, 2003;473(1):35-40; Cosford N. et al., Bioorg Med Chem Lett. Feb. 10, 2003;13(3):351-4; and Anderson J. et al., J Pharmacol Exp Ther. December 2002;303(3):1044-51 (each of the preceding references is herein incorporated by reference).

10 Non-limiting examples of leptins, leptin derivatives, and leptin agonists/modulators useful in combination with the nicotinic acid receptor agonists of the present invention include recombinant human leptin (PEG-OB, Hoffman La Roche) and recombinant methionyl human leptin (Amgen). Leptin derivatives (e.g., truncated forms of leptin) useful in the present invention
15 include those described in US 5,552,524, US 5,552,523, US 5,552,522, US 5,521,283, WO 96/23513, WO 96/23514, WO 96/23515, WO 96/23516, WO 96/23517, WO 96/23518, WO 96/23519, and WO 96/23520 (each of the preceding references is herein incorporated by reference).

Non-limiting examples of opioid antagonists useful in combination with
20 the nicotinic acid receptor agonists of the present invention include nalmeferne (RevexTM), 3-methoxynaltrexone, naloxone, and naltrexone, as well as opioid antagonists described in WO 00/21509 (herein incorporated by reference).

Non-limiting examples of orexin receptor antagonists useful in combination with the nicotinic acid receptor agonists of the present invention
25 include SB-334867-A, as well as those described in WO 01/96302, WO 01/68609, WO 02/51232, and WO 02/51838 (each of the preceding references is herein incorporated by reference).

Non-limiting examples of CNTF (specific ciliary neurotrophic factors) useful in combination with the nicotinic acid receptor agonists of the present
30 invention include GI-181771 (Glaxo-SmithKline); SR146131 (Sanofi Aventis); butabindide; PD170,292, PD 149164 (Pfizer).

Non-limiting examples of CNTF derivatives and CNTF agonists/modulators useful in combination with the nicotinic acid receptor agonists of the present invention include axokine (Regeneron) and those

described in WO 94/09134, WO 98/22128, and WO 99/43813 (each of which is herein incorporated by reference).

Non-limiting examples of 5HT_{2c} agonists useful in combination with the nicotinic acid receptor agonists of the present invention include BVT933,
5 DPCA37215, WAY161503, and R-1065, as well as those described in US 3,914,250, WO 02/36596, WO 02/48124, WO 02/10169, WO 01/66548, WO 02/44152, WO 02/51844, WO 02/40456, and WO 02/40457 (each of which is herein incorporated by reference).

Non-limiting examples of Mc4r agonists useful in combination with the
10 nicotinic acid receptor agonists of the present invention include CHIR86036 (Chiron); ME-10142, and ME-10145 (Melacure), as well as those described in WO 01/991752, WO 01/74844, WO 02/12166, WO 02/11715, and WO 02/12178 (each of which is herein incorporated by reference).

Non-limiting examples of monoamine reuptake inhibitors useful in
15 combination with the nicotinic acid receptor agonists of the present invention include sibutramine (MeridiaTM/ReductilTM), as well as those described in WO 01/27068, WO 01/62341, US 4,746,680, US 4,806,570, US 5,436,272, and US 2002/0006964 (each of which is herein incorporated by reference).

Non-limiting examples of serotonin reuptake inhibitors useful in
20 combination with the nicotinic acid receptor agonists of the present invention include dexfenfluramine, fluoxetine, and those described in US 6,365,633, WO 01/27060, and WO 01/162341 (each of which is herein incorporated by reference).

Non-limiting examples of GLP-1 agonists useful in combination with the
25 nicotinic acid receptor agonists of the present invention include exendin-3 and exendin-4.

A non-limiting example of an acyl-estrogen useful in combination with the nicotinic acid receptor agonists of the present invention includes oleoyl-estrone.

30 Non-limiting examples of 11 β HSD-1 inhibitors useful in combination with the nicotinic acid receptor agonists of the present invention include those described in WO 03/065983 and WO 03/104207 (both of which are herein incorporated by reference).

A non-limiting example of a lipase inhibitor useful in combination with the nicotinic acid receptor agonists of the present invention include orlistat.

Anti-diabetic agents useful in combination with the nicotinic acid receptor agonists of the present invention include sulfonylureas, meglitinides, α -amylase inhibitors, α -glucoside hydrolase inhibitors, PPAR- γ agonists, PPAR α/γ agonists, biguanides, PTP-1B inhibitors, DP-IV inhibitors, insulin secreatagogues, fatty acid oxidation inhibitors, A2 antagonists, c-jun amino-terminal kinase inhibitors, insulin, insulin mimetics, glycogen phosphorylase inhibitors, VPAC2 receptor agonists, glucokinase activators, and non-thiazolidinedione PPAR ligands. Non-limiting examples of sulfonylureas useful in combination with the nicotinic acid receptor agonists of the present invention include acetohexamide, chlorpropamide, diabinese, glibenclamide, glipizide, glyburide, glimepiride, gliclazide, glipentide, gliquidone, glisolamide, tolazamide, and tolbutamide.

Non-limiting examples of meglitinides useful in combination with the nicotinic acid receptor agonists of the present invention include repaglinide and nateglinide.

Non-limiting examples of α -amylase inhibitors useful in combination with the nicotinic acid receptor agonists of the present invention include tendamistat, trestatin, and AI-3688.

Non-limiting examples of α -glucoside hydrolase inhibitors useful in combination with the nicotinic acid receptor agonists of the present invention include acarbose, adipose, camiglibose, emiglitate, miglitol, voglibose, pradimicin-Q, salbostatin, CDK-711, MDL-25,637, MDL-73,945, and MOR 14.

Non-limiting examples of PPAR- γ agonists useful in combination with the nicotinic acid receptor agonists of the present invention include balaglitazone, ciglitazone, darglitazone, englitazone, isaglitazone (MCC-555), pioglitazone, rosiglitazone, troglitazone, tesaglitazar, netoglitazone, GW-409544, GW-501516, CLX-0921, 5-BTSD, GW-0207, LG-100641, LY-300512, LY-519818, R483 (Roche), and T131 (Tularik).

Non-limiting examples of PPAR α/γ agonists useful in combination with the nicotinic acid receptor agonists of the present invention include CLX-0940, GW-1536, GW-1929, GW-2433, KRP-297, L-796449, LR-90, MK-0767, and SB 219994.

Non-limiting examples of biguanides useful in combination with the nicotinic acid receptor agonists of the present invention include buformin, metformin, and phenformin.

Non-limiting examples of PTP-1B inhibitors (protein tyrosine
5 phosphatase-1B inhibitors) useful in combination with the nicotinic acid receptor agonists of the present invention include A-401,674, KR 61639, OC-060062, OC-83839, OC-297962, MC52445, and MC52453.

Non-limiting examples of DP-IV inhibitors (dipeptidyl peptidase IV
10 inhibitors) useful in combination with the nicotinic acid receptor agonists of the present invention include isoleucine thiazolidide, NVP-DPP728, P32/98, LAF 237, TSL 225, valine pyrrolidide, TMC-2A/2B/2C, CD-26 inhibitors, and SDZ 274-444.

Non-limiting examples of insulin secretagogues useful in combination with the nicotinic acid receptor agonists of the present invention include
15 linoglriride and A-4166.

Non-limiting examples of fatty acid oxidation inhibitors useful in combination with the nicotinic acid receptor agonists of the present invention include clomoxir and etomoxir.

Non-limiting examples of A2 antagonists useful in combination with the
20 nicotinic acid receptor agonists of the present invention include midaglizole, isaglidole, deriglidole, idazoxan, earoxan, and fluparoxan.

Non-limiting examples of insulin mimetics useful in combination with the nicotinic acid receptor agonists of the present invention include biota, LP-100, novarapid, insulin detemir, insulin lispro, insulin glargine, insulin zinc
25 suspension (lente and ultralente), Lys-Pro insulin, GLP-1 (73-7) (insulintropin), and GLP-1 (7-36)-NH₂.

Non-limiting examples of glycogen phosphorylase inhibitors useful in combination with the nicotinic acid receptor agonists of the present invention include CP-368,296, CP-316,819, and BAYR3401.

Non-limiting examples of non-thiazolidinedione PPAR ligands useful in
30 combination with the nicotinic acid receptor agonists of the present invention include JT-501 and farglitazar (GW-2570/GI-262579).

Anti-hypertensive agents useful in combination with the nicotinic acid receptor agonists of the present invention include diuretics, β -adrenergic

blockers, α -adrenergic blockers, aldosterone inhibitors, alpha 1 blockers, calcium channel blockers, angiotensin converting enzyme inhibitors, neutral endopeptidase inhibitors, angiotensin II receptor antagonists, endothelin antagonists, vasodilators, alpha 2a agonists, and α/β adrenergic blockers.

5 Non-limiting examples of diuretics useful in combination with the nicotinic acid receptor agonists of the present invention include chlorthalidone, chlorthiazide, dichlorophenamide, hydroflumethiazide, indapamide, hydrochlorothiazide, bumetanide, ethacrynic acid, furosemide, torsemide, amiloride, triamterene, spironolactone, and epi renone.

10 Non-limiting examples of β -adrenergic blockers useful in combination with the nicotinic acid receptor agonists of the present invention include acebutolol, atenolol, betaxolol, bevantolol, bisoprolol, bopindolol, carteolol, carvedilol, celiprolol, esmolol, indenolol, metaprolol, nadolol, nebivolol, penbutolol, pindolol, propanolol, sotalol, tertatolol, tilisolol, and timolol.

15 Non-limiting examples of alpha 1 blockers useful in combination with the nicotinic acid receptor agonists of the present invention include terazosin, urapidil, prazosin, bunazosin, trimazosin, doxazosin, naftopidil, indoramin, WHIP 164, and XEN010.

20 Non-limiting examples of calcium channel blockers useful in combination with the nicotinic acid receptor agonists of the present invention include amlodipine, aranidipine, azelnidipine, barnidipine, benidipine, bepridil, cinaldipine, clevidipine, diltiazem, efonidipine, felodipine, gallopamil, isradipine, lacidipine, lemdidipine, lercanidipine, nicardipine, nifedipine, nilvadipine, nimodepine, nisoldipine, nitrendipine, manidipine, pranidipine, and
25 verapamil.

30 Non-limiting examples of angiotensin converting enzyme inhibitors useful in combination with the nicotinic acid receptor agonists of the present invention include alacepril, benazepril, ceronapril, captopril, cilazapril, delapril, enalapril, fosinopril, imidapril, losinopril, moveltopril, moexipril, quinapril, quinaprilat, ramipril, perindopril, peridopril, quanipril, spirapril, temocapril, trandolapril, and zofenopril.

 Non-limiting examples of neutral endopeptidase inhibitors useful in combination with the nicotinic acid receptor agonists of the present invention

include omapatrilat, cadoxatril, ecadotril, fosidotril, sampatrilat, AVE7688, and ER4030.

Non-limiting examples of angiotensin II receptor antagonists useful in combination with the nicotinic acid receptor agonists of the present invention
5 include candesartan, eprosartan, irbesartan, losartan, prazosartan, tasosartan, telisartan, valsartan, EXP-3137, FI6828K, RNH6270, losartan monopotassium, and losartan potassium-hydrochlorothiazide.

Non-limiting examples of endothelin antagonists useful in combination with the nicotinic acid receptor agonists of the present invention include
10 tezosentan, A308165, and YM62899.

Non-limiting examples of vasodilators useful in combination with the nicotinic acid receptor agonists of the present invention include hydralazine (apresoline), clonidine (catapres), minoxidil (loniten), and nicotiny alcohol (roniacol).

15 Non-limiting examples of alpha 2a agonists useful in combination with the nicotinic acid receptor agonists of the present invention include lofexidine, tiamenidine, moxonidine, rilmenidine, and guanobenz.

Non-limiting examples of α/β adrenergic blockers useful in combination with the nicotinic acid receptor agonists of the present invention include
20 nipradilol, arotinolol, and amosulalol.

DP receptor antagonists useful in combination with the nicotinic acid receptor agonists of the present invention include those described in US 2004/0229844 (herein incorporated by reference).

Non-limiting examples of additional agents that can be combined with
25 the nicotinic acid receptor agonists of the present invention include aspirin, Niaspan, Norvasc[®] (amlodipine), NSAIDS agents (e.g., Celecoxib (Celebrex[®]), Diclofenac (Cataflam[®], Voltaren[®], Arthrotec[®]), Diflunisal (Dolobid[®]), Etodolac (Lodine[®]), Fenoprofen (Nalfon[®]), Flurbiprofen (Ansaid[®]), Ibuprofen (Motrin[®], ADVIL[®], NUPRIN[®], Tab-Profen[®], Vicoprofen[®],
30 Combunox[®]), Indomethacin (Indocin[®], Indo-Lemmon[®], Indomethagan[®]), Ketoprofen (Oruvail[®]), Ketorolac (Toradol[®]), Mefenamic acid (Ponstel[®], commercially available from First Horizon Pharmaceutical), flufenamic acid ([N-(3-trifluoromethylphenyl)anthranilic acid]), Meloxicam (Mobic[®]), Naburnetone (Relafen[®]), Naproxen (Naprosyn[®], ALEVE[®], Anaprox[®],

Naprelan[®], Naprapac[®]), Oxaprozin (Daypro[®]), Piroxicam (Feldene[®]), Sulindac (Clinoril[®]) and Tolmetin (Tolectin[®])), antihypertensive agents (Prazosin[®], Propranolol, nadolol, timolol, metoprolol, pindolol, labetalol, guanethidine, reserpine, clonidine, methyldopa, guanabenz, captopril, enalapril, lisinopril, 5 losartan, verapamil, diltiazem, nifedipine, hydrochlorothiazide, chlorothalidone, furosemide, triamterene, hydralazine, minoxidil), PGE2 receptor antagonists (e.g., EP2 and EP4).

Non-limiting examples of additional agents that can be combined with the nicotinic acid receptor agonists of the present invention include

10 homocysteinase, orphan GPCR modulator, HRE-based gene therapy, gene therapy, dual PPAR α/γ agonists, recombinant FGF-1, VRI-1, CRx-150, VEGF-114 based therapy, CT-500, regadenosan, CK-1827452, JAK2 tyrosine kinase inhibitors, adipose-derived regenerative cells, STARBURST dendrimer-based MRI contrast agents, TBC-11299, HEMOxygenation,

15 heparin, GO-EPO, IDN-6734, ISIS-301012, HIF-alpha gene therapy, α 2b adrenoceptor antagonists, KI-0002, adenosine modulators, Ki-23095, PR-5 (Melacure), L-364373, histone deacetylase inhibitors, adenylate cyclase inhibitors (E.g., HI-30435 from Millennium), MITO-0139 (from MitoKor), NV-04 (from Novogen), M-118 (Momenta), hypoxia response element, PI-99 (from

20 progen), NEXVAS (from Resverlogix), CS-207 (from Shenzhen Chipscreen Biosciences), estrogen-regulated gene therapy, SLV-327 (from SolvaY), TNX-832 (from Sunol Molecular Corp), SLx-2101 (from Surface Logix), recombinant human annexin (from SurroMed), Chymase inhibitors (e.g, from Toa Eiyo), VM-202 (from ViroMed), liver x receptor modulators (e.g., from

25 Exelixis/Bristol Myers Squibb), Heberkinasa (from Y. M. Biosciences), atorvastatin-amlodipine combination, AGN-195795 (Allergan), angiotensin (1-7) agonists (e.g., from Arena), Toprol XL/hydrochlorothiazide (from AstraZeneca), Teczem (Aventis), sGC stimulators, calcium channel blockers, CYT-006-AngQb (CytosBiotechnology), renin inhibitors (e.g., from

30 Roche/Speedel), Coxagen (from geneRx+ Inc), MC-4262 (from Medicure), VNP-489 (from Novartis), felodipine (from Pierre Fabre SA), 2-methoxyestradiol (from PR Pharmaceuticals), α 1 adrenoreceptor antagonists (e.g., from Recordati SpA), lercanidipine-enalapril combination (from Recordati SpA). NO donors (e.g., from Renopharm), CR-3834 (from

Rottapharm Gr), iloprost (from Schering AG), SPP-1100 (from The Speedel Group),, angiotensinogen, MC-4232 (from Medicure), ACE inhibitor (from Servier), LCP-Feno/Stat. (from LifeCycle Pharma), APA-01/statin combination (from Phosphagenics Ltd), KH-01502 (from Kos), KS-01019 (from Kos),
5 niacin-lovastatin combination (from Kos/Merck KGaA), MK-0524/extended release niacin/simvastatin combination (from Merck), MK-0524/extended release combination (from Merck), Pro-NAD (from Niadyne Inc), beraprost, perindopril erbumine, barnidipine, irbesartan, valsartan, valsartan-HCTZ conmbination, meclinetant, TAK-536, SR-121463, irbesatran + HCTZ
10 combination, darusentan, PMD-2850, CR-2991, SLV-306, bisoprolol fumarate+ HCTZ combination, NV-04, FG-3019, TRC-4149, AVE-7688, PV-903, diltiazem, QC-BT16, cardiotherpay (from Cytopia), treprostinil sodium, enalapril+diltiazem combination, eprosartan mesylate +HCTZ combination, renin inhibitor (from Vitae), LG-105 inhibitors (from Lexicon(, LG-844 inhibitors
15 (from Lexicon), NO-enhancing PDE inhibitors, hyaluronidase, propranolol hydrochloride, BIO-236, RWJ-351647, metoprolol, YM-222546, bLN-5, olmesartan+azelnidipine combination (from Sanyo), moxonidine + HCTZ combination, NS-304, BIO-123, aldosterone antagonists, clonidine, BIO-003 and CR-3834.

20 In addition, the nicotinic acid receptor agonists of the present invention can also be used in combination with two or more therapeutic agents. A non-limiting example of two or more therapeutic agents useful in combination with the nicotinic acid receptor agonists of the present invention is the combination of a compound of the present invention with VYTORIN® (a combination of
25 simvastatin and ezetimibe).

The invention disclosed herein is exemplified by the following preparations and examples which should not be construed to limit the scope of the disclosure. Alternative mechanistic pathways and analogous structures will be apparent to those skilled in the art.

30 Where NMR data are presented, ¹H spectra were obtained on either a Varian VXR-200 (200 MHz, ¹H), Varian Gemini-300 (300 MHz) or XL-400 (400 MHz) and are reported as ppm down field from Me₄Si with number of protons, multiplicities, and coupling constants in Hertz indicated

parenthetically. Where LC/MS data are presented, analyses was performed using an Applied Biosystems API-100 mass spectrometer and Shimadzu SCL-10A LC column: Altech platinum C18, 3 micron, 33mm x 7mm ID; gradient flow: 0 min – 10% CH₃CN, 5 min – 95% CH₃CN, 7 min – 95%
5 CH₃CN, 7.5 min – 10% CH₃CN, 9 min – stop. The retention time and observed parent ion are given.

The following solvents and reagents may be referred to by their abbreviations in parenthesis:

Thin layer chromatography: TLC

10 dichloromethane: CH₂Cl₂

ethyl acetate: AcOEt or EtOAc

methanol: MeOH

trifluoroacetate: TFA

triethylamine: Et₃N or TEA

15 butoxycarbonyl: n-Boc or Boc

nuclear magnetic resonance spectroscopy: NMR

liquid chromatography mass spectrometry: LCMS

high resolution mass spectrometry: HRMS

milliliters: mL

20 millimoles: mmol

microliters: μ l

grams: g

milligrams: mg

room temperature or rt (ambient): about 25°C.

25 N-bromosuccinimide: NBS

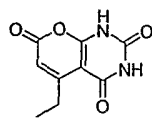
N-chlorosuccinimide: NCS

30

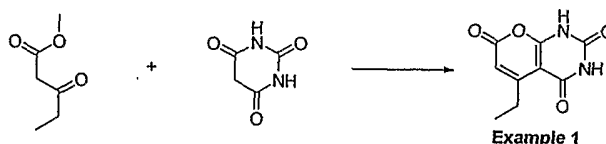
EXAMPLES

Experimental

PREPARATIVE EXAMPLE 1

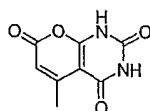


Example 1

Step A:

- 5 Methyl propionylacetate (12.5 g, 96.1 mmol, 1.23 eq.) and barbituric acid (10 g, 78.1 mmol, 1 eq.) were mixed together and without solvent, the mixture was heated to 195°C in air for 2 hr., at which time all of the liquids had evaporated. The solid was washed with boiling distilled water twice. The remaining solid was recrystallized with 2-methoxyethanol/water to give 4 g of
- 10 **Example 1** as a yellow solid (20% yield).
- ^1H NMR (CD_3OD): δ 1.20 (t, 3 H, $J = 7.3$ Hz), 3.00 (q, 2 H, $J = 7.3$ Hz), 5.80 (s, 1 H)
- ^{13}C NMR (CD_3OD): δ 12.6, 27.4, 92.0, 104.2, 149.5, 158.4, 161.8, 162.1, 164.1
- 15 Mass for $\text{C}_9\text{H}_9\text{N}_2\text{O}_4$ (MH) $^+$: 209. Found: 209.

PREPARATIVE EXAMPLE 2



Example 2

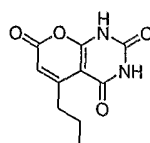
- Example 2** was prepared by a method analogous to the method used
- 20 to prepare **Example 1**, except that methyl acetylacetate was used instead of methyl propionylacetate.

^1H NMR (CD_3OD): δ 2.41 (s, 3 H) 5.75 (s, 1 H)

Mass for $\text{C}_8\text{H}_7\text{N}_2\text{O}_4$ (MH) $^+$: 195. Found: 195.

PREPARATIVE EXAMPLE 3

25



Example 3

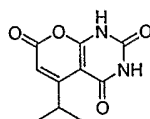
Example 3 was prepared by a method analogous to the method used to prepare **Example 1**, except that methyl butanoylacetate was used instead of methyl propionylacetate.

^1H NMR (CD_3OD): δ 0.96 (t, 3 H, $J = 7.6$ Hz), 1.57 (m, 2 H), 2.86 (m, 2 H),

5 5.75 (s, 1 H)

Mass for $\text{C}_{10}\text{H}_{11}\text{N}_2\text{O}_4$ (MH^+): 223. Found: 223.

PREPARATIVE EXAMPLE 4



Example 4

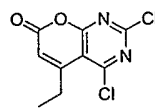
10

Example 4 was prepared by a method analogous to the method used to prepare **Example 1**, except that ethyl isobutylacetate was used instead of methyl propionylacetate, and **Example 4** was purified by HPLC (5% acetonitrile in water to 95% acetonitrile in 10 min).

15 ^1H NMR (CD_3OD): δ 1.14 (d, 6 H, $J = 6.8$ Hz), 4.03 (m, 1 H), 5.86 (s, 1 H)

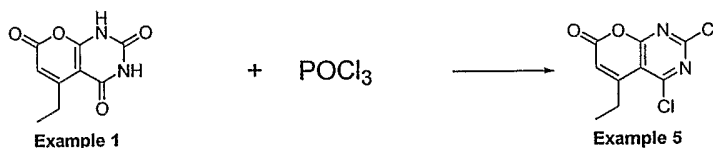
Mass for $\text{C}_{10}\text{H}_{11}\text{N}_2\text{O}_4$ (MH^+): 223. Found: 223.

PREPARATIVE EXAMPLE 5



Example 5

20 Step A:



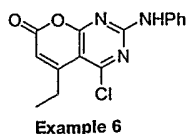
Example 1 (5 g, 24.04 mmol, 1 eq), POCl_3 (36.86g, 240 mmol, 10 eq.)

25 and pyridine (0.95g, 12 mmol, 0.5 eq) were mixed and heated to 115°C for 8 hours. After cooling to room temperature, the solvent was removed and the brownish residue was purified using flash chromatography with 20% EtOAc/hexane as the eluting solvent. The desired product (4 g) was obtained in 68% yield.

30 ^1H NMR (CD_3OD): δ 1.29 (t, 3 H, $J = 7.2$ Hz), 3.12 (m, 2 H), 6.39 (s, 1 H)

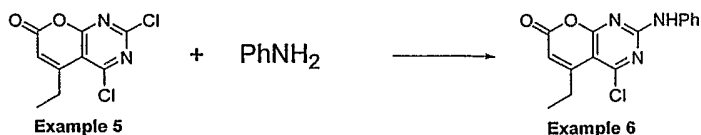
Mass for $\text{C}_9\text{H}_7\text{Cl}_2\text{N}_2\text{O}_2$ (MH^+): 245. Found: 245.

PREPARATIVE EXAMPLE 6



Step A:

5



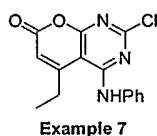
Compound 1 (0.15 g, 0.61 mmol, 1 eq.) and aniline (0.06g, 0.64 mmol, 1.05 eq) were mixed in 3 mL of anhydrous THF and stirred for 12 hours.

10 Solvent was removed and the residue was purified by prep TLC with 25% EtOAc/hexane as the eluting solvent to give desired product as first fraction (7 mg, 4% yield).

¹H NMR (CD₃OD): δ 1.27 (t, 3 H, J = 7.2 Hz), 3.05 (m, 2 H), 6.11 (s, 1 H), 7.11 (t, 1 H, J = 7.6 Hz), 7.34 (m, 2 H), 7.48 (br s, 1 H), 7.60 (d, 2 H, J = 8.0 Hz)

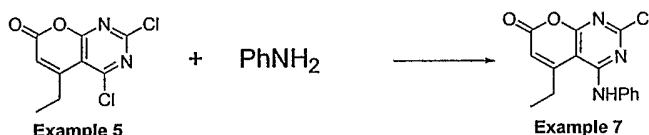
15 Mass for C₁₅H₁₃ClN₃O₂ (MH)⁺: 302. Found: 302.

PREPARATIVE EXAMPLE 7



Step A:

20

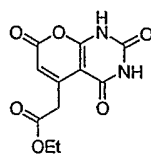


Example 7 was prepared using the method used to prepare **Example 6**, except that **Example 7** was obtained as the second fraction by prep TLC (8 mg, 4% yield).

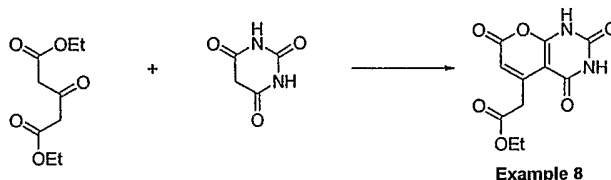
25 ¹H NMR (CD₃OD): δ 1.43 (t, 3 H, J = 7.2 Hz), 2.96 (m, 2 H), 6.22 (s, 1 H), 7.37 – 7.48 (m, 5H)

Mass for C₁₅H₁₃ClN₃O₂ (MH)⁺: 302. Found: 302.

PREPARATIVE EXAMPLE 8



Example 8

Step A:

Example 8

5

Example 8 was prepared using a method analogous to the method used to prepare **Example 1**, except that diethyl 1,3-acetonedicarboxylate was used instead of methyl propionylacetate.

^1H NMR (CD_3OD): δ 1.20 (t, 3 H, $J = 7.3$ Hz), 3.88 (s, 2 H), 4.10 (q, 2 H, $J =$

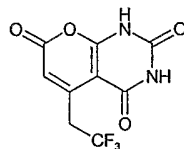
10 7.3 Hz), 5.81 (s, 1 H)

^{13}C NMR (CD_3OD): δ 13.4, 39.6, 61.2, 92.2, 108.1, 149.7, 153.1, 157.8, 161.7, 162.0, 170.3

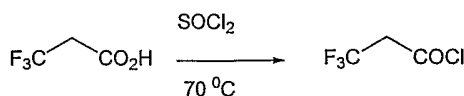
Mass for HRMS for $\text{C}_{11}\text{H}_{11}\text{N}_2\text{O}_6$ (MH^+): calcd 267.0617, found 267.0623.

PREPARATIVE EXAMPLE 9

15



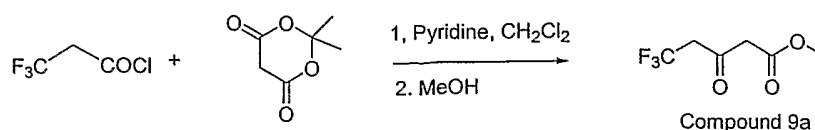
Example 9

Step A:

20 A mixture of 3,3,3,-trifluoropropionic acid (16 g, 125 mmol), thionyl chloride (29.75 g, 250 mmol), and DMF (0.5 mL) was heated to 70°C for 4 hours. The reaction mixture was distilled under reduced pressure to give 3,3,3,-trifluoropropionyl chloride (11.5 g, 72%).

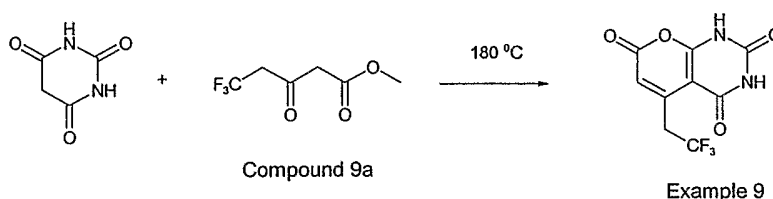
Step B:

25



Compound 9a

Into a solution of Meldrum's acid (2,2-dimethyl-4,6-dioxo-1,3-dioxane; 9 g, 62 mmol) and pyridine (9.8 g, 68 mmol) in anhydrous CH_2Cl_2 (10 mL), which cooled to 0°C , was added 3,3,3-trifluoropropionyl chloride (10 g, 68 mmol). The resulting reaction mixture was stirred under N_2 at 0°C for 1 hour then at room temperature for 2 hours. The reaction mixture was then concentrated under reduced pressure. The resulting paste was mixed with MeOH (20 mL), and heated to 80°C for 5 hours. The solvent was removed and the resulting mixture was distilled under reduced pressure to give **Compound 9a** (6.2 g, 54%).



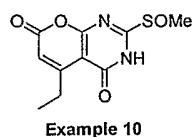
10

A mixture of **Compound 9a** (2.2 g, 12 mmol) and barbituric acid was heated to 180°C for 1 hour to provide a black solid. After cooling to room temperature, the black solid was dissolved into hot water (70 mL). The resulting mixture was extracted with ethyl acetate (4 x 50 mL). The organic solution was dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by reverse phase HPLC eluting with formic acid (0.1%)/acetonitrile to give **Example 9** (0.17 g, 5 %). Electrospray MS $[\text{M}+1]^+$ 263.

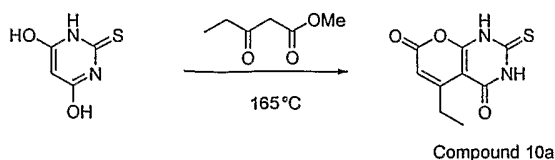
15

PREPARATIVE EXAMPLE 10

20



Step A:



25

A mixture of 4,6-dihydroxy-2-mercapto-pyrimidine (20.0 g, 138.7 mmol) and methyl propionylacetate (21.8 mL, 173.4 mmol) was heated at 165°C until the ester was completely reacted. The reaction mixture was cooled down and poured into water (75 mL) and then filtered through a sintered funnel. The

solid residue was washed with water (2 x 20 mL) and dried under vacuum to yield **Compound 10a** (11.6 g, 37%).

Step B:

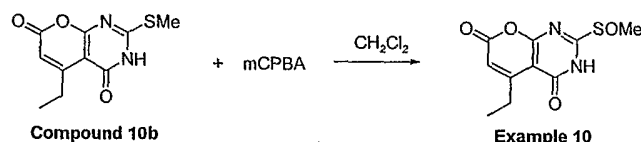


5

MeI (2.23 mL, 35.72 mmol) was added to a suspension of **Compound 10a** (4.0 g, 17.86 mmol) in DMF (40 mL) at room temperature. The reaction mixture was stirred at room temperature overnight. The reaction mixture was then poured into water (250 mL) and filtered through a sintered funnel. The solid residue was washed with water (2 x 50 mL) and dried under vacuum to give **Compound 10b** (4.1 g, 96%).

10

Step C:

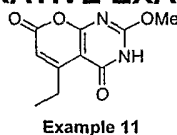


15

m-CPBA (3.1 g, 70%, 12.6 mmol) was added to a suspension of **Compound 10b** (2.0 g, 8.4 mmol) in CH_2Cl_2 (150 mL) at room temperature. The solvent was removed from the suspension after 3 hours and the crude product was purified using silica gel flash column chromatography, eluting first with hexane/EtOAc (v/v = 1/1) then $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (v/v = 2/1) to give **Example 10** (2.0 g, 94%). Electrospray MS $[\text{M}+1]^+$ 255.1.

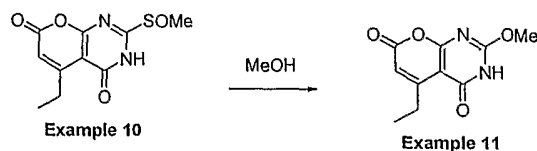
20

PREPARATIVE EXAMPLE 11



Step A:

25

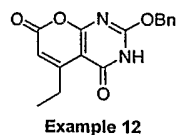


Example 10 (0.35 g, 1.37 mmol) in MeOH (40 mL) was heated at reflux overnight. After cooling to room temperature, the solvent was removed under reduced pressure and the crude product was purified using silica gel

30

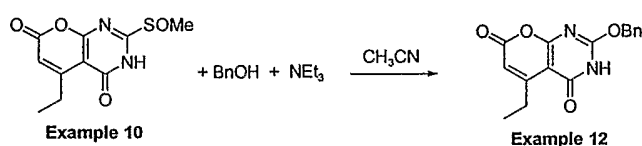
flash column chromatography eluting with CH₂Cl₂/MeOH (v/v = 50/1) to give **Example 11** (0.23 g, 76%). Electrospray MS [M+1]⁺ 223.1.

PREPARATIVE EXAMPLE 12



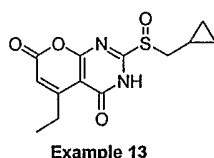
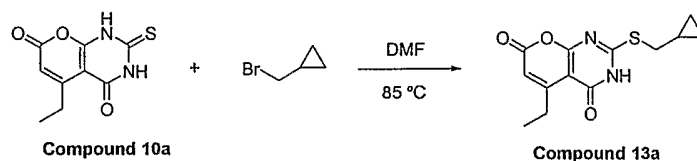
5

Step A:



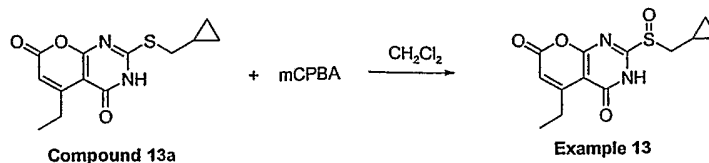
- 10 BnOH (2.46 mL, 23.76 mmol) was added to a solution of **Example 10** (0.404 g, 1.58 mmol) and NEt₃ (0.22 mL, 1.58 mmol) in CH₃CN (12.0 mL) at room temperature. The reaction mixture was heated at 85°C overnight. After cooling to room temperature, HOAc (0.09 mL, 1.58 mmol) was added and the solvent was removed under reduced pressure. The crude product was purified
- 15 using silica gel flash column chromatography eluting with CH₂Cl₂/MeOH (v/v = 50/1) to give **Example 12** (0.20 g, 42%). Electrospray MS [M+1]⁺ 299.1.

PREPARATIVE EXAMPLE 13

20 Step A:

- Cyclopropyl methyl bromide (1.30 mL, 13.4 mmol) was added to a suspension of **Compound 10a** (0.5 g, 2.24 mmol) in DMF (5.0 mL) at room temperature. The reaction mixture was stirred at 85°C for two days. The
- 25 reaction mixture was cooled down and poured into water (75 mL) and then filtered through a sintered funnel. The solid residue was washed with water (2 x 20 mL) and dried under vacuum to give **Compound 13a** (0.55 g, 88%).

Step B:

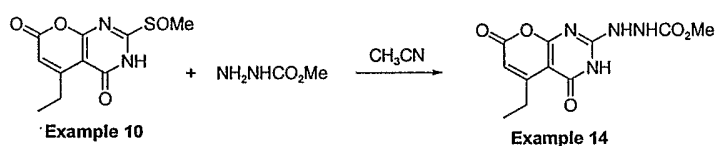


- m*-CPBA (0.33 g, 70%, 1.35 mmol) was added to a suspension of **Compound 13a** (0.25 g, 0.9 mmol) in CH₂Cl₂ (30 mL) at room temperature.
- 5 Solvent was removed after 3 hours, and the crude product was purified using silica gel flash column chromatography eluting with EtOAc/CH₂Cl₂/MeOH (v/v = 4/1/2) to give **Example 13** (0.15 g, 57%). Electrospray MS [M+1]⁺ 295.1.

PREPARATIVE EXAMPLE 14

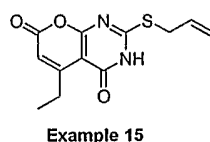


10 Step A:

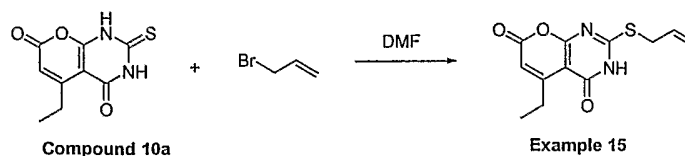


- 15 A mixture of **Example 10** (0.205 g, 0.804 mmol) and NH₂NHCO₂Me (0.145 g, 1.608 mmol) in MeCN (4.0 mL) was heated at reflux for 3 hours. After cooling to room temperature, the solvent was removed under reduced pressure and the crude product was washed with water (3 x 25 mL) with filtration. The solid was dried under vacuum to give **Example 14** (0.2 g, 89%).
- 20 Electrospray MS [M+1]⁺ 281.1.

PREPARATIVE EXAMPLE 15



25 Step A:

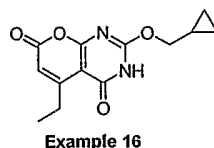


Allyl bromide (1.74 mL, 20.1 mmol) was added to a suspension of **Compound 10a** (1.5 g, 6.7 mmol) in DMF (15.0 mL) at room temperature.

The reaction mixture was stirred at 45°C overnight. The reaction mixture was cooled down and poured into water (200 mL) and then filtered through a sintered funnel. The solid residue was washed with water (2 x 40 mL) and dried under vacuum to give **Example 15** (1.55 g, 92%). Electrospray MS

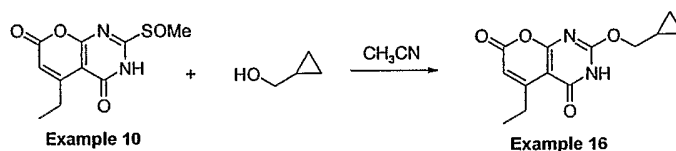
5 $[M+1]^+$ 265.1.

PREPARATIVE EXAMPLE 16



Step A:

10

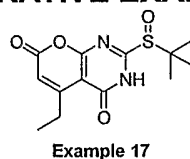


Cyclopropyl carbinol (0.79 mL, 9.8 mmol) was added to a solution of **Example 10** (0.050 g, 0.196 mmol) in CH_3CN (0.8 mL) at room temperature.

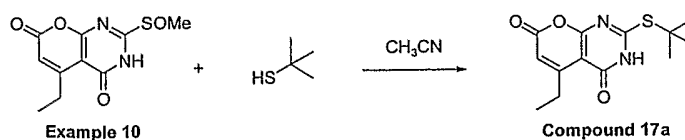
15 The reaction mixture was heated at 85°C overnight. After cooling to room temperature, the solvent was removed under reduced pressure. The crude product was purified using silica gel flash column chromatography eluting with hexane/EtOAc (v/v = 1/1) to give **Example 16** (0.027 g, 52%). Electrospray MS $[M+1]^+$ 263.1.

20

PREPARATIVE EXAMPLE 17



Step A:



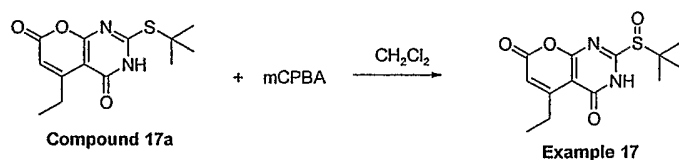
25

A mixture of **Example 10** (0.10 g, 0.392 mmol) and *t*-BuSH (0.66 mL, 5.88 mmol) in 1,4-dioxane (2.0 mL) was heated at reflux overnight. After cooling to room temperature, the solvent was removed under reduced pressure. The crude product was purified using silica gel flash column

chromatography eluting with hexane/EtOAc (v/v = 1/1) to give **Compound 17a** (0.045 g, 41%).

Step B:

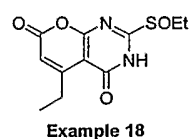
5



m-CPBA (0.049 g, 70%, 0.20 mmol) was added to a suspension of **Compound 17a** (0.040 g, 0.143 mmol) in CH₂Cl₂ (2.5 mL) at room temperature. Solvent was removed after 3 hours and the crude product was purified using silica gel flash column chromatography eluting first with hexane/EtOAc (v/v = 1/1) then with CH₂Cl₂/MeOH (v/v = 5/1) to give **Example 17** (0.030 g, 71%). Electrospray MS [M+1]⁺ 297.1.

PREPARATIVE EXAMPLE 18

15



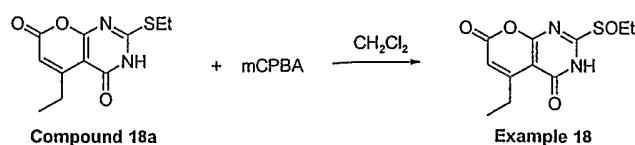
Step A:



EtI (2.1 g, 13.4 mmol) was added to a suspension of **Compound 10a** (1.5 g, 6.7 mmol) in DMF (20 mL). After stirring at room temperature overnight, the reaction mixture was poured into water (50 mL) and filtered through a Buchner funnel. The solid residue was washed with water (2 x 50 mL) and dried under vacuum to give **Compound 18a** (1.3 g, 76%).

25

Step B



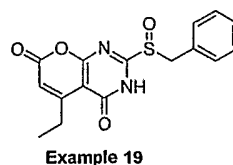
m-CPBA (74 mg, 70%, 3 mmol) was added to a suspension of **Compound 18a** (0.5g, 2 mmol) in CH₂Cl₂ (50 mL) at room temperature. After stirring at room temperature 3 hours, the solvent was removed, and the crude

product was purified using silica gel flash column chromatography eluting with AcOH/MeOH/CH₂Cl₂ (v/v/v = 0.1/4.9/95) to give **Example 18** (0.4 g, 74%).

Electrospray MS [M+1]⁺ 269.

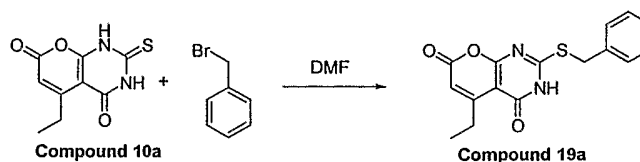
PREPARATIVE EXAMPLE 19

5



Step A:

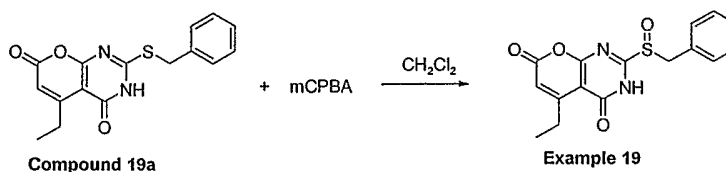
10



Benzyl bromide (1.54 g, 9 mmol) was added to a suspension of **Compound 10a** (1g, 4.5 mmol) in DMF (20 mL). After stirring at room temperature overnight, the reaction mixture was poured into water (50 mL) and filtered through a Buchner funnel. The solid residue was washed with water (2 x 50 mL) and dried under vacuum to give **Compound 19a** (1.3 g, 92%).

Step B:

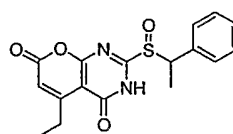
20



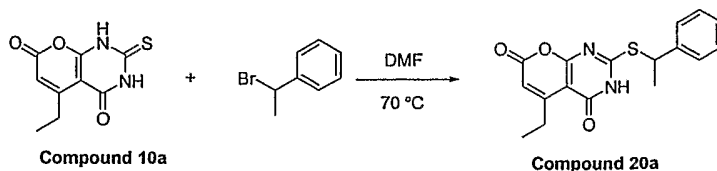
m-CPBA (72 mg, 70%, 3 mmol) was added to a suspension of **Compound 19a** (0.5g, 2 mmol) in CH₂Cl₂ (50 mL) at room temperature. After stirring at room temperature 3 hours, the solvent was removed, and the crude product was purified using silica gel flash column chromatography eluting with AcOH/MeOH/CH₂Cl₂ (v/v/v = 0.1/2.9/97) to give **Example 19** (0.5 g, 76%).

Electrospray MS [M+1]⁺ 331.

PREPARATIVE EXAMPLE 20



Example 20

Step A:

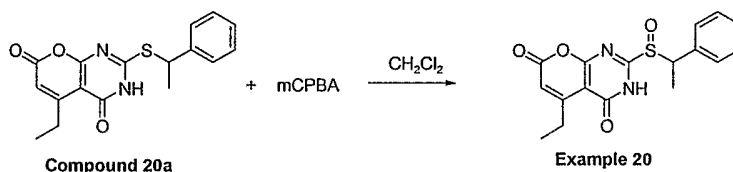
Compound 10a

Compound 20a

5

(1-Bromoethyl)benzene (3.4 g, 18 mmol) was added to a suspension of **Compound 10a** (1 g, 4.5 mmol) in DMF (20.0 mL) at room temperature. The reaction mixture was stirred at 70°C for one day. The reaction mixture was cooled down and poured into water (50 mL) and then filtered through a

10 Buchner funnel. The solid residue was washed with water (2 x 20 mL) and dried under vacuum to **Compound 20a** (1.3 g, 87%). Electrospray MS $[M+1]^+$ 329.

Step B:

Compound 20a

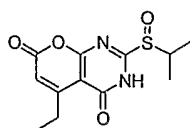
Example 20

15

m-CPBA (0.3 g, 70%, 1.2 mmol) was added to a suspension of **Compound 20a** (0.33 g, 1 mmol) in CH_2Cl_2 (30 mL) at room temperature. Solvent was removed after 3 hours and the crude product was purified using

20 silica gel flash column chromatography eluting with 5 % EtOH in EtOAc/hexanes (v/v = 1:1) to give **Example 20** (0.1 g, 50%). Electrospray MS $[M+1]^+$ 345.

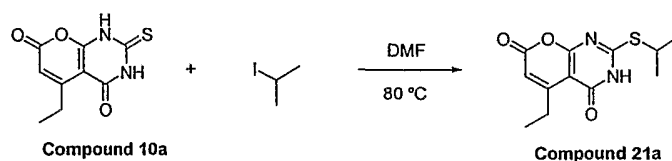
PREPARATIVE EXAMPLE 21



Example 21

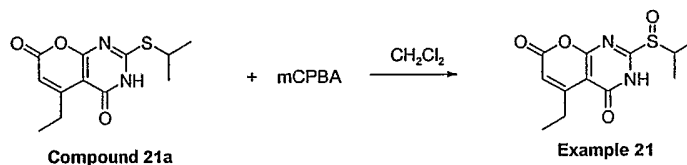
25

Step A:



2-iodopropane (1.53 g, 9 mmol) was added to a suspension of **Compound 10a** (1 g, 4.5 mmol) in DMF (20 mL). The reaction mixture was stirred at 80°C for one day. The reaction mixture was cooled down and
 5 poured into water (50 mL) and then filtered through a Buchner funnel. The solid residue was washed with water (2 x 20 mL) and dried under vacuum to give **Compound 21a** (1.05 g, 88%).

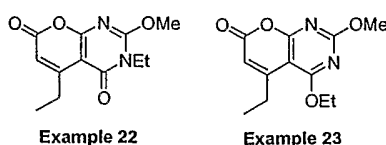
Step B



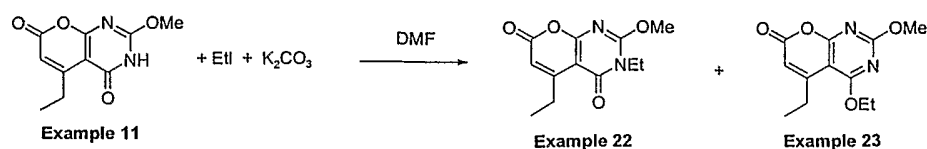
10

m-CPBA (0.74 g, 70%, 3 mmol) was added to a suspension of **Compound 21a** (0.53 g, 2 mmol) in CH₂Cl₂ (30 mL) at room temperature. Solvent was removed after 3 hours, the crude product was purified using a silica gel flash column chromatography eluting with 0.1% AcOH in
 15 MeOH/CH₂Cl₂ (v/v = 2:98) to give **Example 21** (0.45 g, 80%). Electrospray MS [M+1]⁺ 283.

PREPARATIVE EXAMPLES 22 and 23



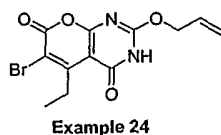
20 Step A:



K₂CO₃ (36.7 mg, 0.266 mmol) was added to a mixture of **Example 11** (29.6 mg, 0.133 mmol) and EtI (0.064 mL, 0.8 mmol) in DMF (1.0 mL) at room
 25 temperature. The reaction was stirred over night before it was diluted with by the addition of EtOAc (50 mL) and water (10 mL). The organic phase was washed with water (3x15 mL), brine (15 mL), and dried over MgSO₄. After filtration and concentration, the crude product was purified using preparative

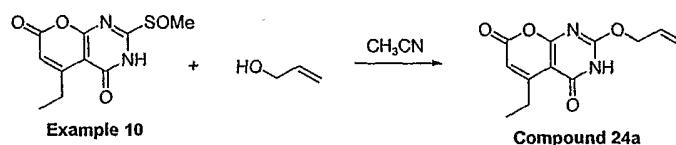
TLC with hexane/CH₂Cl₂/EtOAc (v/v/v = 7/3/1) as eluent to give **Example 22** (7.0 mg, 21%) and **Example 23** (20 mg, 60%). Electrospray MS [M+1]⁺ 251.1.

PREPARATIVE EXAMPLE 24

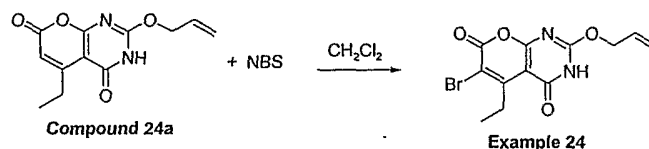


5

Step A:



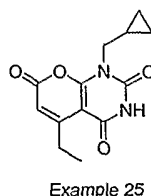
10 **Example 10** (0.216 g, 0.847 mmol) in allyl alcohol (3.0 mL) was heated at reflux overnight. After cooling to room temperature, the solvent was removed under reduced pressure and the crude product was purified using silica gel flash column chromatography eluting with EtOAc/MeOH (v/v = 5/1) to give **Compound 24a** (0.1 g, 48%).

15 Step B:

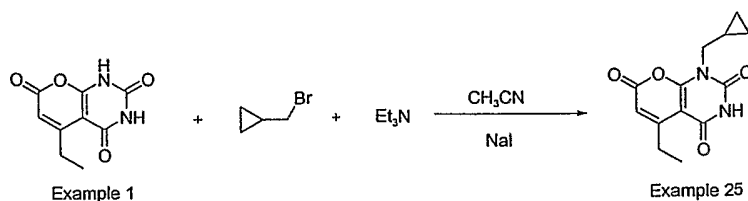
20 NBS (36 mg, 0.202 mmol) was added to a solution of **Compound 24a** (0.040 g, 0.161 mmol) in CH₂Cl₂ (2.0 mL) at room temperature. Solvent was removed over 1 hour and the crude product was purified using silica gel flash column chromatography eluting with hexane/EA (v/v = 1/1) to give **Example 24** (0.025 g, 48%). Electrospray MS [M+1]⁺ 327.1.

PREPARATIVE EXAMPLE 25

25



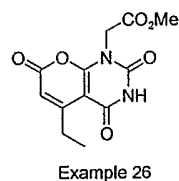
Step A:



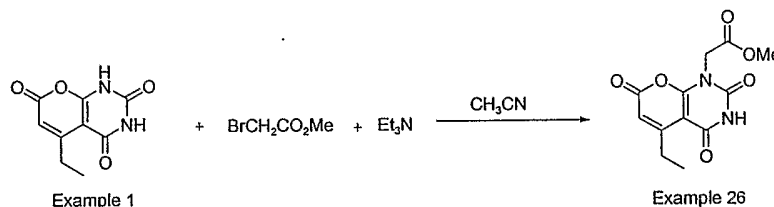
Example 1 (0.5 g, 2.4 mmol) was taken up in CH₃CN (10 mL).

- 5 Triethylamine (0.33 mL, 2.4 mmol) was added to the suspension followed by cyclopropyl methyl bromide (0.26 mL, 2.64 mmol) and NaI (0.36 g, 2.4 mmol). The reaction mixture was heated to reflux overnight. After cooling to room temperature, the solvent was evaporated in vacuo. The crude product was purified by crystallization from EtOAc/hexanes to give **Example 25** (0.25 g,
- 10 40%).

PREPARATIVE EXAMPLE 26



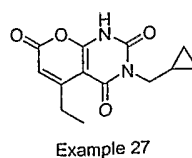
15 Step A:

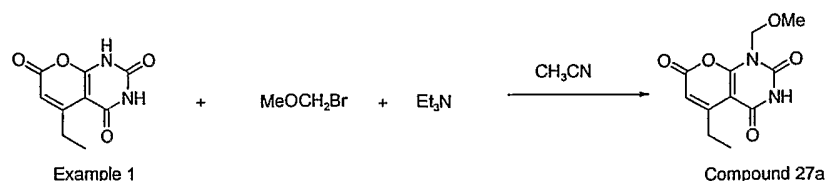


Example 1 (0.1 g, 0.48 mmol) was taken up in CH₃CN (3.0 mL).

- 20 Triethylamine (0.067 mL, 0.48 mmol) was added to the suspension followed by methyl bromoacetate (0.046 mL, 0.48 mmol). The reaction mixture was allowed to stir overnight at room temperature. The solvent was removed under reduced pressure and the crude mixture was purified by column chromatography eluting with EtOAc/hexanes (2/3: v/v) to yield **Example 26**
- 25 (0.06 g, 45%).

PREPARATIVE EXAMPLE 27



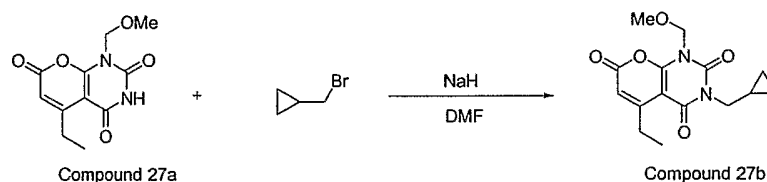
Step A:

5

Example 1 (1.0 g, 4.8 mmol) was taken up in CH₃CN (20 mL).

Triethylamine (0.67 mL, 4.8 mmol) was added to the suspension followed by bromomethyl methyl ether (0.44 mL, 4.8 mmol). The reaction mixture was allowed to stir at room temperature for 10 min after which it was concentrated.

10 The crude mixture was purified by column chromatography eluting with EtOAc/hexanes (2/3: v/v) to yield **Compound 27a** (0.6 g, 50%).

Step B:

15

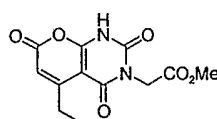
Sodium hydride (0.058 g, 1.46 mmol) was added to a mixture of **Compound 27a** (0.335 g, 1.33 mmol) in 8 mL DMF at 0°C followed by cyclopropyl methyl bromide (0.142 mL, 1.46 mmol). The suspension was allowed to stir at room temperature overnight before being diluted with EtOAc (10 mL) and quenched by the addition of water (5 mL). The aqueous phase was extracted with EtOAc (2 x 5 mL). The organic layers were combined, dried over MgSO₄, and concentrated to give the crude product. The crude mixture was purified by column chromatography eluting with EtOAc/hexanes (2/3: v/v) to yield **Compound 27b** (0.175 g, 43%).

25 Step C:

30 Boron tribromide (2.85 mL, 2.85 mmol, 1.0 M solution in DCM) was added to a solution of **Compound 27b** (0.175 g, 0.57 mmol) in CH₂Cl₂ (8.0

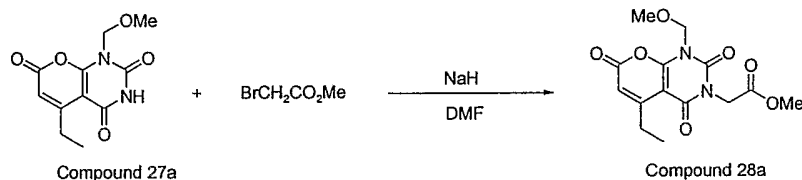
mL) at -78°C . The reaction was allowed to stir for 2 h before being quenched with water (5.0 mL). The reaction mixture was extracted with EtOAc (2 x 5 mL). The organic layers were combined, dried over MgSO_4 , and concentrated to give the crude product. The crude mixture was purified by column chromatography eluting with EtOAc/hexanes (2/3: v/v) to yield **Example 27** (0.1 g, 67%).

PREPARATIVE EXAMPLE 28



Example 28

10 Step A:



Sodium hydride (0.016 g, 0.396 mmol) was added to a mixture of **Compound 27a** (0.100 g, 0.396 mmol) in 2 mL DMF at 0°C followed by methyl bromoacetate (0.041 mL, 0.44 mmol). The suspension was allowed to stir at room temperature overnight before being diluted with EtOAc (5 mL) and quenched by the addition of water (5 mL). The aqueous phase was extracted with EtOAc (2 x 5 mL). The organic layers were combined, dried over MgSO_4 , and concentrated to give the crude product. The crude mixture was purified by column chromatography eluting with EtOAc/hexanes (2/3: v/v) to yield **Compound 28a** (0.07 g, 54%).

Step B:



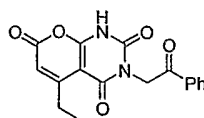
25

Boron tribromide (1.1 mL, 1.1 mmol, 1.0 M solution in DCM) was added to a solution of **Compound 28a** (0.07 g, 0.22 mmol) in CH_2Cl_2 (3.0 mL) at -78°C . The reaction was allowed to stir for 2 h before being quenched with water (5.0 mL). The reaction mixture was extracted with EtOAc (2 x 5 mL).

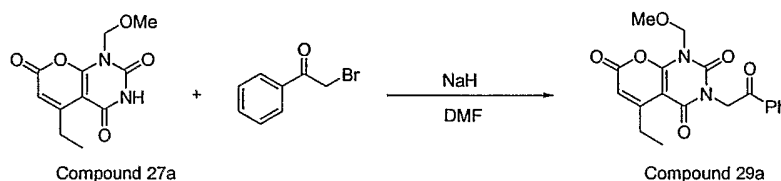
30

The organic layers were combined, dried over MgSO_4 , and concentrated to give the crude product. The crude mixture was purified by column chromatography eluting with EtOAc/hexanes (2/3: v/v) to yield **Example 28** (0.02 g, 33%).

5

PREPARATIVE EXAMPLE 29

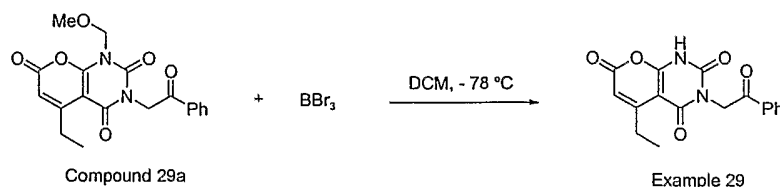
Example 29

Step A:

10

Sodium hydride (0.080 g, 1.98 mmol) was added to a mixture of **Compound 27a** (0.500 g, 1.98 mmol) in 8 mL DMF at 0°C followed by 2-bromoacetophenone (0.434 g, 1.98 mmol). The suspension was allowed to stir at room temperature overnight before being diluted with EtOAc (5 mL) and quenched by the addition of water (5 mL). The aqueous phase was extracted with EtOAc (2 x 5 mL). The organic layers were combined, dried over MgSO_4 , and concentrated to give the crude product. The crude mixture was purified by column chromatography eluting with EtOAc/hexanes (2/3: v/v) to yield **Compound 29a** (0.37 g, 50%).

20

Step B:

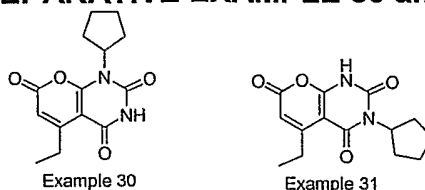
25

Boron tribromide (4.7 mL, 4.7 mmol, 1.0 M solution in DCM) was added to a solution of **Compound 29a** (0.350 g, 0.95 mmol) in CH_2Cl_2 (10.0 mL) at -78°C. The reaction was allowed to stir for 2 h before being quenched with water (5.0 mL). The reaction mixture was extracted with EtOAc (2 x 15 mL). The organic layers were combined, dried over MgSO_4 , and concentrated to

30

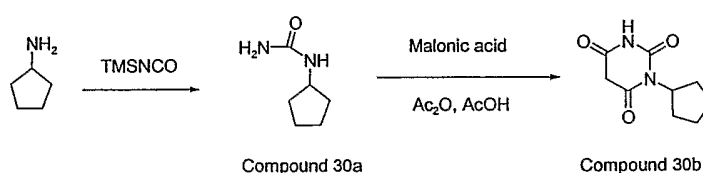
give the crude product. The crude mixture was purified by column chromatography eluting with EtOAc/hexanes (2/3: v/v) to yield **Example 29** (0.175 g, 56%).

PREPARATIVE EXAMPLE 30 and 31



5

Step A:

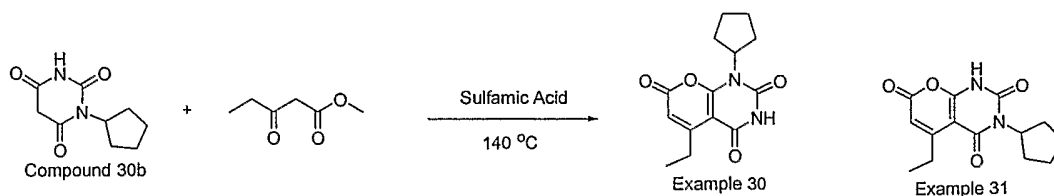


10 To a CH_2Cl_2 solution of cyclopentylamine was added trimethylsilyl isocyanate. The reaction mixture was stirred overnight. To this was added 200 ml of CH_3OH , and the mixture was stirred for another 2 hrs. The reaction mixture was concentrated and was titrated using diethyl ether to give an off-white precipitate. The precipitate was filtered through a Buchner funnel to

15 give cyclopentyl urea **Compound 30a** as a white crystalline solid compound (13.0 g, 86%). To this urea **Compound 30a** (5.0 g, 38.7 mmol) in acetic acid (11 mL), was added malonic acid (4.0g, 38.7 mmol) followed by acetic anhydride (18 mL) and the reaction was stirred at 70°C for 12 hrs. The reaction mixture was concentrated, cooled in an ice bath and titrated using 4/1

20 $\text{EtO}_2/\text{EtOAc}$. A pale yellow crystalline solid precipitated out. The precipitate was filtered and washed 2-3 times using cold diethyl ether to obtain a pale yellow solid **Compound 30b** (2.5 g, 33%).

Step B:

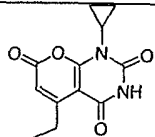
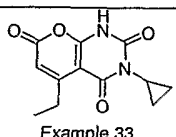
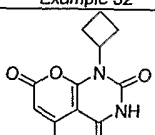
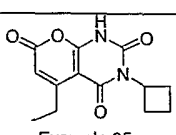
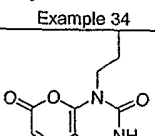
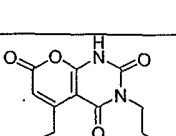
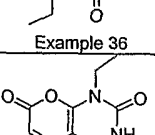
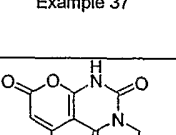
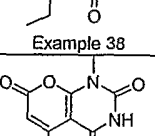
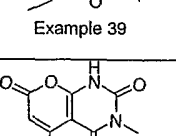
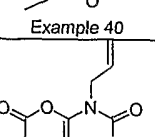
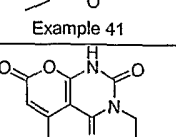


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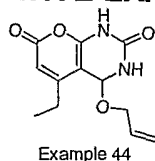
Compound 30b (0.75 g, 1.0 equiv., 3.82 mmol) was condensed with methyl propional acetate (0.48mL, 3.82 mmol) in the presence of sulfamic acid and heated to 140°C for 6 hrs, forming a dark brown solid. The reaction

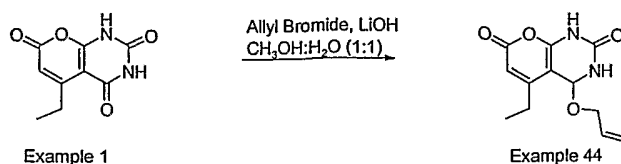
mixture was diluted with EtOAc, washed with H₂O, dried using Na₂SO₄ and concentrated to give a crude mixture. Prep TLC purification of the crude mixture in 95/5 CH₂Cl₂/CH₃OH yielded both the N₁ and N₃ isomers, **Example 30** LCMS: (M+1) 277.1 and **Example 31** LCMS: (M+1). 277.1

5 A similar two-step procedure was used to synthesize **Examples 32-43**.

substituents	N-1 products	LCMS: (M+1) of N-1 products	N-3 products	LCMS: (M+1) of N-3 products
cyclopropyl	 Example 32	249.1	 Example 33	249.1
cyclobutyl	 Example 34	263.1	 Example 35	263.1
Pr	 Example 36	251.1	 Example 37	251.1
Et	 Example 38	237.1	 Example 39	237.1
Me	 Example 40		 Example 41	223.0
allyl	 Example 42	249.1	 Example 43	249.1

PREPARATIVE EXAMPLE 44

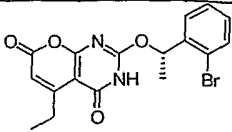
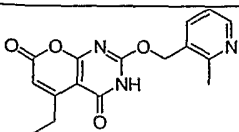
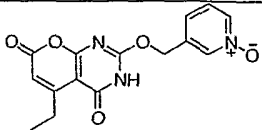
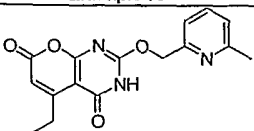
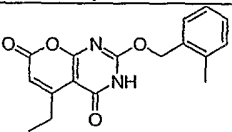
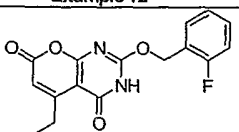
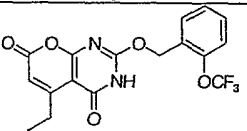
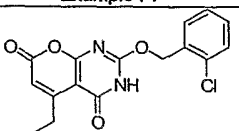
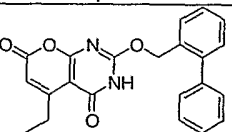
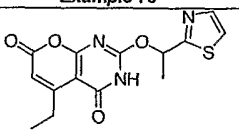
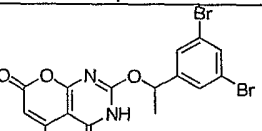




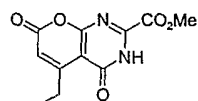
To **Example 1** (0.456 g, 2.2 mmol) in MeOH:H₂O (1:1) was added allyl bromide followed by LiOH, and the reaction mixture was heated to 82°C for 8 hours. The progress of the reaction was monitored by TLC which indicated presence of some starting material. The reaction mixture was then heated for another 6 hours. An orange-red precipitate was produced, which was filtered from the solution using diethyl ether. The filtrate was purified using prep TLC 95/5 CH₂Cl₂/CH₃OH to give **Example 44** LCMS: (M+1).249.0

The following **Examples 45-47, 51, 61-64, 66-67, 69-79** were prepared by a procedure similar to that used for the preparation of **Example 12**, using **Example 10** and the appropriate corresponding alcohol.

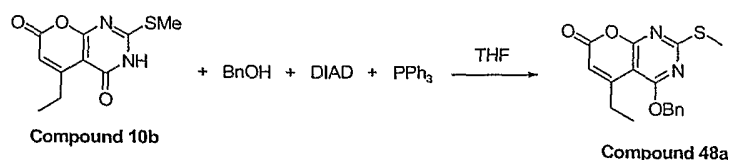
PREPARATIVE EXAMPLE	Electrospray LCMS [M+1] ⁺	PREPARATIVE EXAMPLE	Electrospray LCMS [M+1] ⁺
<p style="text-align: center;">Example 45</p>	367.1	<p style="text-align: center;">Example 46</p>	367.1
<p style="text-align: center;">Example 47</p>	317.1	<p style="text-align: center;">Example 51</p>	300.1
<p style="text-align: center;">Example 61</p>	359.1	<p style="text-align: center;">Example 62</p>	391.1
<p style="text-align: center;">Example 63</p>	327.1	<p style="text-align: center;">Example 64</p>	327.1
<p style="text-align: center;">Example 66</p>	300.1	<p style="text-align: center;">Example 67</p>	316.1

PREPARATIVE EXAMPLE	Electrospray LCMS [M+1] ⁺	PREPARATIVE EXAMPLE	Electrospray LCMS [M+1] ⁺
 Example 69	391.2	 Example 70	314.1
 Example 71	316.1	 Example 72	314.1
 Example 73	313.1	 Example 74	317.1
 Example 75	383.1	 Example 76	333.1
 Example 77	375.1	 Example 78	320.1
 Example 79	469.1		

PREPARATIVE EXAMPLE 48



Example 48

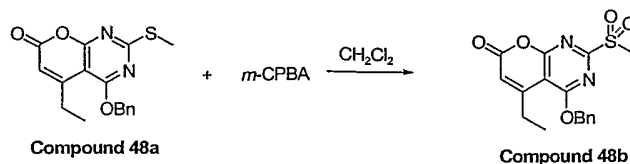
5 Step A:

DIAD (0.488 mL, 2.52 mmol) was added dropwise to a solution of
 10 **Compound 10b** (0.5 g, 2.10 mmol), BnOH (0.261 mL, 2.52 mmol) and PPh₃
 (0.661 g, 2.52 mmol) in THF (6.0 mL) at room temperature. The resulting
 reaction mixture was stirred for 5 hours before it was worked up by silica gel

flash column chromatography using a solid sample loading method, eluting with hexane/EtOAc (v/v = 5/1) to give **Compound 48a** (0.25 g, 36%).

Step B:

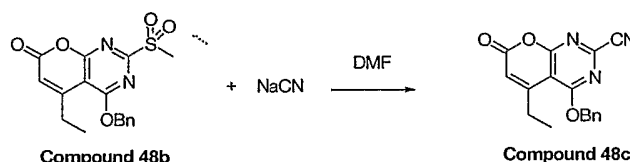
5



m-CPBA (0.384 g, 1.55 mmol, 60-70%) was added at room temperature to a solution of **Compound 48a** (0.17 g, 0.518 mmol) in CH_2Cl_2 (5 mL). The reaction mixture was stirred for 5 hours before it was quenched with addition of Me_2S (76 μL , 1.55 mmol). The mixture was then diluted with EtOAc and washed with NaHCO_3 solution. The organic phase was washed with water, brine, and dried (Na_2SO_4). Solvent was removed under reduced pressure, and the crude product was purified by silica gel flash column chromatography eluting with hexane/ CH_2Cl_2 /EtOAc (v/v/v = 7/3/2) to give **Compound 48b** (0.15 g, 80%).

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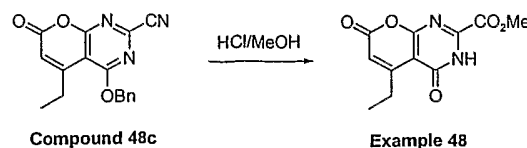
Step C:



NaCN (14.0 mg, 0.286 mmol) was added to a solution of **Compound 48b** (85.8 mg, 0.238 mmol) in DMF (1.5 mL) at room temperature. The reaction mixture was stirred at room temperature for 2 hours before it was worked up by dilution with EtOAc and water. The organic phase was washed with water (2x), brine, and dried (MgSO_4). Solvent was removed under reduced pressure, and the crude product was purified by silica gel flash column chromatography, eluting with hexane/ CH_2Cl_2 /EtOAc (v/v/v = 5/1/1) to give **Compound 48c** (37 mg, 50%).

25

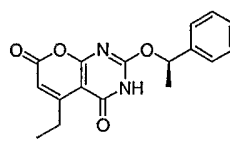
Step D:



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A solution of **Compound 48c** (10 mg, 0.0326 mmol) in 4.0 M HCl in dioxane (0.7 mL) and MeOH (0.7 mL) in a sealed tube was heated at 70°C for 7 hours. The mixture was cooled to room temperature and solvent was removed under reduced pressure to give crude product. The crude product was purified with preparative thin layer silica gel chromatography eluting with hexane/CH₂Cl₂/MeOH (v/v/v = 6/4/1) to give **Example 48** (5 mg, 61%).
Electrospray MS [M+1]⁺ 251.1.

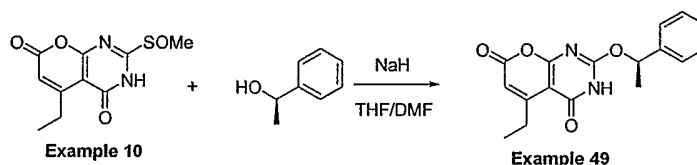
PREPARATIVE EXAMPLE 49



Example 49

10

Step A:



Example 10

Example 49

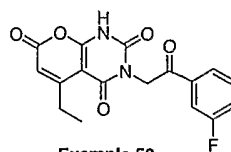
(R)-Phenethanol (0.24 mL, 2.0 mmol) was added dropwise to a suspension of NaH (87.4 mg, 2.0 mmol, 55% in mineral oil) in THF (3.0 mL) at room temperature. The mixture was stirred for 2 hours until the solution was clear. The alkoxide thus formed was then added dropwise to a solution of the **Compound 10** (0.27 g, 1.0 mmol) in DMF (3.0 mL) at room temperature. The reaction mixture was stirred for 2 hours before it was quenched by the addition of HOAc (0.11 mL, 2.0 mmol). The reaction mixture was taken up in EtOAc/CH₂Cl₂ (8/2), washed with diluted HCl (0.1 M), water and brine, then dried (MgSO₄). The solvent was removed under reduced pressure. The crude product was purified using silica gel flash column chromatography eluting with hexane/CH₂Cl₂/EtOAc (v/v/v = 7/3/2) to give **Compound 49** (0.25 g, 80%).
Electrospray MS [M+1]⁺ 313.1.

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PREPARATIVE EXAMPLE 50

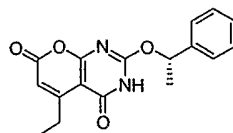


Example 50

30

Example 50 was prepared by a procedure similar to that used to prepare **Example 29**, using **Compound 27a** and the appropriate corresponding bromide. Electrospray MS $[M+1]^+$ 345.1.

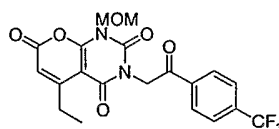
PREPARATIVE EXAMPLE 52



Example 52

Example 52 was prepared by a procedure similar to that used to prepare **Example 49**, using **Example 10** and (S)-phenethanol. Electrospray MS $[M+1]^+$ 313.1.

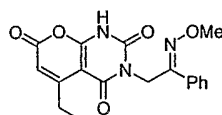
PREPARATIVE EXAMPLE 53



Example 53

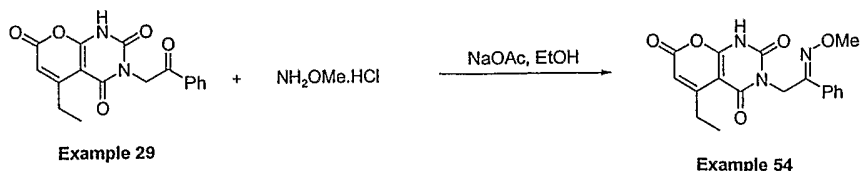
Example 53 prepared by a procedure similar to that used in Step A of the preparation of **Example 29**, using **Compound 27a** and the appropriate corresponding bromide. Electrospray MS $[M+1]^+$ 439.1.

PREPARATIVE EXAMPLE 54



Example 54

Step A:



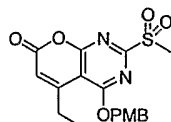
Example 29

Example 54

Example 29 (0.05 g, 0.153 mmol) was taken up in ethanol (3.0 mL). Methoxylamine hydrochloride (0.051 g, 0.61 mmol) was added to the mixture followed by sodium acetate (0.038 g, 0.46 mmol). The reaction mixture was stirred at 60°C overnight. After being cooled to room temperature, the solvent was removed under reduced pressure, diluted with CH_2Cl_2 (5 mL) and water

(5 mL). The product was extracted from CH₂Cl₂ (2 x 5 mL), dried over MgSO₄, concentrated. The crude product was dissolved in minimum CH₂Cl₂, diluted with hexanes and filtered to give **Example 54**. Electrospray MS [M+1]⁺ 356.1.

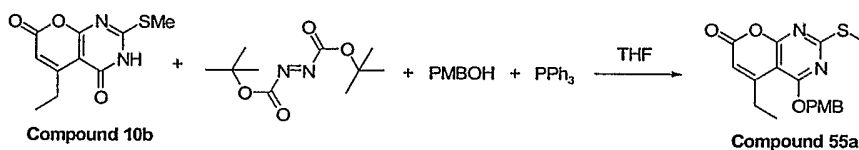
PREPARATIVE EXAMPLE 55



Example 55

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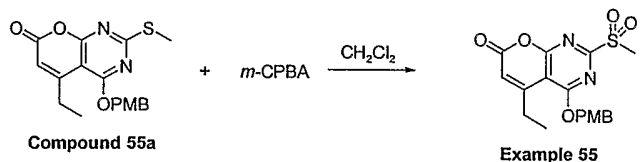
Step A:



10 Di-*t*-butyl diazodicarboxylate (2.32 g, 10.08 mmol) was added to a solution of **Compound 10b** (2.0 g, 8.4 mmol), 4-methoxybenzyl alcohol (1.39 g, 10.08 mmol) and PPh₃ (2.64 g, 10.08 mmol) in THF (20.0 mL) at room temperature. The resulting reaction mixture was stirred for 4 hours before it was worked up by direct silica gel flash column chromatography using a solid sample loading method, eluting with hexane/CH₂Cl₂/EtOAc (v/v/v = 9/1/1) to give **Compound 55a** (1.6 g, 53%).

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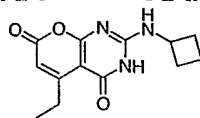
Step B:



20 *m*-CPBA (0.47 g, 1.92 mmol, 60-70%) was added at room temperature to a solution of **Compound 55a** (0.287 g, 0.80 mmol) in CH₂Cl₂ (8 mL). The reaction mixture was stirred for 5 hours before it was quenched by the addition of Me₂S (124 μL, 1.92 mmol). The mixture was then diluted with EtOAc and washed with NaHCO₃ solution. The organic phase was washed with water, brine, and dried (Na₂SO₄). Solvent was removed under reduced pressure, crude product was purified with silica gel flash column chromatography eluting with hexane/CH₂Cl₂/EtOAc (v/v/v = 7/3/2) to give **Example 55** (0.15 g, 80%). Electrospray MS [M+1]⁺ 391.1.

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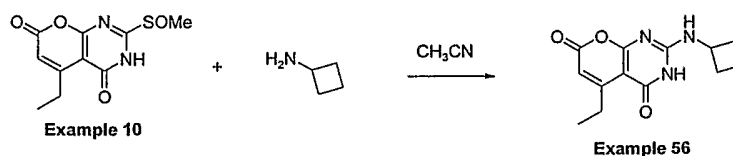
PREPARATIVE EXAMPLE 56



Example 56

Step A:

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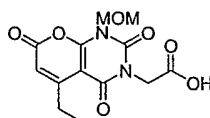


Example 10

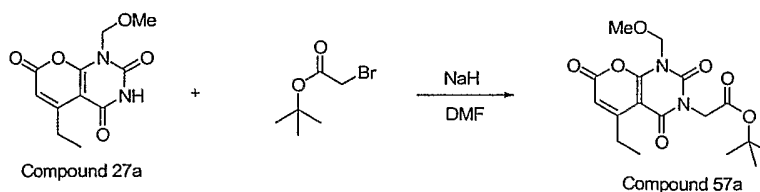
Example 56

Cyclobutylamine (0.14 g, 2 mmol) was added to a suspension of **Example 10** (0.25 g, 1 mmol) in CH_3CN (15 mL). The reaction mixture was stirred at room temperature for 16 hours. Solvent was removed and the crude product was purified using silica gel flash column chromatography eluting with 10% NH_4OH in $\text{MeOH}/\text{CH}_2\text{Cl}_2$ (v/v = 3:97) to give **Example 56** (0.045 g, 17%). Electrospray MS $[\text{M}+1]^+$ 262.1

PREPARATIVE EXAMPLE 57



Example 57

Step A:

Compound 27a

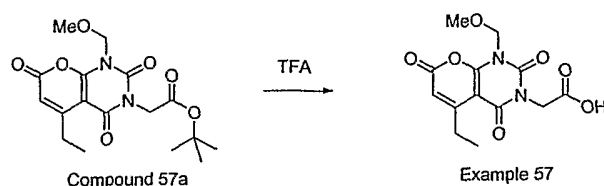
Compound 57a

20

A mixture of **Compound 27a** (2 g, 7.9 mmol) in DMF (100 mL), t-butyl bromoacetate (1.7 g, 8.7 mmol), and diisopropyl ethyl amine (1.1 g, 8.7 mmol) was stirred at 40°C for 4 hours, then at room temperature for 16 hours. The reaction mixture was mixed with water (200 mL), and then extracted with ethyl acetate (100 mL x 3). The organic solution was dried (Na_2SO_4) and concentrated. The crude product was purified using silica gel flash column chromatography eluting with $\text{MeOH}/\text{CH}_2\text{Cl}_2$ (v/v = 2:98) to give **Compound 57a** (1.8 g, 62%). Electrospray MS $[\text{M}+1]^+$ 367.2.

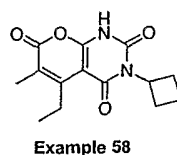
Step B:

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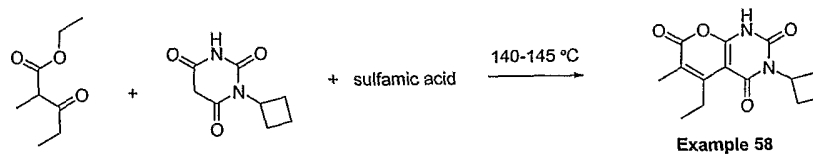


A mixture of **Compound 57a** (0.95g, 2.6 mmol) in CH_2Cl_2 (5 mL) and trifluoroacetic acid (1.5g, 13 mmol) was stirred at room temperature for 4 hours. Removal of solvent and excess trifluoroacetic acid gave **Example 57** (0.8g, 100%). Electrospray MS $[\text{M}+1]^+$ 311.2

PREPARATIVE EXAMPLE 58

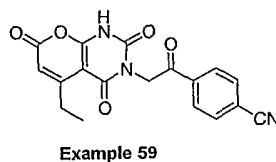


10 Step A:



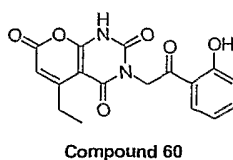
To a mixture of mono-cyclobutylbarbituric acid (300 mg, 1.6 mmol) and 2-Methyl-3-oxo-pentanoic acid ethyl ester (1.041g, 6.59 mmol) was added sulfamic acid (77 mg, 0.8 mmol). The mixture was heated at 140-145°C for 48h. The residue was loaded onto preparative silica gel plates and eluted with 5% MeOH/ CH_2Cl_2 to afford **Example 58** (42 mg, 9%). LCMS: $\text{M}+1$: 277.1

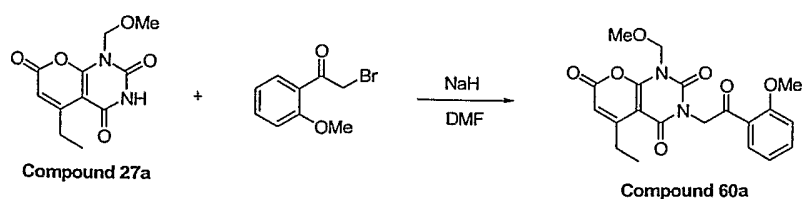
PREPARATIVE EXAMPLE 59



EXAMPLE 59 was prepared using a two step procedure similar to that used for the preparation of **Example 29**, using **Compound 27a** and the appropriate corresponding bromide. Electrospray MS $[\text{M}+1]^+$ 252.1.

PREPARATIVE EXAMPLE 60

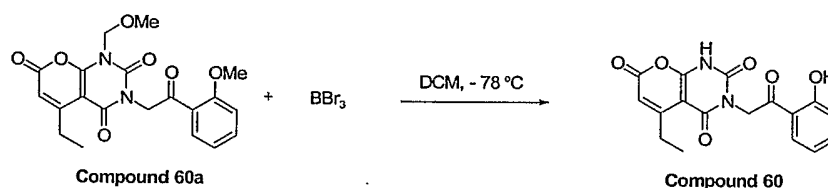


Step A:

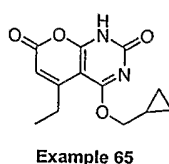
- 5 Sodium hydride (0.035 g, 0.869 mmol) was added to a mixture of **Compound 27a** (0.200 g, 0.79 mmol) in 3 mL DMF at 0°C followed by 2-methoxyphenacyl bromide (0.2 g, 0.87 mmol). The suspension was allowed to stir at room temperature overnight before being diluted with EtOAc (10 mL) and quenched by the addition of water (5 mL). The aqueous phase was
- 10 extracted with EtOAc (2 x 5 mL). The organic layers were combined, dried over MgSO₄, and concentrated to give the crude product. The crude mixture was purified by column chromatography eluting with EtOAc/hexanes (2/3: v/v) to yield **Compound 60a**.

Step B:

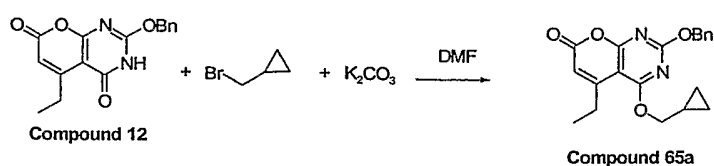
15



- Boron tribromide (1.3 mL, 1.31 mmol, 1.0 M solution in DCM) was added to a solution of **Compound 60a** (0.105 g, 0.262 mmol) in CH₂Cl₂ (5.0 mL) at -78°C. The reaction mixture was allowed to stir for 2 h before being quenched with water (5.0 mL). The reaction mixture was extracted with EtOAc (2 x 5 mL). The organic layers were combined, dried over MgSO₄, and concentrated to give the crude product. The crude mixture was purified by column chromatography eluting with EtOAc/hexanes (2/3: v/v) to yield
- 25 **Compound 60**. Electrospray MS [M+1]⁺ 343.1.

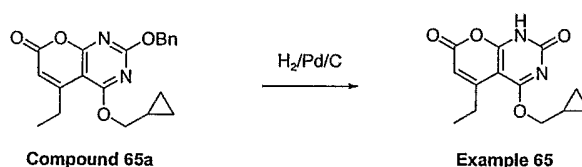
PREPARATIVE EXAMPLE 65Step A:

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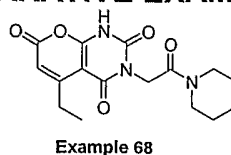
- 5 K_2CO_3 (64.7 mg, 0.47 mmol) was added to a mixture of **Example 12** (70 mg, 0.235 mmol) and cyclopropyl methyl bromide (0.068 mL, 0.705 mmol) in DMF (2.0 mL) at room temperature. The reaction mixture was stirred overnight before it was diluted by the addition of EtOAc (50 mL) and water (10 mL). The organic phase was washed with water (3x15 mL), brine (15 mL), and dried over MgSO_4 . After filtration and concentration, the crude product was purified using preparative TLC with hexane/ CH_2Cl_2 /EtOAc (v/v/v = 7/3/1) as eluent to give **Compound 65a** (26 mg, 31%).

Step B:



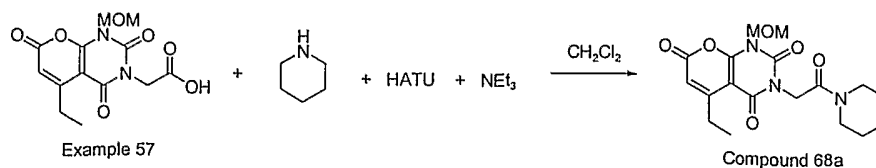
- 15 **Compound 65a** (26 mg, 0.074 mmol) in EtOH (5.0 mL) was treated at room temperature with Pd/C (7.8 mg, 10 wt%) and was hydrogenated with a H_2 balloon for 30 minutes. The reaction mixture was filtered through a short pad of Celite and the residue was washed with EtOH (15 mL). Solvent was removed under reduced pressure and the crude product was purified using preparative TLC with hexane/ CH_2Cl_2 /MeOH (v/v/v = 3/7/1) as eluent to give **Example 65** (6 mg, 30%). Electrospray MS $[\text{M}+1]^+$ 263.1.

PREPARATIVE EXAMPLE 68



Step A:

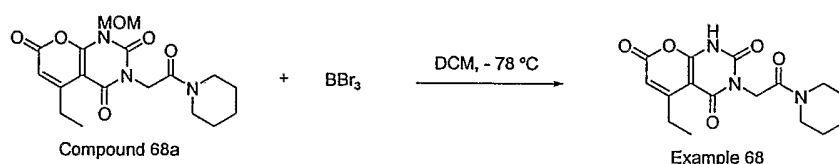
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The mixture of **Example 57** (0.1g, 0.32 mmol) in CH_2Cl_2 (5 mL), piperidine (0.027 g, 0.32 mmol), HATU (0.24g, 0.64 mmol), and triethylamine

(0.098 g, 0.96 mmol) was stirred at room temperature for 2 hours. The reaction mixture was mixed with water (20 mL), and then extracted with CH_2Cl_2 (10 mL x 2). The organic solution was dried (Na_2SO_4) and concentrated. The crude product was purified using silica gel flash column chromatography eluting with EtOAc/hexanes (v/v = 1:1) to give **Compound 68a** (0.065 g, 54%). Electrospray MS $[\text{M}+1]^+$ 378.2.

Step B:

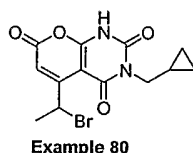


10

1M BBr_3 solution in CH_2Cl_2 (0.75 mL, 0.75 mmol) was added to a solution of **Compound 68a** (0.056 g, 0.15 mmol) at -78°C . After the reaction mixture was stirred at -78°C for 2 hours, water (5 mL) was added. The organic solution was dried (Na_2SO_4) and concentrated. The crude product was purified using silica gel flash column chromatography eluting with 10% NH_4OH in $\text{MeOH}/\text{CH}_2\text{Cl}_2$ (v/v = 3:97) to give **Example 68** (0.01 g, 20%). Electrospray MS $[\text{M}+1]^+$ 334.2.

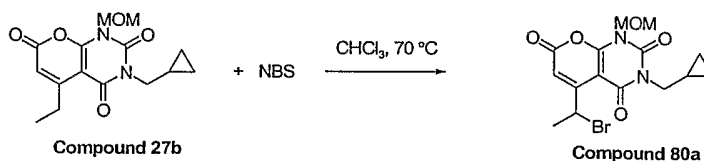
15

PREPARATIVE EXAMPLE 80



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Step A:



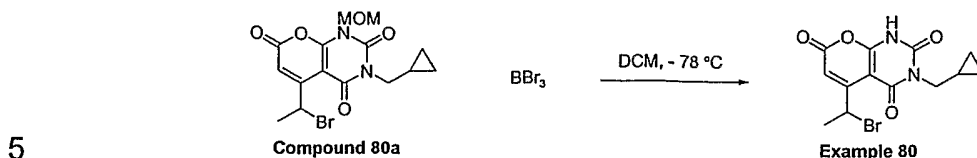
Compound 27a (0.1 g, 0.33 mmol) was taken up in CH_2Cl_2 at room temperature. NBS was then added and the reaction was stirred for 4 hours. After no progress in the reaction was observed, a mixture of NBS (0.061 g, 0.34 mmol) in chloroform (4 mL) was added. The reaction mixture was heated for 12 hrs at 70°C . Both the TLC (30/70 EtOAc/ Hexane) and mass spectrogram indicated that the reaction was complete. The reaction mixture was cooled to room temperature and diluted with CH_2Cl_2 and washed with H_2O . The organic phase was dried with Na_2SO_4 and solvent was removed to

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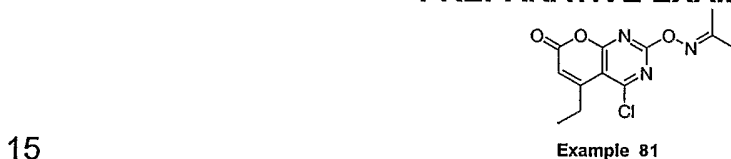
give the crude product. Preparative silica gel chromatography purification in EtOAc/Hexane (v/v = 30/70) yielded **Compound 80a** (0.075 g, 60 %).

Step B:

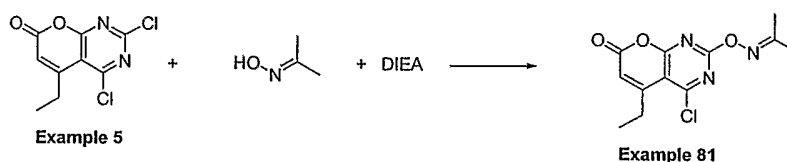


Compound 80a (0.070g, 0.18 mmol) was taken up in CH_2Cl_2 and the mixture was cooled to -78°C . 1M BBr_3 (0.909 mL, 0.9 mmol) was added. The reaction mixture was stirred for 4 hours. Upon completion of the reaction, the mixture was diluted with CH_2Cl_2 , washed with H_2O , dried with Na_2SO_4 , and then solvent was removed to give crude product. The crude product was purified by preparative silica gel chromatography using 30/70 EtOAc/ Hexane, to give **Example 80**. Electrospray MS $[\text{M}+1]^+$ 341.2.

PREPARATIVE EXAMPLE 81



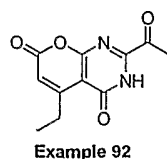
Step A:



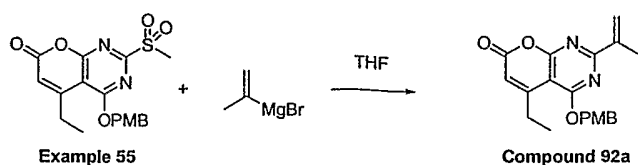
To a mixture of **Example 5** (84 mg, 0.34 mmol) and acetone oxime (27.5 mg, 0.37 mmol) was added DIEA (0.09 ml, 0.52 mmol) and the mixture was stirred for 3 days. The mixture was concentrated and was subjected to silica gel column chromatography to give **Example 81** (30 mg, 31%). LCMS: $\text{M}+1$: 282.1

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PREPARATIVE EXAMPLE 92

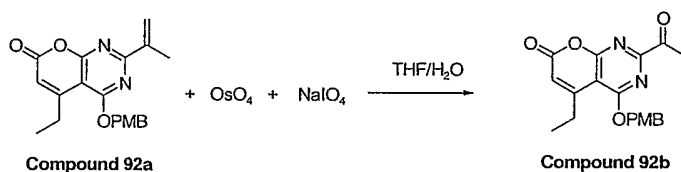


Step A:



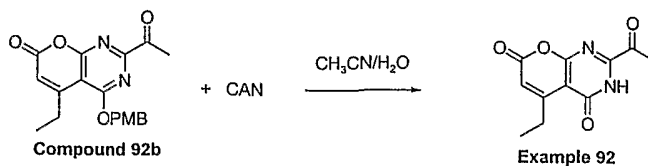
Isopropenyl magnesium bromide (0.95 mL, 0.475 mmol, 0.5 M in THF) was added dropwise to a solution of **Example 55** (0.133 g, 0.341 mmol) in THF (4.0 mL) at 0°C. The mixture was stirred at 0°C for 2 hours before it was quenched with HCl (0.2 M). The mixture was taken up in EtOAc and washed with water and brine. The organic phase was dried over MgSO_4 . Solvent was removed under reduced pressure and the crude product was purified with silica gel flash column chromatography eluting with hexane/ CH_2Cl_2 /EtOAc (v/v/v = 4/1/1) to give **Compound 92a** (59 mg, 49%).

Step B:



NaIO_4 (70.1 mg, 0.328 mmol) was added to a solution of **Compound 92a** (46.2 mg, 0.131 mmol) and OsO_4 (22.2 μL , 4 wt% in water) in THF (5.0 mL) and water (5.0 mL) at room temperature. The reaction mixture was stirred overnight before it was quenched by the addition of Me_2S (20 μL , 0.328 mmol). The mixture was diluted with EtOAc and washed with HCl (0.5 M), water and brine. The organic phase was dried over MgSO_4 . Solvent was removed under reduced pressure and the crude product was purified by silica gel flash column chromatography eluting with hexane/ CH_2Cl_2 /EtOAc (v/v/v = 2/1/1) to give **Compound 92b** (39 mg, 84%).

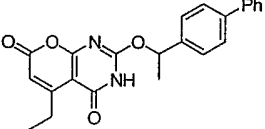
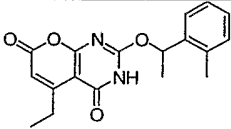
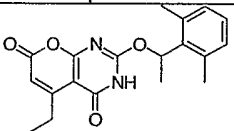
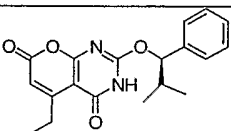
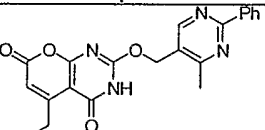
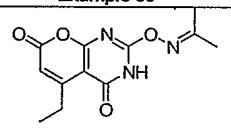
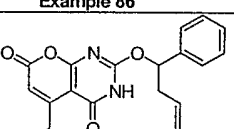
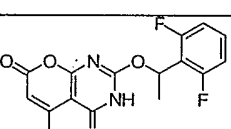
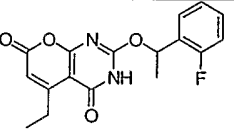
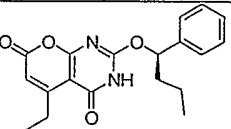
Step C:



Ceric ammonium nitrate (70.9 mg, 0.129 mmol) was added to a solution of **Compound 92b** (20.8 mg, 0.059 mmol) in MeCN (3.0 mL) and water (0.3 mL) at room temperature. The reaction mixture was stirred for 2 hours before it was diluted with EtOAc. The organic phase was washed with

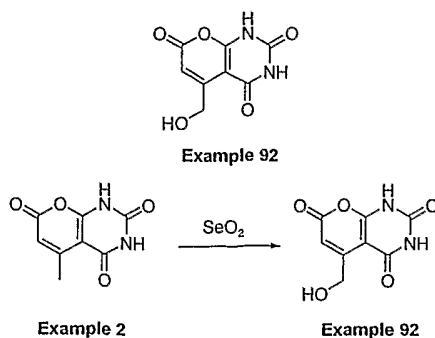
HCl (0.5 M), water, brine and dried over MgSO_4 . Solvent was removed under reduced pressure and crude product was purified using preparative TLC with hexane/ CH_2Cl_2 /MeOH (v/v/v = 2/8/1) as eluent to give **Example 92** (8 mg, 58%). Electrospray MS $[\text{M}+1]^+$ 235.1.

- 5 **Examples 82-91** were prepared by procedures similar to those used for the preparation of **Example 49**, using **Example 10** and the appropriate corresponding alcohols.

PREPARATIVE EXAMPLE	Electrospray LCMS $[\text{M}+1]^+$	PREPARATIVE EXAMPLE	Electrospray LCMS $[\text{M}+1]^+$
 Example 82	389.1	 Example 83	327.1
 Example 84	341.1	 Example 85	341.1
 Example 86	391.1	 Example 87	264.1
 Example 88	339.1	 Example 89	349.1
 Example 90	331.1	 Example 91	341.1

10

PREPARATIVE EXAMPLE 92

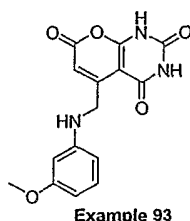


Example 2 (0.71 g, 3.66 mmol, 1 eq) and SeO_2 (0.46 g, 1.1 eq) were mixed together in 1,4-dioxane (10.5 mL) and THF (1.5 mL) and the mixture was heated to 90°C in air for 24 hr. 5% of the resulting crude product was purified by directly loading it onto a reverse-phase HPLC column to afford the
5 desired product **Example 92** (7.4 mg) as a white solid.

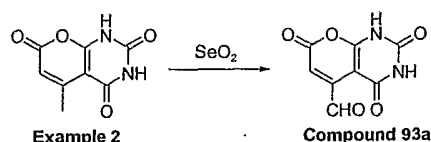
^1H NMR (CD_3OD): δ 4.80 (s, 2 H) 6.20 (s, 1 H)

Mass of $\text{C}_8\text{H}_7\text{N}_2\text{O}_5$ (MH) $^+$: 211. Found: 211.

PREPARATIVE EXAMPLE 93



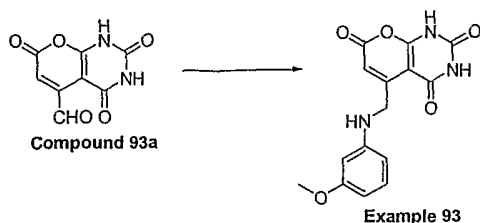
10 Step A:



Compound 93a was prepared by a procedure similar to that used to prepare alcohol **Example 92**, except that the alcohol was allowed to oxidize further to the corresponding aldehyde. After purification several times using
15 reverse-phase HPLC, **Compound 93a** (90 mg) was obtained.

Mass of $\text{C}_8\text{H}_5\text{N}_2\text{O}_5$ (MH) $^+$: 209. Found: 209.

Step B:



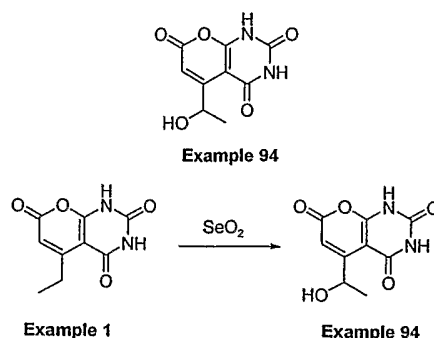
20 **Compound 93b** (90 mg, 0.43 mmol, 1 eq)) was mixed with 3-methoxyaniline (109 mg, 2 equiv.) and sodium triacetoxyborohydride (185 mg, 2 equiv.) in 2 mL of THF. After stirring overnight, the reaction mixture was quenched with methanol. Preparative TLC afforded 15.3 mg of the desired product **Example 93**.

^1H NMR (CD_3OD): δ 3.60 (s, 3 H) 4.60 (s, 2 H) 5.75 (s, 1 H) 6.20 (m, 3 H) 6.95 (m, 1 H)

Mass of $\text{C}_{15}\text{H}_{14}\text{N}_3\text{O}_5$ (MH) $^+$: 316. Found: 316.

PREPARATIVE EXAMPLE 94

5



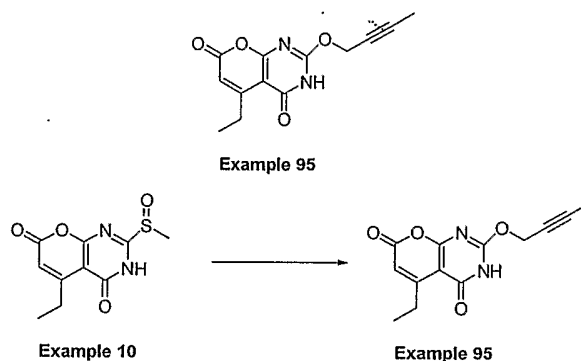
Example 94 was prepared by a procedure similar to that used to prepare **Example 92**, except that **Example 1** was oxidized instead of **Example 2**.

10 ^1H NMR (CD_3OD): δ 1.38 (d, 2 H, $J = 6.8$ Hz) 5.50 (q, 1 H, $J = 6.8$ Hz) 6.20 (s, 1 H)

Mass of $\text{C}_9\text{H}_9\text{N}_2\text{O}_5$ (MH) $^+$: 225. Found: 225.

PREPARATIVE EXAMPLE 95

15



2-butyne-1-ol (140 mg, 2 mmol, 2 equiv.) in 4 mL of THF was treated with 1.6 M $n\text{-BuLi}$ (1.2 mL, 2 equiv.) at 0°C for 5 min to provide an alkoxide solution. **Example 10** (0.25 g, 1 mmol, 1 equiv.) was then added to the alkoxide solution. After stirring 1.5 hr, 0.12 g of acetic acid (2 equiv.) was added to the solution. The solvent was removed and extraction with diethyl ether and water provided a white solid. The solid was washed with cold diethyl ether and dried under vacuum. 80 mg of the desired product **Example 95** was obtained.

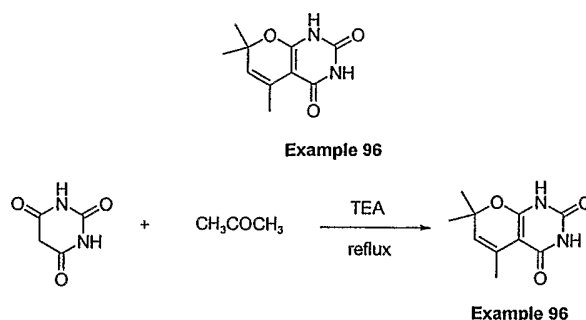
20

^1H NMR (CDCl_3): δ 1.20 (t, 2 H, $J = 6.8$ Hz) 1.83 (s, 3 H) 3.00 (q, 2 H, $J = 6.98$ Hz) 5.00 (s, 2 H) 6.00 (s, 1 H)

Mass of $\text{C}_{13}\text{H}_{13}\text{N}_2\text{O}_4$ (MH) $^+$: 261. Found: 261.

PREPARATIVE EXAMPLE 96

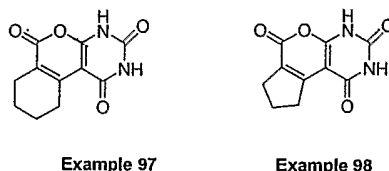
5



Barbituric acid (1.0 g, 7.81 mmol) was taken up in excess acetone. Triethylamine (2 mL) was added, and the reaction mixture was refluxed overnight after which it was cooled and filtered. The crude solid was purified by preparative TLC (8:1:1/EtOAc:DCM:MeOH) to yield the desired product, **Example 96**.

Electrospray MS $[\text{M}+1]^+$ for **Example 96** is 209.0

PREPARATIVE EXAMPLES 97 and 98

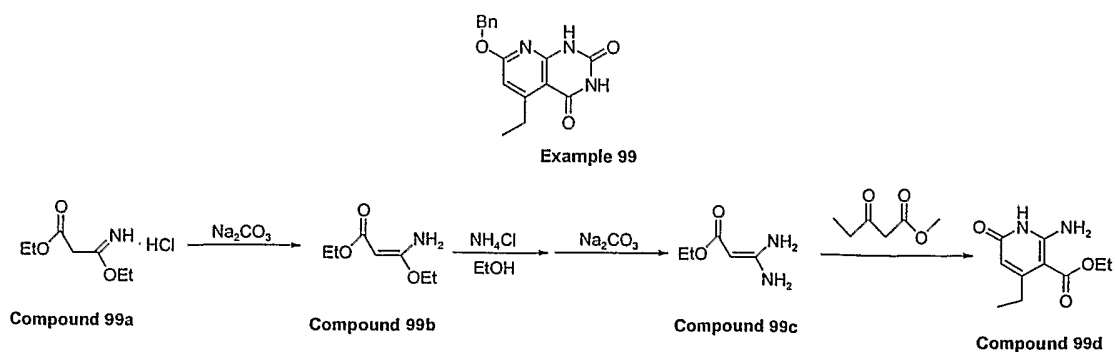


Examples 97 and **98** were prepared by methods analogous to the method used to prepare **Example 1**, except that 2-oxo-cyclohexanecarboxylic acid methyl ester and 2-oxo-cyclopentanecarboxylic acid methyl ester, respectively, were used instead of methylpropionylacetate.

Electrospray MS $[\text{M}+1]^+$ for **96** and **97** are 235.1.

20

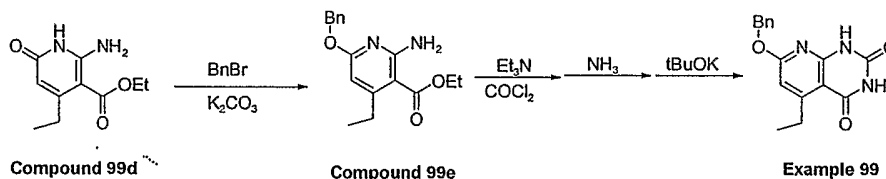
PREPARATIVE EXAMPLE 99



Commercially available (Aldrich) **Compound 99a** (75 g, 383 mmol) was stirred with cold aqueous Na_2CO_3 (15%, 450 mL) for 2 h. Extraction with EtOAc and drying over Na_2CO_3 provided **Compound 99b** as a colorless oil, which was immediately treated with NH_4Cl (19.5 g, 364 mmol) in 200 mL of dry EtOH at 50°C for 60 h. The crude product mixture was cooled and the solvent was removed. The resulting light yellow solid was treated with cold K_2CO_3 (30 %, 300 mL H_2O) for 0.5 h. Extraction with EtOAc gave **Compound 99c** as a light yellow solid (37.92 g). This solid was reacted with methyl propionylacetate (38.0 g, 292 mmol), 2 mL pyridine, in 400 mL of dry EtOH at 100°C for 24 h. After cooling and filtration, the solid was washed with EtOH and 18 g of **Compound 99d** as a white solid was obtained (22% yield from **Compound 99a**).

^1H NMR (CDCl_3): δ 1.20 (t, 3 H, $J = 7.3$ Hz) 1.40 (t, 3 H, $J = 7.1$ Hz) 2.90 (q, 2 H, $J = 7.3$ Hz) 4.30 (q, 2 H, $J = 7.1$ Hz) 5.75 (s, 1 H)

Mass of $\text{C}_{10}\text{H}_{15}\text{N}_2\text{O}_3$ (MH) $^+$: 211. Found: 211.



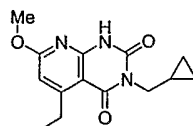
Compound 99d (3.0 g, 14.28 mmol) was treated with BnBr (2.44 g, 1 eq) and K_2CO_3 (3.94 g, 2 eq) in 100 mL acetone at 70°C for 17 h. The solvent was removed and chromatographic purification (5% EtOAc in hexane) provided 2.53 g pure **Compound 99e** in 58% yield.

Compound 99e (0.3 g, 1 mmol) was treated with Et_3N (0.22 g, 2.2 eq), COCl_2 (1.9 M in toluene, 0.53 mL, 1 equiv) in 5 mL DCM at -78°C for 45 min. The reaction mixture was warmed to room temperature in 1 h. NH_3 (0.5 M in 1,4-dioxane, 2 mL, 1 eq) was added and the reaction mixture was stirred overnight. The solvent was then removed, 3 mL anhydrous THF was added along with t-BuOK (1 M in THF, 1 mL, 1 equiv), and the mixture was stirred overnight. The solvent was removed, hexane and a small amount of MeOH were added and the resulting white solid was collected. The solid was further washed with anhydrous diethyl ether to give 3.8 mg of **Example 99** as a white solid.

^1H NMR (CDCl_3): δ 1.20 (t, 3 H, $J = 7.3$ Hz) 3.10 (q, 2 H, $J = 7.3$ Hz) 5.40 (s, 2 H) 6.40 (s, 1 H) 7.20-7.40 (m, 4 H) 8.30 (m, 2 H)

Mass of $\text{C}_{16}\text{H}_{16}\text{N}_3\text{O}_3$ (MH) $^+$: 298. Found: 298.

PREPARATIVE EXAMPLE 100



Example 100

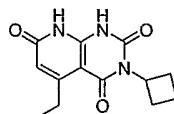
5

Example 100 was prepared following procedures similar to those used to prepare **Example 99**, except that methyl iodide was used instead of BnBr, and cyclopropylmethylamine was used instead of ammonia.

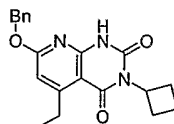
^1H NMR (CDCl_3): δ 0.40 (m, 4 H) 1.18-1.25 (m, 4 H) 3.10 (q, 2 H, $J = 7.2$ Hz) (3.82 (d, 2 H, $J = 7.4$ Hz) 3.90 (s, 3 H) 6.38 (s, 1 H) 8.10 (br s, 1 H)

Mass of $\text{C}_{14}\text{H}_{18}\text{N}_3\text{O}_3$ (MH) $^+$: 276. Found: 276.

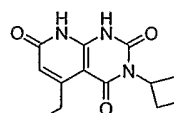
PREPARATIVE EXAMPLE 101



Example 101



Compound 101a



Example 101

15 Intermediate **Compound 101a** was prepared using procedures similar to those used to prepare **Example 99**, except that cyclobutylamine was used instead of ammonia.

^1H NMR (CDCl_3): δ 1.20 (t, 2 H, $J = 7.3$ Hz) 1.60-1.80 (m, 2 H) 2.10 (m, 2 H) 3.00 (m, 2 H) 3.10 (q, 2 H, $J = 7.3$ Hz) 5.30 (m, 1 H) 5.40 (s, 2 H) 6.40 (s, 1 H) 7.20-7.40 (m, 5 H) 8.20 (br s, 1 H)

Mass of $\text{C}_{20}\text{H}_{22}\text{N}_3\text{O}_3$ (MH) $^+$: 352. Found: 352.

Compound 101a (70 mg) was treated with 3% Pd/C (50 mg), 10 mL MeOH under a hydrogen atmosphere (hydrogen balloon) overnight. After filtration, prep HPLC purification provided 1.2 mg of **Example 101**.

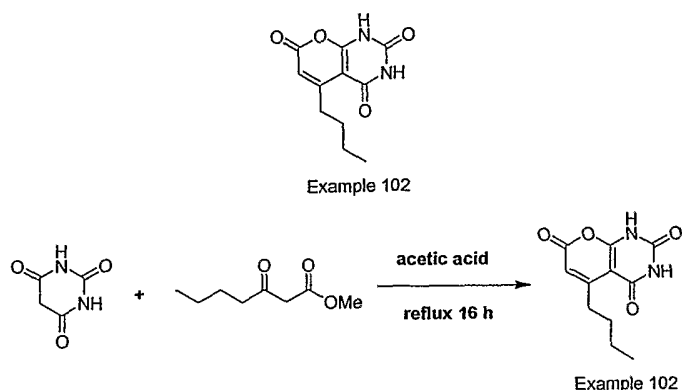
20

^1H NMR (CDCl_3): δ 1.20 (t, 2 H, $J = 7.3$ Hz) 1.60-1.80 (m, 2 H) 2.10 (m, 2 H) 2.95 (m, 2 H) 3.20 (q, 2 H, $J = 7.3$ Hz) 5.30 (m, 1 H) 6.40 (s, 1 H) 8.00 (br s, 1 H).

Mass of $\text{C}_{14}\text{H}_{17}\text{N}_3\text{O}_3$ (MH^+): 276. Found: 276.

5

PREPARATIVE EXAMPLE 102

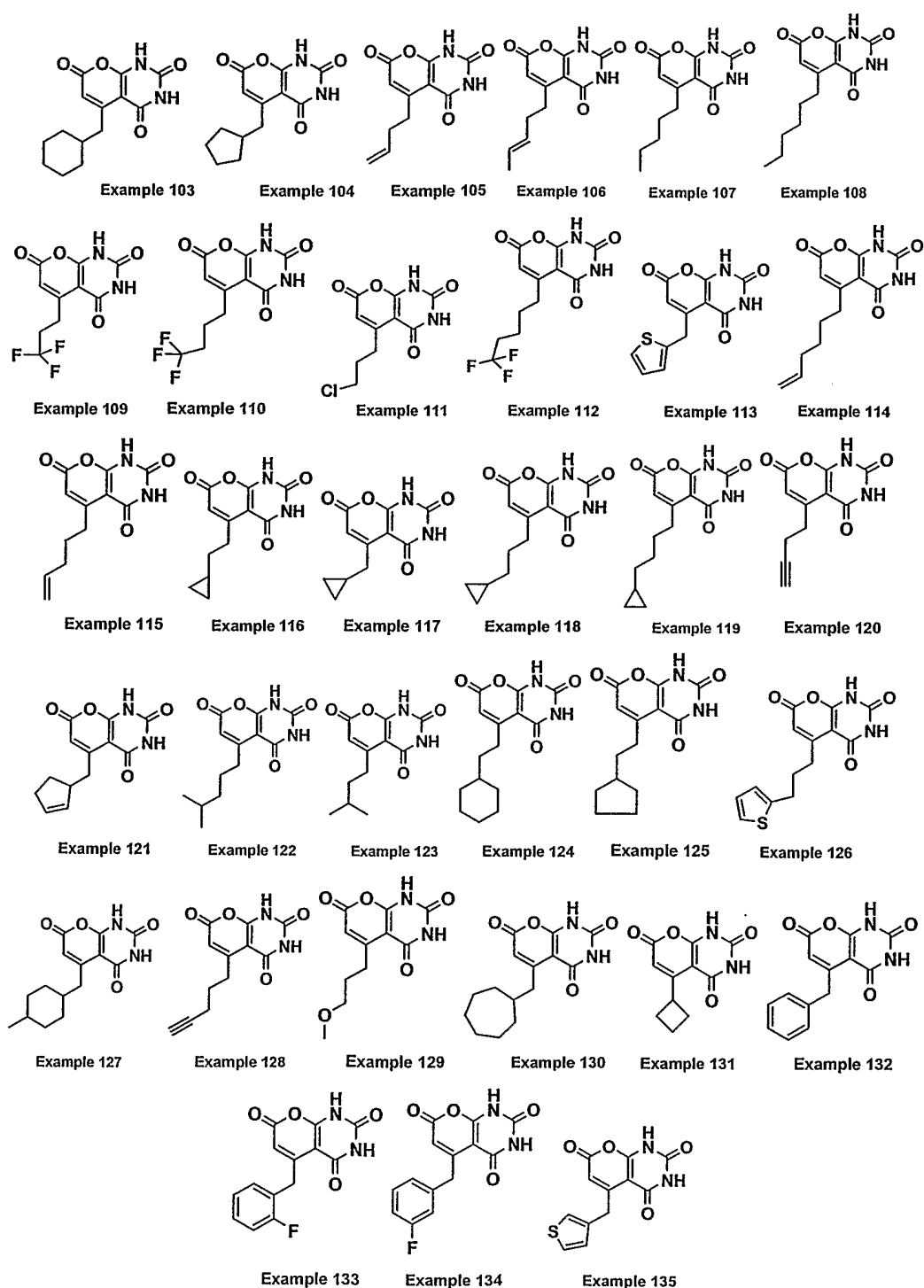


In a 25 mL round bottomed flask equipped with a magnetic stirring bar and a nitrogen balloon was placed 1.0 g of barbituric acid (7.8 mmol) and 1.52 mL of 3-oxoheptanoic acid methyl ester (9.6 mmol, 1.23 equiv.). 8 mL of acetic acid was added to the reaction mixture and was refluxed for 16 h after which the reaction was cooled to room temperature. The excess acetic acid was concentrated and dried in vacuo to give crude product **Example 102** along with unreacted starting materials. The crude product was stirred with 20 mL of boiling water for a few minutes and filtered. The precipitate was washed with boiling water (2 x 10 mL) and dried to yield 0.65 g (35% yield) of **Example 102**.

^1H NMR (DMSO): δ 0.9 (t, 3 H, $J = 7.5$ Hz) 1.32-1.40 (m, 2 H) 1.45-1.51 (m, 2 H) 2.84-2.87 (t, 2 H, $J = 7.5$ Hz) 5.82 (s, 1 H) 11.34 (s, 1 H) 12.72 (br s, 1 H)

Mass of $\text{C}_{11}\text{H}_{12}\text{N}_2\text{O}_4$ (MH^+): 236.22. Found: 237.1.

EXAMPLES 103-135



5

Examples 103-135 were prepared using procedures similar to those used to prepare **Example 102**, except that an appropriately substituted keto-ester was used instead of 3-oxoheptanoic acid methyl ester.

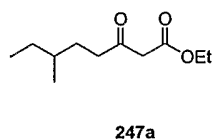
10 The **examples 200, 210, 241, 242, 245, 246, 252-260, 274-278, 280, 281, 282, 284, 285, 291** were prepared by a procedure similar to that used for the preparation of **Example 30 and 31**.

The **examples 201, 202, 204-209, 211-218, 224-240, 243, 244, 247-251, 261-273, 279, 283, 286-290, 293, 294-297** were prepared by a procedure similar to that used for the preparation of **example 102**, using barbituric acid and the corresponding keto ester.

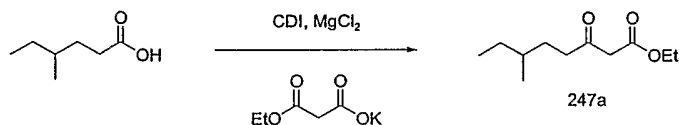
- 5 The preparation of ketoesters starting material where appropriate is shown below.

The preparation of keto ester starting material for examples **247** is as follows

Preparative example 247a



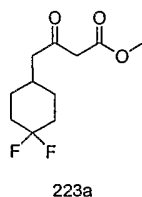
10



15

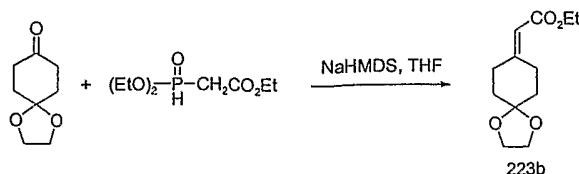
4-Methylhexanoic acid (3.0 g, 23.08 mmol) was taken in 40 mL THF. 1,1'-Carbonyldiimidazole (4.49 g, 27.69 mmol) was added and the reaction was stirred at room temperature for 1 h after which MgCl_2 (2.2 g, 23.08 mmol) and ethyl potassium malonate (5.89 g, 34.62 mmol) was added. The reaction was allowed to run at room temperature overnight. The crude reaction mixture was filtered through a short pad of silica gel and eluted with EtOAc/hexanes (1:3) to yield compound **247a**.

Preparative example 223a



20

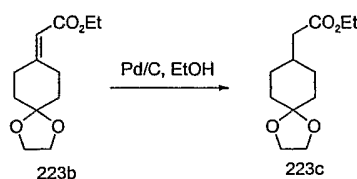
The starting material for the preparation of example **223** is as follows.



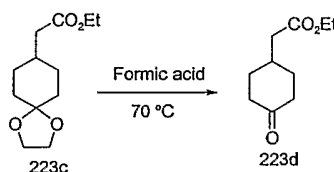
25

Step 1: A solution of triethyl phosphonate (44.8g, 200 mmol) in THF (30 ml) at 0 °C was treated with a 1M solution (200 ml) of sodium bis(trimethylsilylamide) in THF. The resulting mixture was stirred at room temperature for 0.5 hour,

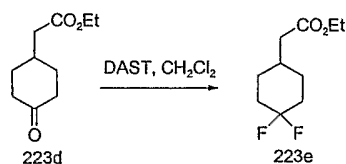
- and then cooled to 0 °C. A solution of 1,4-cyclohexanedione mono ethylene ketal (15.6g, 200 mmol) in THF (50 ml) was added dropwise, and the resulting solution was stirred at room temperature for 18 hours. The reaction mixture was then cooled to 0 °C, treated with cold aqueous citric acid, and the mixture
- 5 was extracted with EtOAc. The extract was washed with satd. aqueous NaHCO₃, brine, dried over Na₂SO₄, filtered, and the filtrate was concentrated. The residue was chromatographed on silica gel, eluting with a gradient of CH₂Cl₂/EtOAc to afford **223b** (21g, 91%).



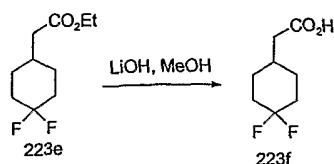
- 10 Step 2: The compound **223b** (20g) was dissolved in EtOH (150 ml) and treated with 10% Pd/C under 1 atm of hydrogen for 3 days. The mixture was filtered and the filtrate was evaporated to **223c** (20.3g, 100%).



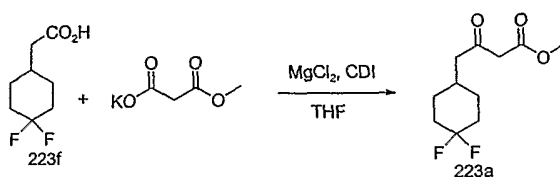
- Step 3: The compound **223c** (7g) was dissolved in formic acid (50 ml) and
- 15 heated at 70 °C for 1 h. The solution was concentrated and the residue was taken up in EtOAc and washed with satd. aqueous NaHCO₃, brine, dried over Na₂SO₄ and concentrated. The residue was chromatographed on silica gel to afford **223d** (5g).



- 20 Step 4: The compound **223d** (4.6 g) was dissolved in CH₂Cl₂ (10 ml) and treated with diethylaminosulfur trifluoride (DAST, 5 ml) at room temperature for 3 hours. The reaction mixture was poured into ice/water (30 ml) and extracted with CH₂Cl₂. The extract was washed with satd. aqueous NaHCO₃, brine, dried over Na₂SO₄ and concentrated to afford **223e** as brown oil (3.2 g,
- 25 62%).



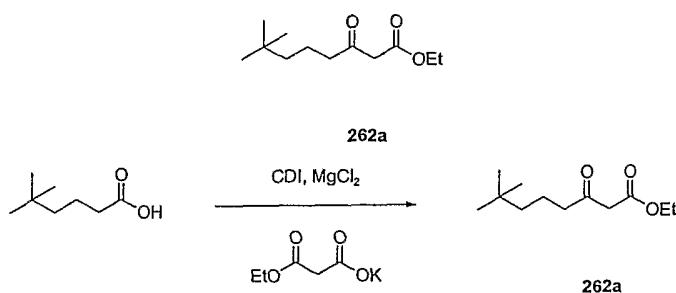
Step 5: The compound **223e** (3.2 g, 15.5 mmol) was dissolved in MeOH (5 ml) and treated with LiOH (559 mg, 23.3 mmol) overnight. The reaction mixture was acidified by 3 N HCl to pH 4 and extracted with CH₂Cl₂. The extract was
5 dried over Na₂SO₄ and concentrated to afford **223f** as brown oil (3 g, 100%).



Step 6: The compound **223f** (900 mg, 5.0 mmol) was dissolved in THF (15 ml), added with CDI (972 mg, 6.0 mmol) and stirred for 45 min. Then methyl malonate potassium salt (1.02 g, 6.0 mmol) and MgCl₂ (570 mg, 6.0 mmol) were added into the above solution. The resulting mixture was stirred overnight and filtered through a short pad of silica gel and washed with EtOAc. The filtrate was concentrated and chromatographed on silica gel to afford **223a** as colorless oil (400 mg, 34%).

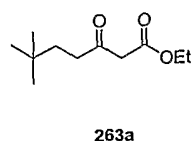
15 The starting materials for structures **262**, **263** were prepared in a manner similar to **218a**.

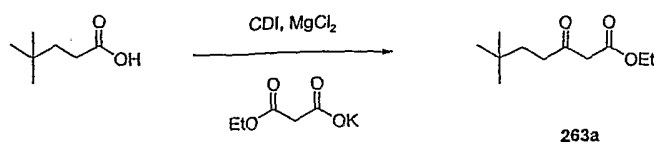
Preparative example 262a



20 Prepared in the same manner as in example 218a.

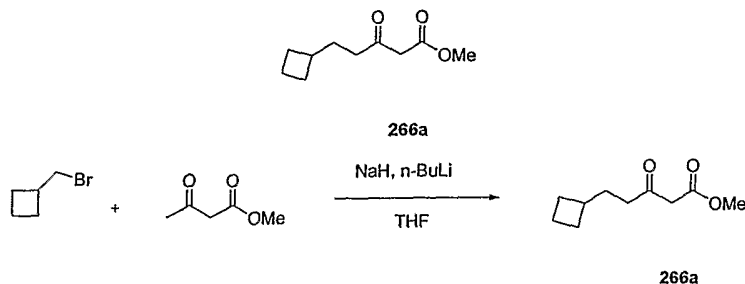
Preparative example 263a





Prepared in the same manner as in example 218a.

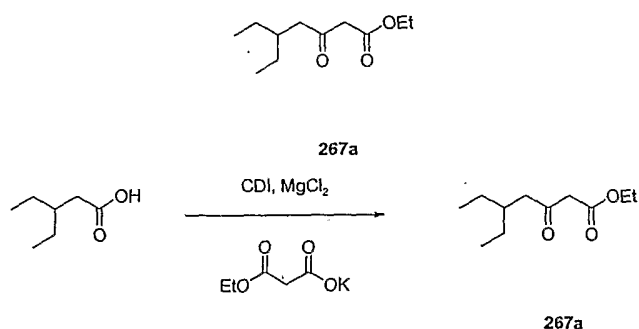
Preparative example 266a



5

Sodium hydride (1.42 g, 35.56 mmol) was taken in THF (20 mL) in a round bottomed flask equipped with a stirring bar and nitrogen balloon. It was cooled to 0 °C and methyl acetoacetate (3.84 mL, 35.56 mmol) dissolved in 10 mL THF was added dropwise. The reaction mixture was stirred at 0 °C for 10 30 min after which *n*-BuLi (2.5 M solution in hexanes, 14.2 mL, 35.56 mmol) was added dropwise. The reaction was allowed to run for 30 min at 0 °C and then cooled to – 25 °C. Bromomethylcyclobutane (4.82 g, 32.32 mmol) dissolved in 20 mL THF was added dropwise and the reaction was stirred at – 25 °C for 4 h followed by room temperature overnight. It was quenched with 15 the addition of sat. NH₄Cl, extracted with EtOAc (2 x 30 mL), dried over MgSO₄, concentrated in vacuo. The crude product was purified by biotage (5% EtOAc/hexanes) to yield compound 266a.

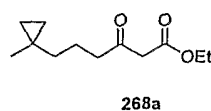
Preparative example 267a

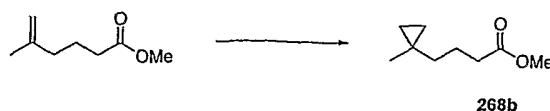


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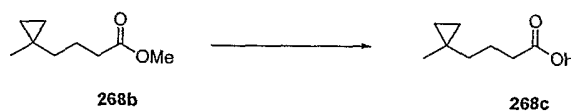
Prepared in the same manner as in example 218a.

Preparative example 268a





- Trifluoroacetic acid (7.84 mL, 105.48 mmol) and diiodomethane (8.5 mL, 105.48 mmol) in 50 mL DCM was cooled to 0 °C. Diethylzinc (1.0 M solution in hexanes, 105.5 mL, 105.48 mmol) was added dropwise. The reaction was allowed to stir at 0 °C for 20 min after which 5-Methyl-5-hexenoic acid methyl ester (5.0 g, 35.16 mmol) in 20 mL DCM was added dropwise. The reaction was allowed to stir at room temperature overnight. The reaction was quenched by the addition of sat. NH₄Cl, extracted with DCM (2 x 30 mL), dried over MgSO₄, concentrated in vacuo to yield compound **268b** which was carried over to the next step without further purification.



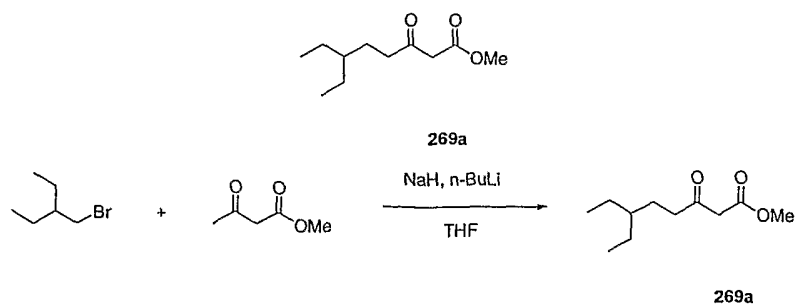
- Ester **268b** (5.0 g, 32 mmol) was taken in MeOH (50 mL) and NaOH (3.2 g, 80 mmol) was added to it. The reaction was allowed to stir at room temperature overnight. The reaction was diluted with water (50 mL) and acidified with conc HCl. It was extracted with Et₂O (2 x 30 mL), washed with brine, dried over MgSO₄, and concentrated in vacuo. The crude product **268c** was used as such without any further purification.



Prepared in the same manner as in example **262a**.

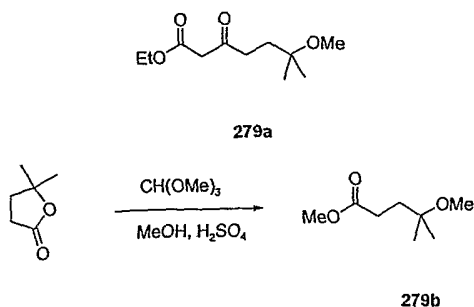
20

Preparative example 269a

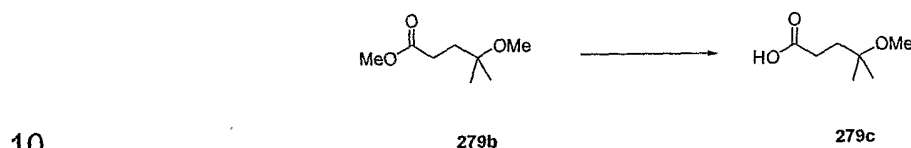


Prepared in the same manner as in example **266a**.

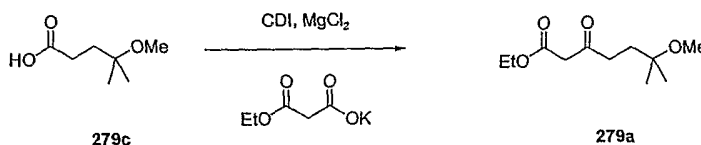
Preparative example 279a



5,5-Dimethyl-dihydro-furan-2-one (5.0 g, 43.8 mmol), trimethyl orthoformate (11.5 mL, 105.12 mmol), and sulfuric acid (0.43 g, 4.38 mmol) were taken in MeOH (50 mL). The reaction mixture was heated to 50 °C overnight. After cooling, the solvent was removed in *vacuo*, quenched with sat. NaHCO₃ and extracted with EtOAc (2 x 30 mL). The organic layer was washed with brine, dried over MgSO₄ and concentrated in *vacuo* to yield compound **279b** which was used without any further purification.

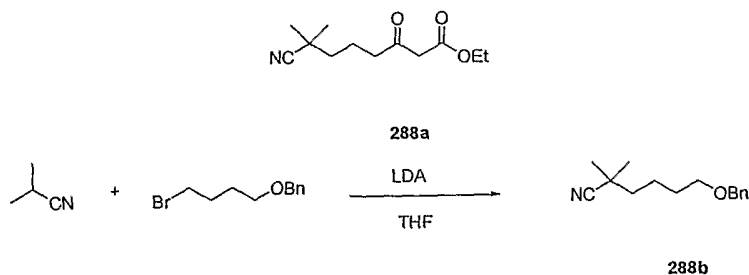


Prepared in the same manner as in example **268c**.



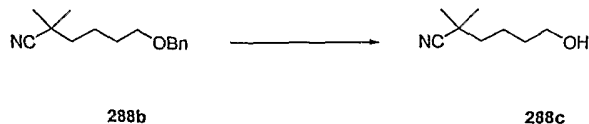
Prepared in the same manner as in example **262a**.

Preparative example 288a



Lithium diisopropylamide (2.0 M solution in THF/heptane/ethyl benzene, 43.4 mL, 86.82 mmol) was taken in THF (30 mL) and cooled to -78 °C. Isobutyronitrile (6 g, 86.82 mmol) in THF (10 mL) was added dropwise and the reaction was stirred at -78 °C for 1 h and 0 °C for 2 h. Benzyl 4-bromobutyl ether (21.1 g, 86.82 mmol) in THF (10 mL) was added dropwise and the reaction mixture was allowed to warm to room temperature overnight. The reaction was quenched by the addition of saturated NH₄Cl and extracted

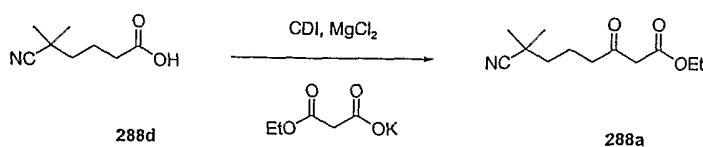
with Et₂O. The organic layer was washed with brine, dried over MgSO₄ and concentrated in *vacuo*. The crude compound obtained was purified by biotage (5% EtOAc/hexanes) to yield compound **288b**.



- 5 Compound **288b** was taken up in CH₂Cl₂ (25 mL) in a 100 mL round bottomed flask equipped with a stirring bar and nitrogen balloon and cooled to – 78 °C. Boron trichloride (1.0 M solution in hexanes, 43.2 mL, 43.2 mmol) was added dropwise and the reaction was allowed to gradually warm to 0 °C. After 1 h the reaction was quenched by the addition of sat. NaHCO₃, extracted with CH₂Cl₂. The organic layer was washed with brine, dried over MgSO₄, and concentrated in *vacuo* to yield the crude compound which was purified by filtering through a short pad of silica gel eluting with 50% EtOAc/hexanes to yield compound **288c**.

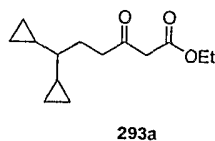


- 15 Compound **288c** (3.0 g, 21.2 mmol) was taken in acetone (20 mL) and cooled to 0 °C. Jones reagent was added dropwise until there was no change in color to green upon addition of the reagent. The excess reagent was quenched by the addition of *i*-PrOH, and water (20 mL) extracted with Et₂O. The organic layer was washed with brine, dried over MgSO₄, and concentrated in *vacuo* to yield compound **288d** which was used without further purification.



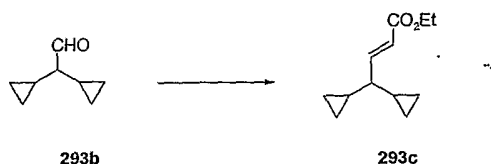
Prepared in the same manner as in example **262a**.

Preparative example 293a

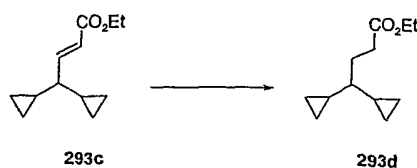




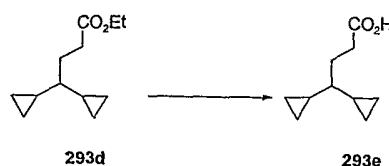
Lithium bis(trimethylsilyl)amide (1.0 M solution in THF, 108.9 mL, 108.9 mmol) was taken up in 100 mL THF in a 500 mL round bottomed flask equipped with a stirring bar and nitrogen balloon. The solution was cooled to 0 °C and (methoxymethyl)triphenylphosphonium chloride (37.3 g, 108.9 mmol) was added portionwise and the dark red solution was stirred at 0 °C for 45 min. Dicyclopentyl ketone (10 g, 90.78 mmol) in THF (10 mL) was added dropwise and the reaction was stirred at 0 °C for 3 h after which the reaction mixture was poured into hexane. The mixture was filtered through silica gel eluting with hexane. Solvent removal gave the crude enol ether. The crude enol ether was taken up in THF (100 mL) and 10 % HCl (100 mL) was added. The reaction was refluxed overnight. Upon cooling, diluted with water and extracted with Et₂O (2 x 50 mL), washed with brine, dried over MgSO₄, concentrated in *vacuo*. The crude mixture **293b** was used as such without further purification.



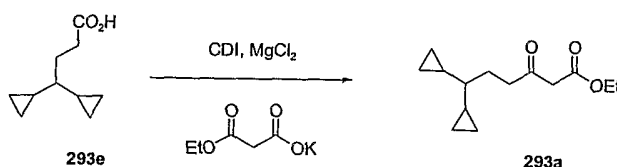
Sodium hydride (6.44 g, 161 mmol) was taken in THF (30 mL) in a 250 mL round bottomed flask equipped with a magnetic stirring bar and nitrogen balloon. The mixture was cooled to 0 °C. Triethylphosphonoacetate (36.1 g, 161 mmol) in 20 mL THF was added dropwise and the mixture was stirred at room temperature for 1 h after which it was cooled back to 0 °C and compound **293b** (10 g, 80.5 mmol) in 20 mL THF was added dropwise and the reaction was allowed to stir at room temperature for 2 h. The reaction was quenched by the addition of water and was extracted with Et₂O. The organic layer was washed with brine, dried over MgSO₄, and concentrated in *vacuo*. The crude was purified by biotage (2% EtOAc/haxanes) to yield compound **293c**.



Compound **293c** was taken up in 100 mL EtOH in a 200 mL round bottomed flask. To the solution was added Pd/C (10 wt%, 7.0 g, 5.7 mmol) and the mixture was hydrogenated using a hydrogen balloon under ambient temperature for 12 h. The mixture was filtered through celite and eluted with EtOH which upon solvent removal gave crude compound **293d**.

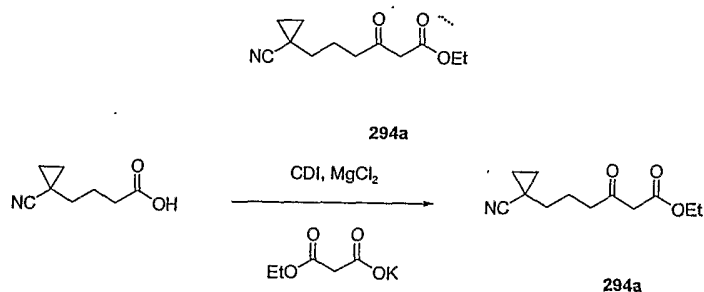


Prepared in the same manner as in example **268c**.



10 Prepared in the same manner as in example **262a**.

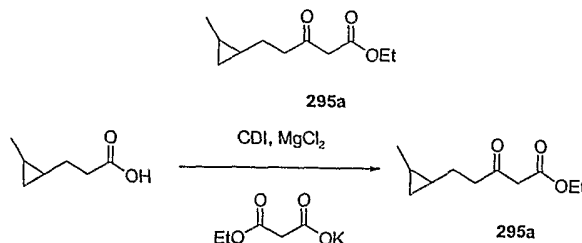
Preparative example 294a



Prepared in the same manner as in example **288a**.

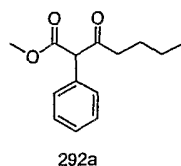
15

Preparative example 295a

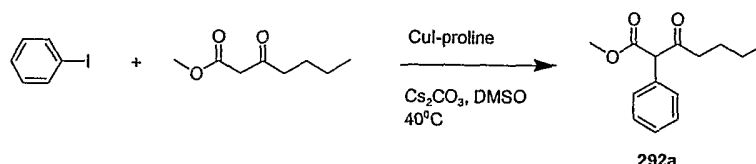


Prepared in the same manner as in example **262a**.

Preparative example 292a

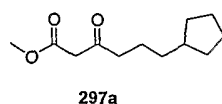


The starting material for the preparation of example **292** is as follows.



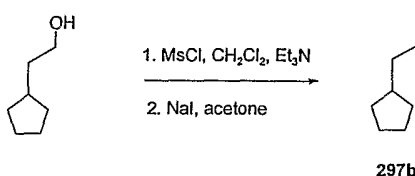
- 5 Into the solution of iodobenzene (10.2 g, 50 mmol) in anhydrous DMSO (150 mL) and 3-oxopentanoic acid methyl ester (15.8 g, 100 mmol) was added copper(I) iodide (1.9 g, 10 mmol), L-proline (2.3g, 20 mmol), and cesium carbonate (65.2g, 200 mmol). After stirred under N₂ at 40 °C for 18 hours, the reaction mixture was dissolved into ethyl acetate (250 mL), washed with
- 10 water (4 x 150 ml). The organic solution was dried with sodium sulfate, and concentrated under reduced pressure. The resulting crude product was purified using silica gel flash column chromatography eluting with ethyl acetate/hexanes (v/v = 5/95) to give compound **292a** (4.5 g, 38%).

Preparative example 297a



15

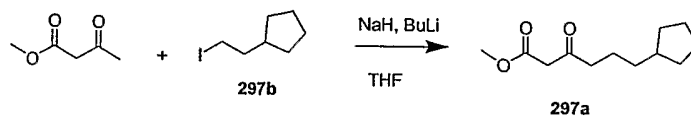
The starting material for the preparation of example **297** is as follows.



- To a solution of 2-cyclopentyl ethanol (11.4 g, 100 mmol), anhydrous CH₂Cl₂ (80 mL), and triethyl amine (12 g, 120 mmol), which cooled to 0 °C,
- 20 was added via syringe MsCl (13.7 g, 120 mmol). After stirring under N₂ at 0 °C for 1 hour then at room temperature for 18 hours, the reaction mixture was washed with water (2 x 100 mL), dried with sodium sulfate, and concentrated under reduced pressure to give a clear oil (19g, 100%). The oil was dissolved into anhydrous CH₂Cl₂ (250 mL) and mixed with NaI (20g, 200 mmol). After
- 25 stirring at room temperature for 18 hours, the reaction mixture was filtered

from solid. The resulting filtrate was concentrated under reduced pressure to give a brown paste. The paste was dissolved into diethyl ether (300 mL), washed with water (2 x 150 mL), dried with sodium sulfate, concentrated under reduced pressure to give compound **297b** (20g, 89%).

5

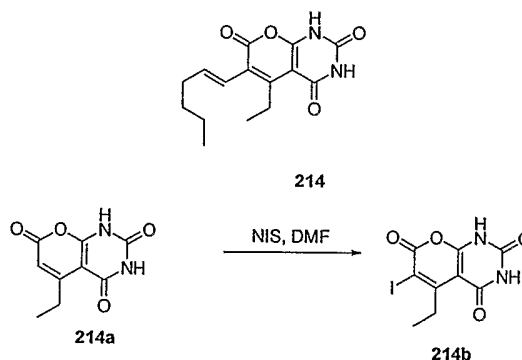


10

To a solution of methyl acetoacetate (5.8 g, 50 mmol) and anhydrous THF (100 mL), which cooled to 0 °C, was added NaH (60%, 2.4g, 60 mmol). After stirring under N₂ at 0 °C for 0.5 hour, n-BuLi (2.5 M in hexanes, 20 mL) was added *via* syringe. After stirring at 0 °C for 0.5 hour, the reaction mixtures was cooled to -25 °C, the compound **297b** was added *via* syringe. The reaction mixture was stirred at 0 °C for 0.5 hour, then room temperature for 18 hours. The reaction mixture was quenched with saturated ammonium chloride (200 mL) and extracted with ethyl acetate (2 x 200 mL) washed with water (2 x 100 mL). The organic solution was dried with sodium sulfate, and concentrated under reduced pressure to give a brown oil, which purified using silica gel flash column chromatography eluting with ethyl acetate/hexanes (v/v = 7/93) to give compound **297a** (3.2g, 32%).

15

Preparative example 214



20

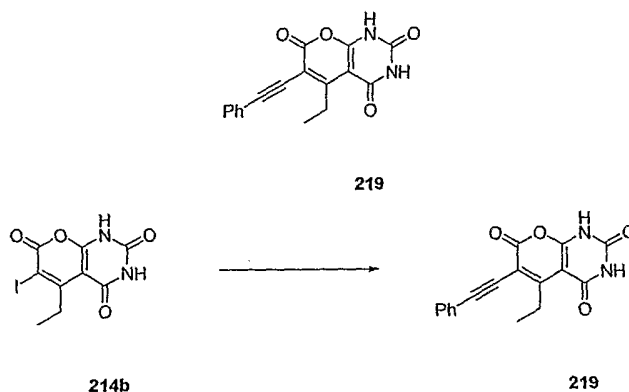
Compound **214a** (10 g, 48.04 mmol) was taken in DMF (50 mL) in a round bottomed flask equipped with a magnetic stirring bar. *N*-Iodosuccinimide (22 g, 97.79 mmol) was added portionwise and the reaction mixture was heated to 50°C overnight. After cooling to ambient temperature, H₂O (100 mL) was added. The product was filtered, washed with water followed by ether to give a white powdery mixture (> 95% yield). The product **214b** was used as such for the next step without any further purification.

25



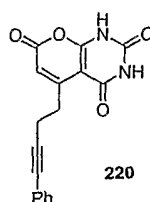
- Compound **214b** (0.1 g, 0.3 mmol) was taken in C_6H_6 (1 mL) in a 10 mL round bottomed flask. $Pd(OAc)_2$ (0.004 g, 0.018 mmol), PPh_3 (0.014 g, 0.054 mmol), and Na_2CO_3 (0.5 mL, 2M solution) was added and the reaction mixture was allowed to stir at room temperature for 30 min. *trans*-1-Hexen-1-ylboronic acid (0.042 g, 0.33 mmol) in EtOH (0.5 mL) was added and the reaction mixture was allowed to reflux (80 °C) overnight. After cooling, the mixture was diluted with H_2O (2 mL), extracted with EtOAc (2 x 10 mL), dried over $MgSO_4$, concentrated and dried to yield the crude compound **214**.
- Purification by preparative TLC (10% MeOH/DCM) to yield compound **214**.

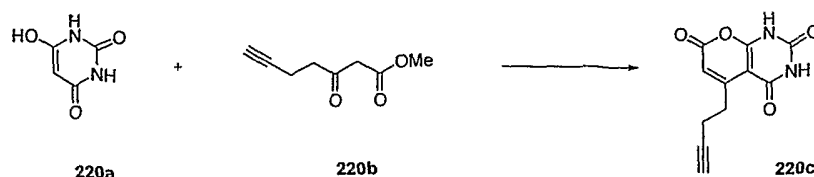
Preparative example 219



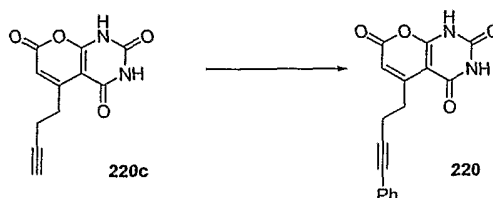
- Compound **214b** (0.1 g, 0.3 mmol) was taken in DMF (3.0 mL) in a 10 mL round bottomed flask. $PdCl_2(PPh_3)_2$ (0.011 g, 0.015 mmol), phenylacetylene (0.061 g, 0.6 mmol), CuI (0.006 g, 0.03 mmol), and triethylamine (0.091 g, 0.9 mmol) was added and the reaction mixture was stirred at room temperature overnight. The reaction mixture was diluted with EtOAc (5 mL), neutralized with 1N HCl, and extracted with EtOAc (2 x 10 mL), dried over $MgSO_4$, concentrated and dried to yield crude **219**. The crude product was taken in ether and filtered to yield pure compound **219**.

Preparative example 220



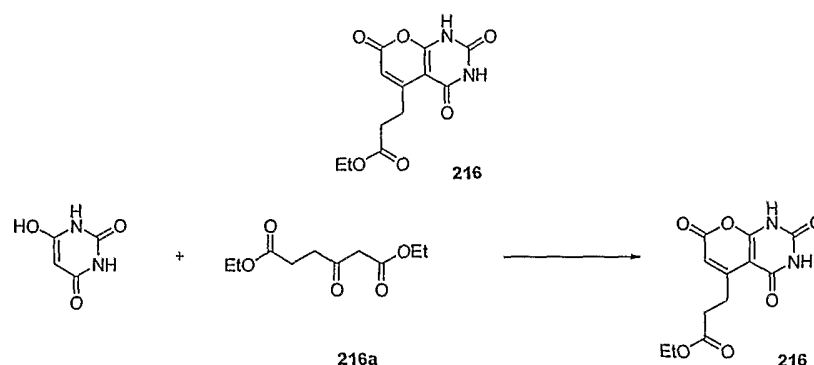


Barbituric acid **220a** (1.0 g, 7.81 mmol) and keto ester **220b** (1.45 g, 9.4 mmol) was taken in glacial acetic acid (8 mL) and the reaction mixture was heated to reflux overnight. After cooling to room temperature, the acetic acid was removed in *vacuo* and hot water was added to remove excess barbituric acid. The procedure was repeated a few times until no starting material was left. It was followed by washing with ether. The product **220c** was dried and needed no further purification.



Compound **220c** (0.1 g, 0.431 mmol) was taken in DMF (1 mL) in a 10 mL round bottomed flask. Iodobenzene (0.053 g, 0.258 mmol), $\text{PdCl}_2(\text{PPh}_3)_2$ (0.003 g, 0.0043 mmol), CuI (0.002 g, 0.0086 mmol), and Et_2NH (0.157 g, 2.15 mmol) was added and the reaction mixture was stirred at room temperature overnight. The reaction was diluted with EtOAc (2 mL), neutralized with 1N HCl and extracted with EtOAc (2 x 10 mL). It was dried over MgSO_4 , concentrated in *vacuo*. The crude product was purified by preparative TLC (20 % MeOH/DCM) to yield compound **220**.

Preparative example 216

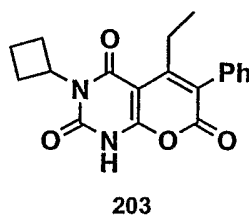


Barbituric acid (1.0 g, 7.81 mmol) and Diethyl β -ketoadipate **216a** (2.03 g, 9.4 mmol) was taken in glacial acetic acid (8 mL) and the reaction mixture was heated to reflux overnight. After cooling to room temperature, the

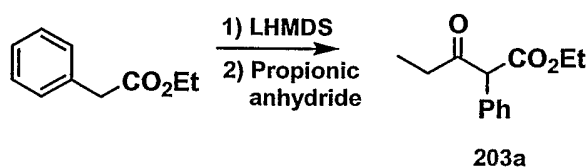
acetic acid was removed in *vacuo* and hot water was added to remove excess barbituric acid. The procedure was repeated a few times until no starting material was left. It was followed by washing with ether. The product **216** was dried and needed no further purification.

- 5 The starting material for the preparation of example **203** is as follows.

Preparative example 203

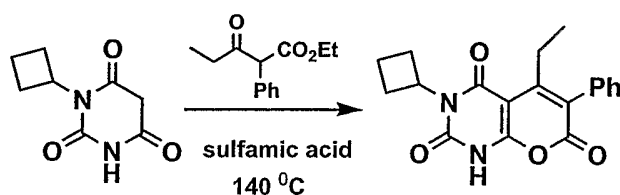


Step 1:



- 10 To a solution of ethylphenylacetate (8.2g, 0.05 mol) in THF at -78 °C was added LHMDS (1M in THF, 100 ml, 0.10 mol) and stirred for 20 min. Propionic anhydride (6.5 ml, 0.05 mol) was added rapidly. The mixture was allowed to warm up to 0 °C and stirred for 30 min. It was quenched with NH₄Cl (aq.) and extracted with EtOAc. Usual work up afforded the crude material
- 15 which was chromatographed on silica gel to obtain product.

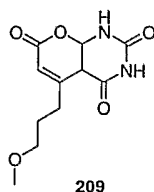
Step 2:

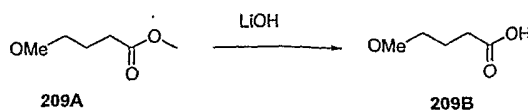


Compound **203** was obtained by normal condensation procedure with cyclobutylbarbituric acid.

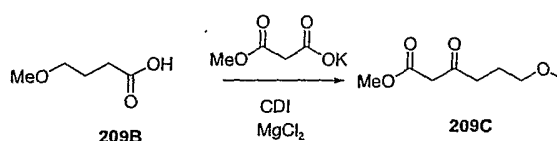
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Preparative example 209

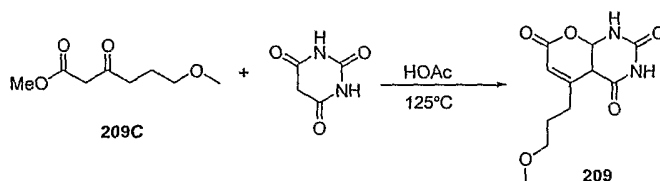


Step A:

Starting material **209a** (9.9 g, 75 mmol) was dissolved in THF (100 mL) and water (25 mL). LiOH (3.4 g, 80.9 mmol), the resulting mixture was stirred at room temperature overnight. 1 N HCl (100 mL) was added and extracted with EtOAc. The organic extracts were combined, washed with brine, dried (MgSO₄) to give compound **209b** (8.8 g, 93%).

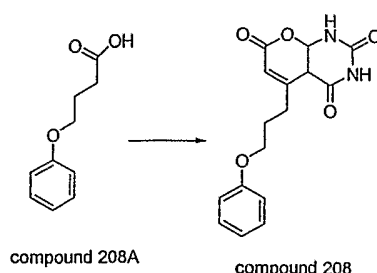
Step B:

Compound 209c (1.9 g, 16.1 mmol) was dissolved in THF (50 mL), CDI (12.3 mmol) was added. The resulting mixture was stirred at room temperature for 1 h. MgCl₂ (1.5 g, 16.1 mmol) and KOCOCH₂CO₂Me (3.8 g, 24.2 mmol) were added, the resulting mixture was stirred at room temperature overnight. EtOAc (100 mL), water (50 mL) were added. The aqueous layer was separated and extracted with EtOAc. The aqueous layer was extracted with EtOAc. The organic extracts were combined, washed with brine, dried (MgSO₄), filtered and concentrated. The residue was separated by silica gel chromatography, with Biotage 40S+ column, eluted with EtOAc: hexanes, 1:10, to give 2.1 g (74%) yellow liquid as **Compound 209d**.

20 Step B:

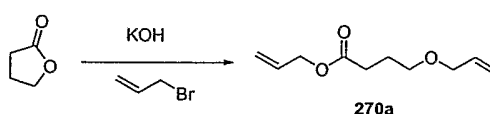
Compound 209c (1.13 g, 6.49 mmol) and barbituric acid (0.5 g, 3.90 mmol) was mixed with HOAc (2 mL) in a sealed tube, and heated in an oil bath at 125°C overnight. The mixture was cooled to room temperature, HOAc was removed and the residue was taken up in MeOH, and filtered. The volume of the mother liquid was reduced until solid started to come out, the beige solid was collected to give **Compound 209** (153 mg, 10%). Electrospray MS [M+1]: 253.1.

Compound 208 was prepared in a similar fashion as in **Compound 209**, from the commercially available **Compound 208a**.



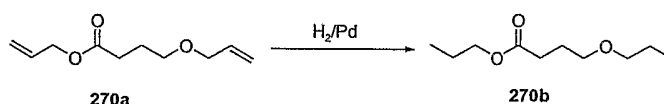
Preparative example 270

5 Step A:



Starting lactone (10 g, 116 mmol) was mixed with allylbromide (30 mL, 346 mmol), toluene (75 mL), and KOH (19.5 g, 348 mmol). The mixture was heated 110°C overnight. The mixture was cooled to room temperature; water (100 mL) was added. The aqueous layer was extracted with EtOAc. The organic extracts were combined, washed with brine, dried (MgSO₄), filtered and concentrated to give a yellow liquid as the desired **Compound 270a** (11.8 g, 55.2%).

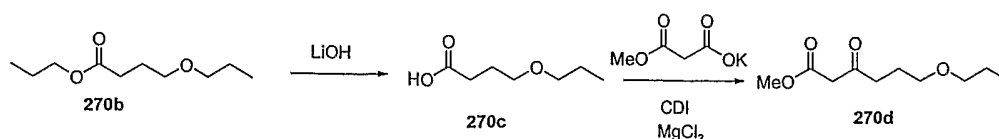
Step B:



15 **270a** **270b**

Compound 270a (3.0 g, 16.3 mmol) was dissolved in EtOH (20 mL), 10 % Pd/C (300 mg) was added. The slurry was stirred under H₂ overnight. The mixture was filtered through Celite, and the filtrate was concentrated to give a yellow liquid as the desired **Compound 270b** (2.5 g, 81%).

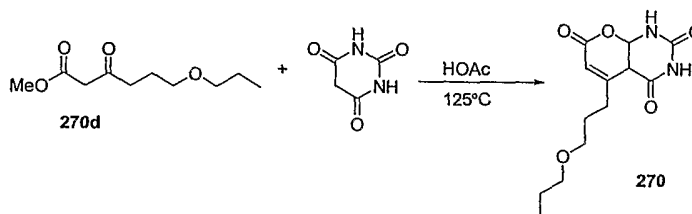
20 Step C:



Compound 270b (3.0 g, 16.3 mmol) was dissolved in THF (20 mL)-H₂O (7 mL), LiOH (1.66 g, 39.5 mmol) was added. The resulting mixture was stirred at room temperature overnight. 1 N HCl (75 mL) was added, and
25 extracted with Et₂O. The organic extracts were combined, dried (MgSO₄)

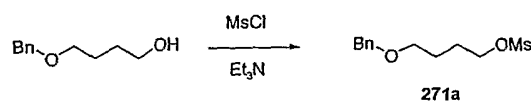
filtered and concentrated. The residue was dissolved in THF (50 mL), CDI (12.3 mmol) was added. The resulting mixture was stirred at room temperature for 1 h. MgCl_2 (1.3 g, 13.6 mmol) and $\text{KOCOCH}_2\text{CO}_2\text{Me}$ (2.9 g, 18.5 mmol) were added, the resulting mixture was stirred at room temperature overnight. EtOAc (100 mL), water (50 mL) were added. The aqueous layer was separated and extracted with EtOAc. The aqueous layer was extracted with EtOAc. The organic extracts were combined, washed with brine, dried (MgSO_4), filtered and concentrated. The residue was separated by silica gel chromatography, with Biotage 40S+ column, eluted with EtOAc: hexanes, 1:10, to give 1.5 g (46%) yellow liquid as **Compound 270d**.

Step D:



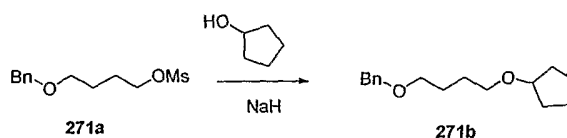
Compound 270d (448 mg, 2.22 mmol) and barbituric acid (340 mg, 2.65 mmol) was mixed with HOAc (2 mL) in a sealed tube, and heated in an oil bath at 125 °C overnight. The mixture was cooled to room temperature, HOAc was removed and the residue was taken up in MeOH, and filtered. The mother liquid was concentrated and separated by preparative TLC, eluted with 1:10:10, HOAc:DCM:EtOAc, to give desired **Compound 270** (72 mg, 11.4%) as a white solid. Electrospray MS $[M+1]$: 281.2.

Preparative example 271

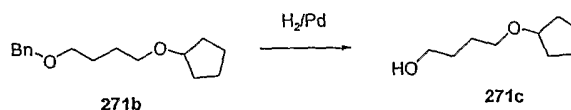
Step A:

Starting alcohol (5.2 g, 28.0 mmol) was dissolved in DCM (100 mL), triethylamine (6 mL, 42.7 mmol) and MsCl (2.6 mL, 33.6 mmol) was added.

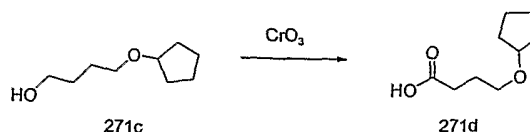
- 5 The resulting solution was stirred at room temperature for 1 h. The mixture was diluted with EtOAc and washed with 1 N HCl (50 mL x 2). The aqueous layers were combined, extracted with EtOAc. The organic layers were combined, washed with brine, dried (MgSO₄), filtered, and concentrated to give **Compound 271a** (7.26 g, 100%).

10 Step B:

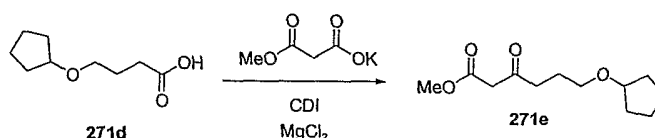
- 15 Cyclopentanol (3.8 mL, 42 mmol) was dissolved in THF (50 mL) under nitrogen. NaH (0.85 g, 95% oil dispersion, 33.7 mmol) was added. The resulting slurry was stirred at room temperature for 1 h. A solution of mesylate **271a** (7.26 g, 28 mmol) in DMF (30 mL) was added via syringe. The resulting mixture was heated at 85 °C overnight. The mixture was cooled to room temperature, and diluted with EtOAc, and washed with water (50 mL x 3). The aqueous layers were combined and extracted with EtOAc. The organic extracts were combined, washed with brine, dried (MgSO₄), filtered and concentrated *in vacuo*. The residue was purified over silica gel column, eluted with EtOAc-hexanes (1:10) to give 4.95 g (71%) of **Compound 271b** as an amber liquid.

Step B:

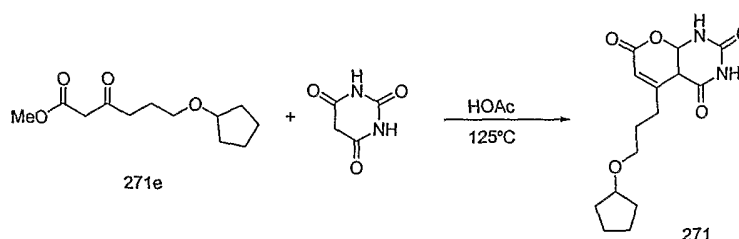
- 25 **Compound 271b** (4.95 g, 20 mmol) was dissolved in EtOH (100 mL), 10% Pd/C (0.55 g) was added and stirred under 1 atm of hydrogen balloon overnight. Filtered through Celite, the filtrate was concentrated *in vacuo*. The residue was purified over silica gel column, eluted with EtOAc-hexanes (1:3) to give 3.1 g (98%) of **Compound 271c** as a colorless liquid.

Step C:

CrO₃ was mixed with 4.7 mL of conc. H₂SO₄. The mixture was diluted with water to 36 mL. **Compound 271c** was dissolved in acetone (30 mL), and Jones reagent was added. The mixture was stirred at room temperature for 1 h, diluted with water and extracted with DCM. The organic extracts were combined, washed with brine, dried (MgSO₄), filtered and concentrated to give 1.99 g (71%).

Step D:

Compound 271d (2.40 g, 14.0 mmol) dissolved in THF (50 mL), CDI (2.48 g, 15.3 mmol) was added. The resulting mixture was stirred at room temperature for 1 h. MgCl₂ (1.5 g, 15.3 mmol) and KOCOCH₂CO₂Me (3.3 g, 20.9 mmol) were added, the resulting mixture was stirred at room temperature overnight. EtOAc (100 mL), water (50 mL) were added. The aqueous layer was separated and extracted with EtOAc. The aqueous layer was extracted with EtOAc. The organic extracts were combined, washed with brine, dried (MgSO₄), filtered and concentrated. The residue was filtered through a pad of silica gel, eluted with EtOAc: hexanes, 1:3, to give 2.2 g (69%) yellow liquid as **Compound 270e**.

Step D:

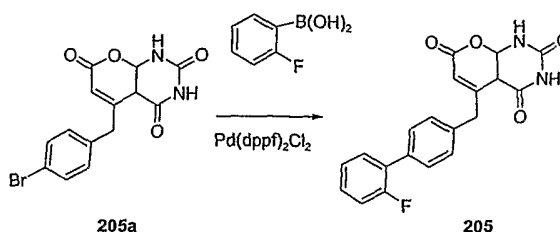
Compound 271e (448 mg, 2.22 mmol) and barbituric acid (340 mg, 2.65 mmol) was mixed with HOAc (2 mL) in a sealed tube, and heated in an oil bath at 125°C overnight. The mixture was cooled to room temperature, HOAc was removed and the residue was taken up in MeOH, and filtered. The mother liquid was concentrated and separated by preparative TLC, eluted

with 1:10:10, HOAc:DCM:EtOAc, to give desired **Compound 271** (55 mg, 4%) as a white solid. Electrospray MS [M+1]: 307.2.

Compound 273, Compound 287 and Compound 290 are prepared in a similar fashion as **Compound 271** from the corresponding alcohols.

5

Preparative example 205

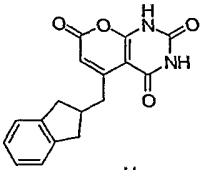
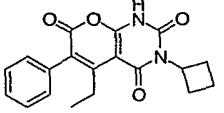
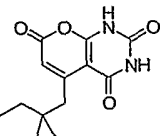
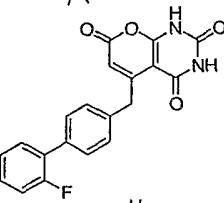
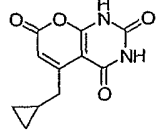
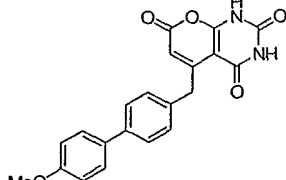
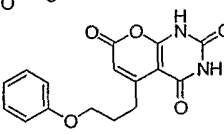
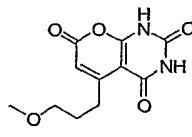
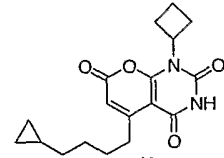
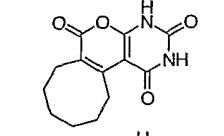
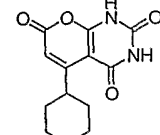


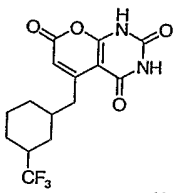
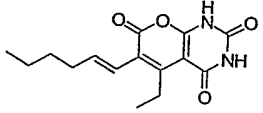
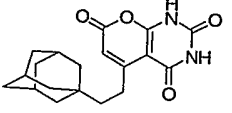
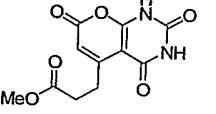
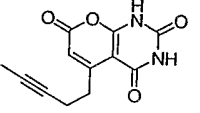
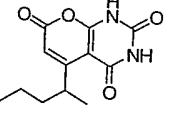
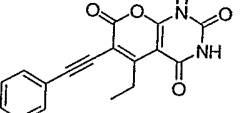
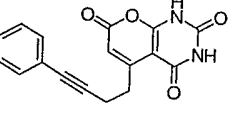
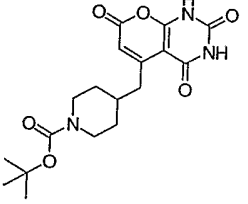
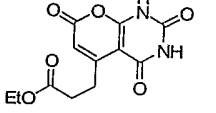
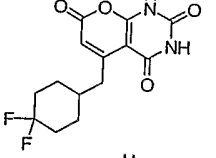
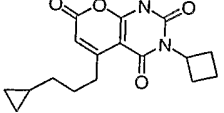
Compound 205a (50 mg, 0.14 mmol) was dissolved in DMF (2 mL) and H₂O (2 mL), Pd(dppf)₂Cl₂ and K₂CO₃ were added. The resulting mixture was heated at 85 °C under nitrogen for 5 h. The mixture was cooled to room temperature and filtered through Celite. The filtrate was concentrated. The residue was dissolved in MeOH, and DCM was added until precipitation persisted. The solid was collected as the desired **Compound 205** (21 mg, 40%). Electrospray MS [M+1]: 481.5.

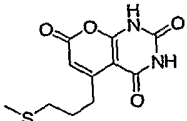
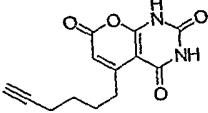
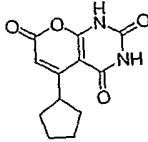
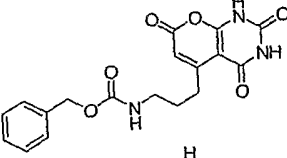
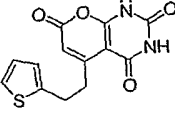
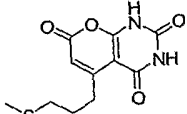
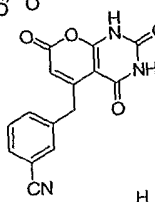
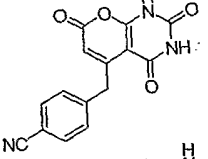
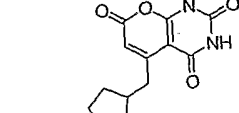
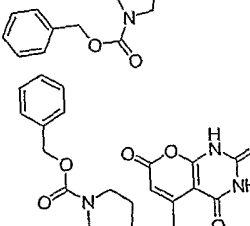
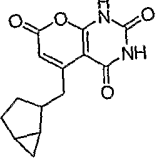
Compound 207 was prepared in a similar fashion as **Compound 205**, using the corresponding boronic acid.

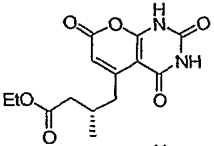
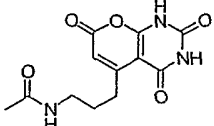
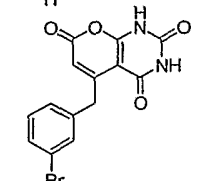
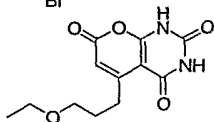
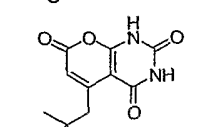
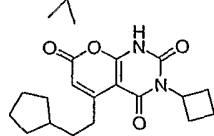
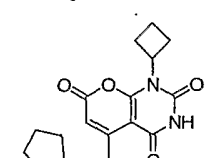
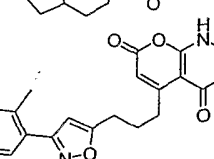
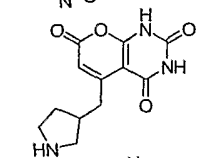
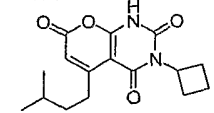
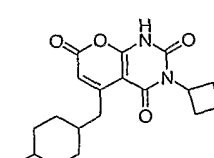
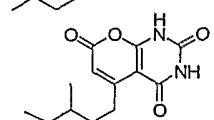
Several compounds of the invention are shown in the Table below as well as in the Tables presented later in this specification. The LCMS data is also shown wherever available. The activity (EC₅₀) data is also shown, wherever measured and available, and is designated A, B or C, where A = 0.001 nM to 100 nM; B is >100 <1000 nM and C is >1000 nM.

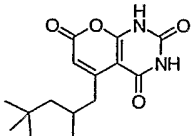
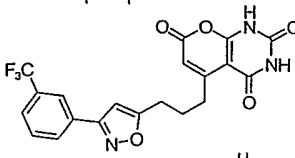
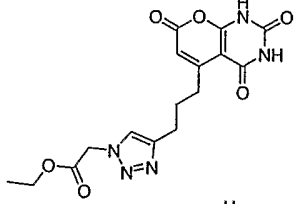
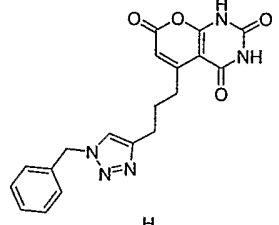
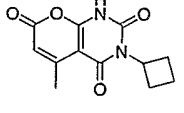
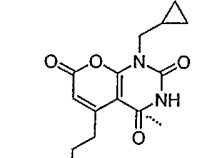
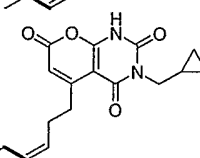
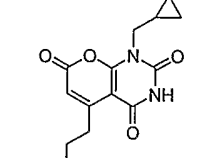
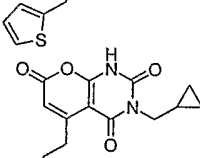
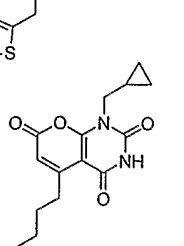
Compound #	MOL. STRUCTURE	NA EC ₅₀ camp nM	Electrospray LCMS [M+1] ⁺
200		B	331.2
201		C	289.2

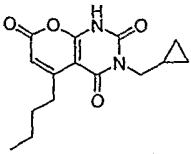
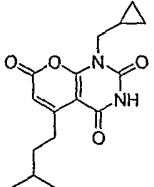
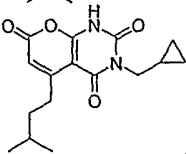
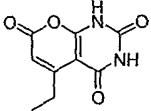
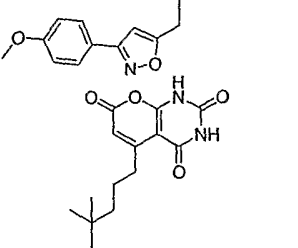
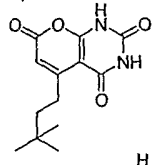
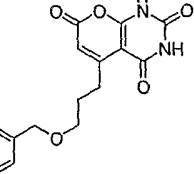
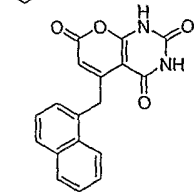
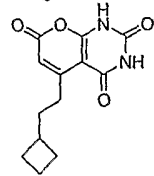
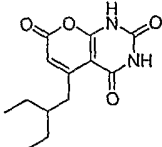
202		B	311.2
203		C	339.1
204		C	265.1
205		B	365.2
206		B	235.1
207		C	377.2
208		C	316.2
209		B	253.1
210		B	331.2
211		C	263.1
212		B	263.1

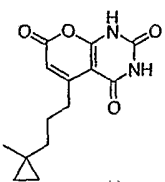
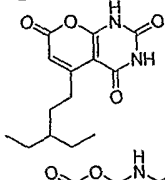
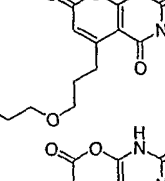
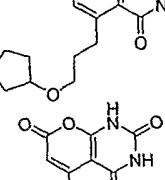
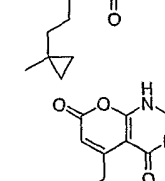
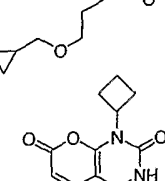
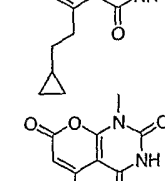
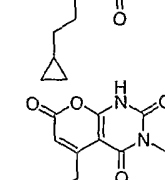
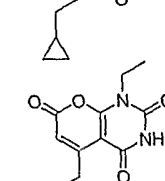
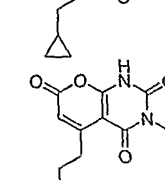

213		B	345.2
214		C	291.2
215		C	343.2
216		B	267.1
217		C	247.1
218		B	251.1
219		C	309.2
220		C	309.2
221		C	378.2
222		C	281.2
223		A	313
224		A	317.2

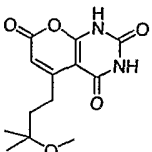
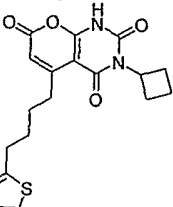
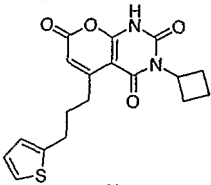
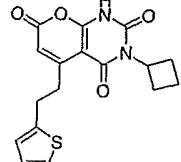
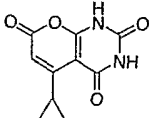
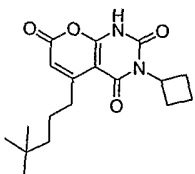
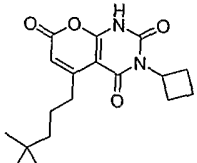
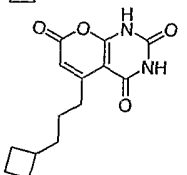
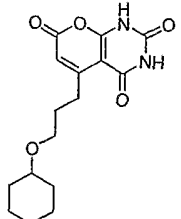
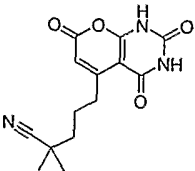
225		A	269.1
226		A	261.1
227		C	249.1
228		C	372.2
229		A	391.2
230		B	301.2
231		C	318.2 (M+Na)
232		C	368.2 (M+Na)
233		C	398
234		C	426
235		A	275.2

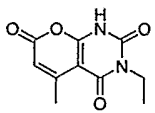
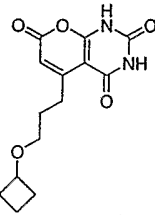
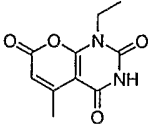
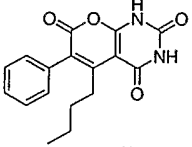
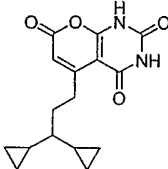
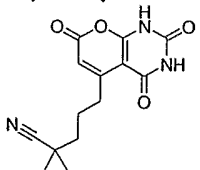
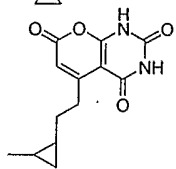
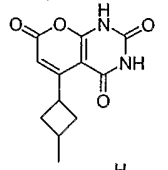
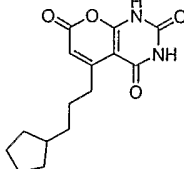
236		C	309.2
237		C	280.2
238		B	349.2
239		A	267.1
240		C	251
241		A	331.2
242		C	331.2
243		B	380
244		C	264
245		A	305.2
246		C	345.2
247		A	265.1

248		C	293.2
249		B	434
250		C	376
251		B	380
252		A	249.1
253		C	317.2
254		C	317.2
255		C	359.2
256		C	359.2
257		C	291.2

258		B	291.2
259		C	305.2
260		C	305.2
261		B	396
262		A	279.2
263		C	265.1
264		C	329.2
265		C	321.2
266		A	263.1
267		C	265.1

268		A	277.2
269		B	279.2
270		A	281.2
271		B	307.2
272		B	263.1
273		B	293.2
274		B	303.2
275		B	263.1
276		B	263.1
277		C	277.2
278		B	277.2

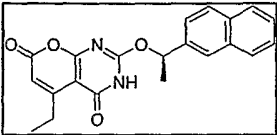
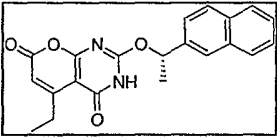
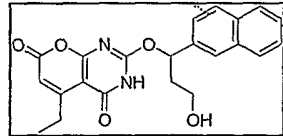
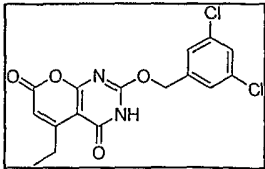
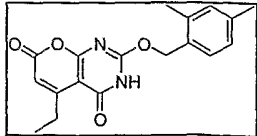
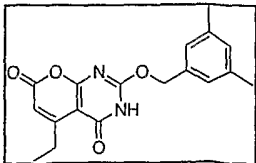
279		C	281.2
280		C	373.2
281		B	359.2
282		B	345.2
283		B	221.1
284		B	333.1
285		B	331.2
286		A	277.2
287		C	321.2
288		C	290.2

289		C	223.1
290		B	315.2 (M+Na)
291		C	223.1
292		B	313.2
293		B	303.2
294		B	288.2
295		B	263.1
296		B	249.1
297		A	291.2

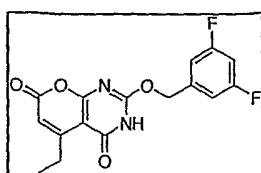
The compounds **500** to **690** were prepared by a procedure similar to that used for the preparation of **Example 49**, using **Example 10**, and the appropriate corresponding alcohol.

Compounds **691** and **698** were prepared by a procedure similar to Example 49, using appropriate oxyaminocarbamate and sulfoxide which was prepared using Example 10.

5

Compound#	Mol. structure	NA EC50 camp nM	Electrospray LCMS [M+1] ⁺
500		B	363.1
501		A	363.1
502		B	343
503		B	368
504		B	327
505		B	327

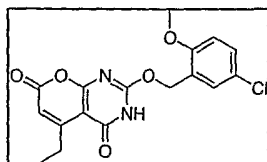
506



C

335

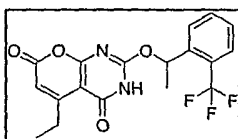
507



A

363

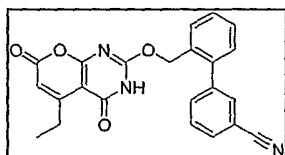
508



C

381.1

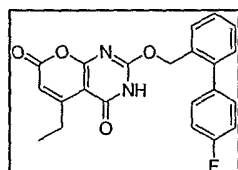
509



B

400

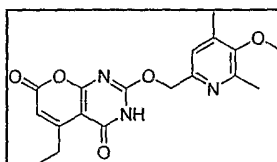
510



C

393

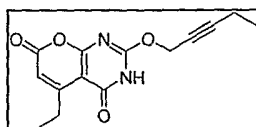
511



C

358.2

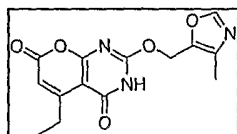
512



A

275

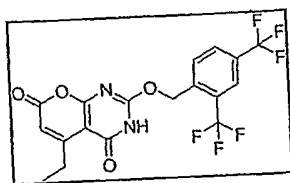
513



B

304

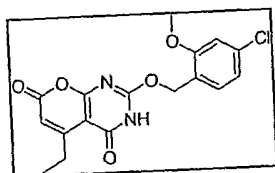
514



C

435

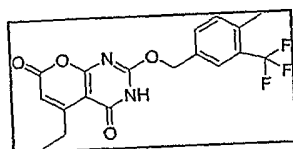
515



B

363

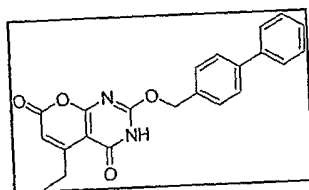
516



C

381

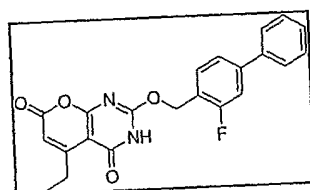
517



C

375.2

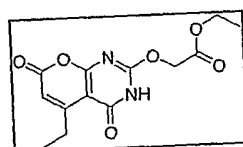
518



B

393.2

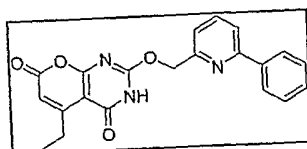
519



C

295.1

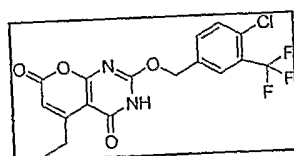
520



C

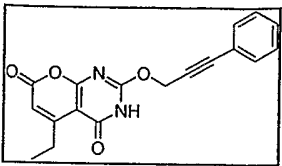
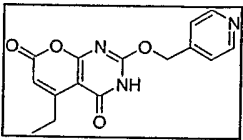
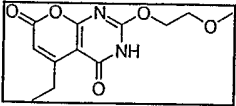
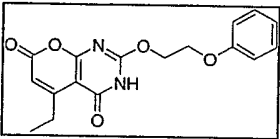
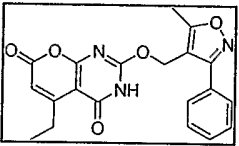
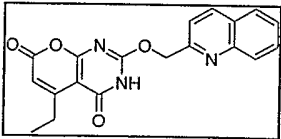
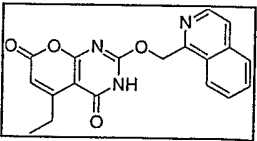
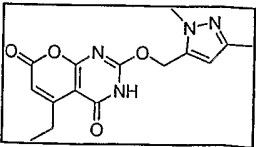
376.2

521

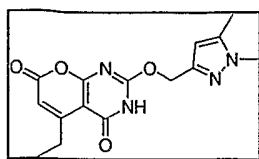


B

401.2

522		B	323
523		A	300.2
524		B	267.1
525		B	329.2
526		B	380
527		B	350
528		B	350
529		B	317

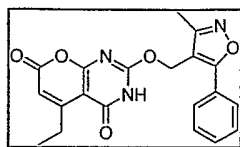
530



B

317

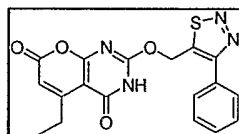
531



B

380

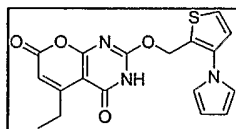
532



B

383

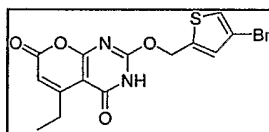
533



C

370

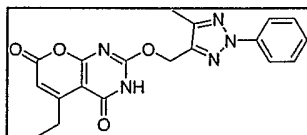
534



B

384

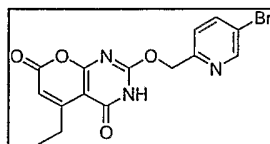
535



B

380

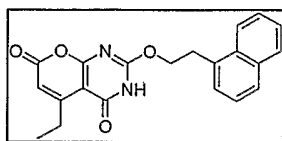
536



B

379

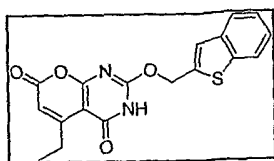
537



C

363

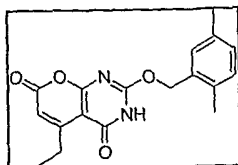
538



B

355

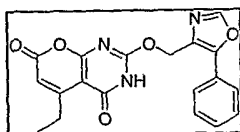
539



B

327

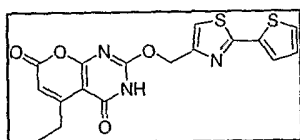
540



B

366

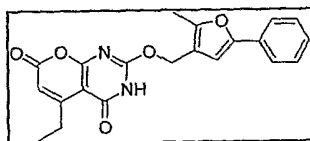
541



B

388

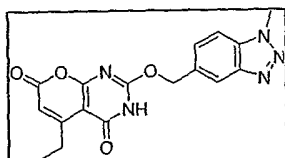
542



C

379

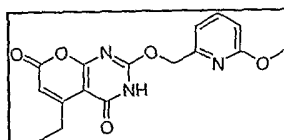
543



B

354

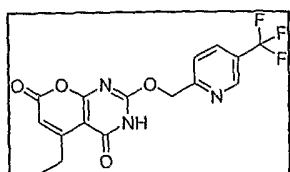
544



B

330.2

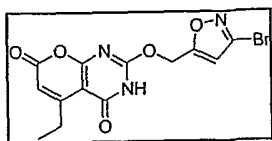
545



B

368.2

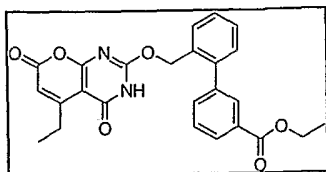
546



B

369.99

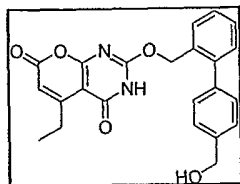
547



B

447

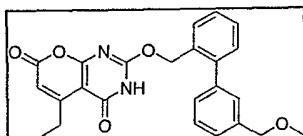
548



B

405

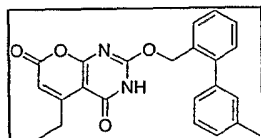
549



B

419

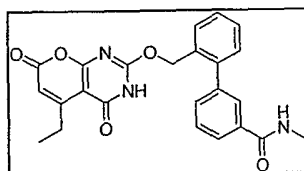
550



C

389

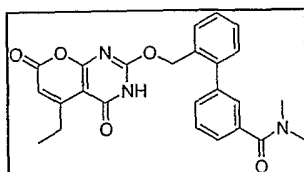
551



B

432

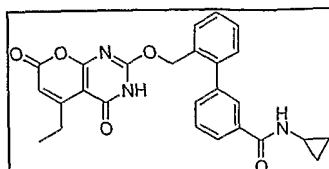
552



B

446

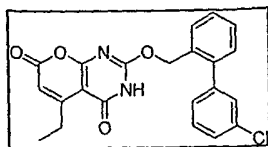
553



C

458

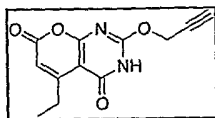
554



C

409

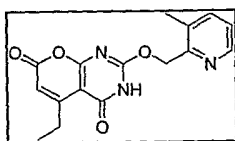
555



B

247

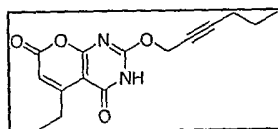
556



C

314.2

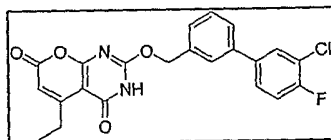
557



A

289

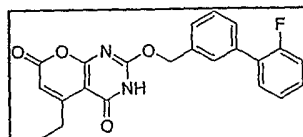
558



C

427

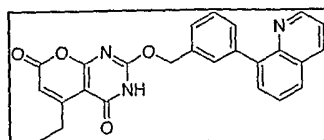
559



B

393

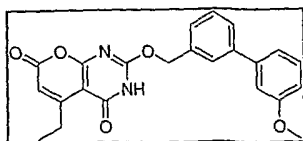
560



C

426

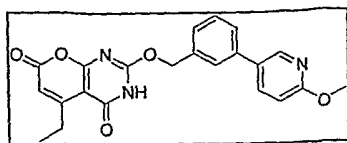
561



B

405

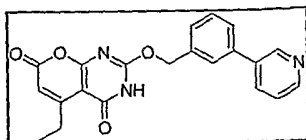
562



B

406

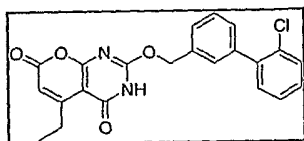
563



B

376

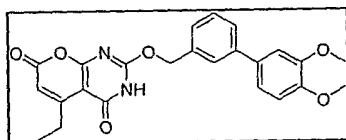
564



B

409

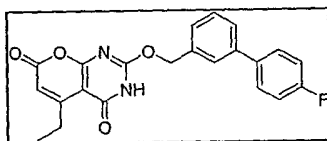
565



B

435

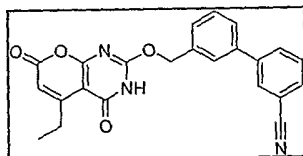
566



C

393

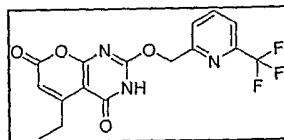
567



B

400

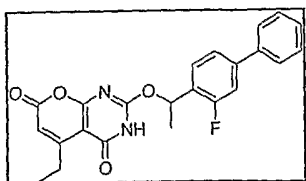
568



B

368.2

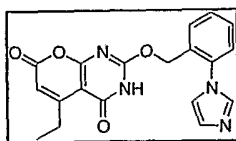
569



A

407.2

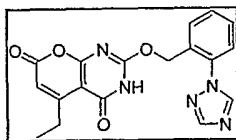
570



B

365.1

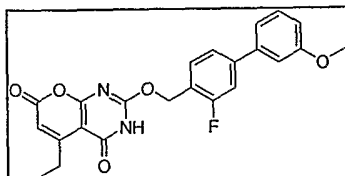
571



B

366.1

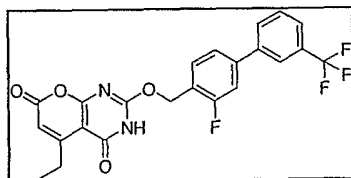
572



B

423.1

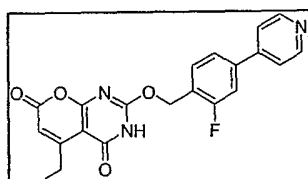
573



B

461.1

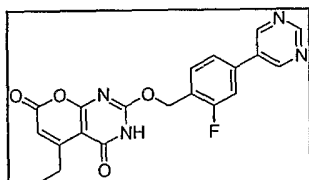
574



B

394.1

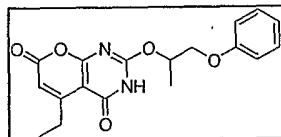
575



B

395.1

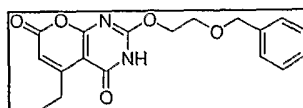
576



C

343.2

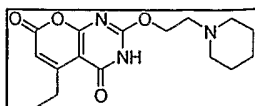
577



B

343.2

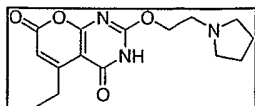
578



C

320.2

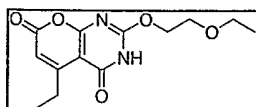
579



C

306.2

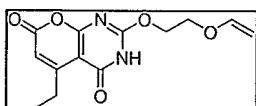
580



C

281.2

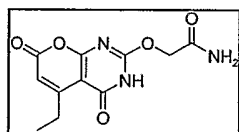
581



C

279.2

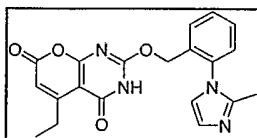
582



B

266.1

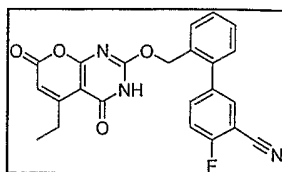
583



B

379.2

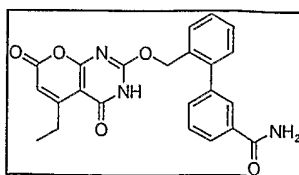
584



B

418

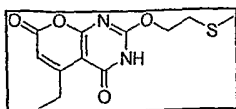
585



B

418

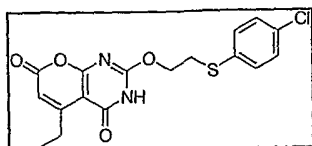
586



A

383.1

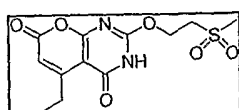
587



C

379.1

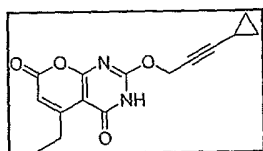
588



C

315.1

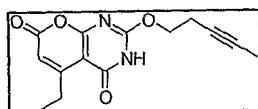
589



A

287

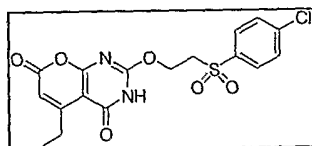
590



B

275

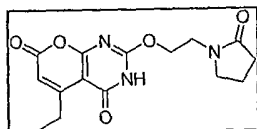
591



A

411.1

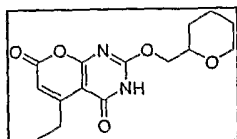
592



B

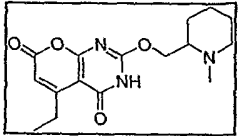
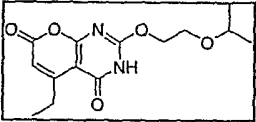
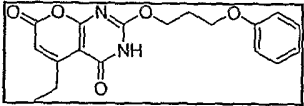
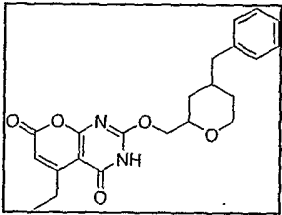
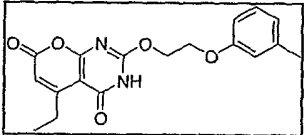
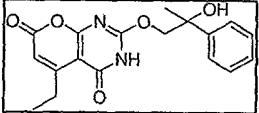
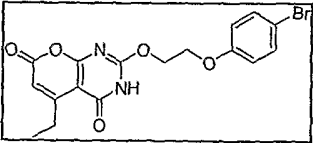
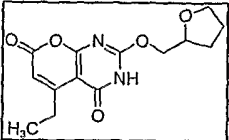
320.2

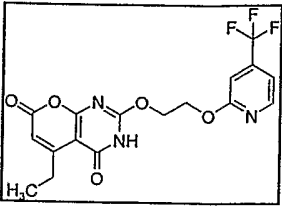
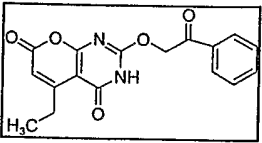
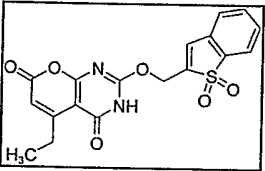
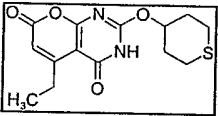
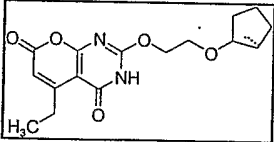
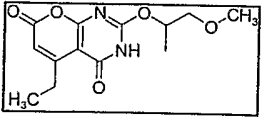
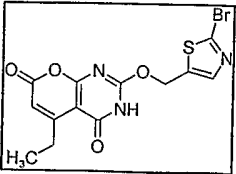
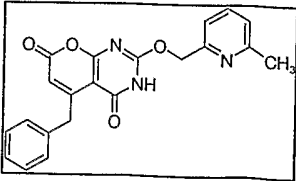
593

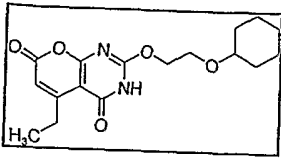
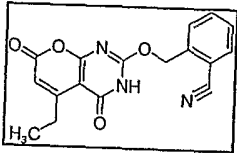
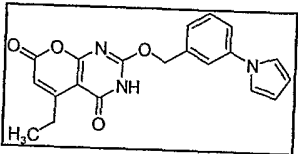
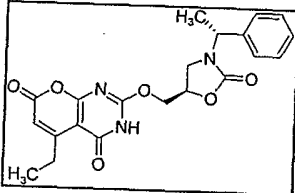
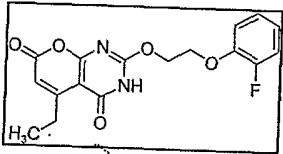
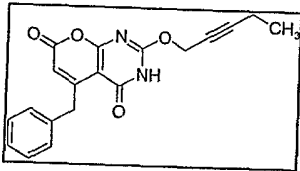
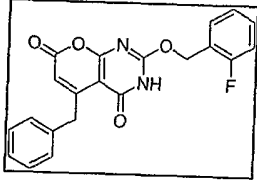
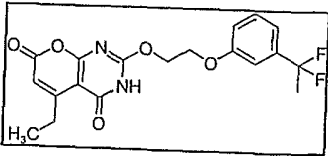
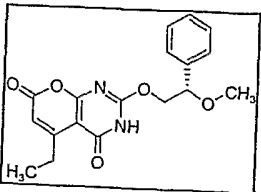


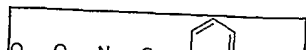
C

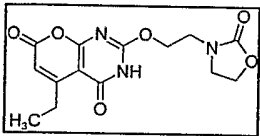
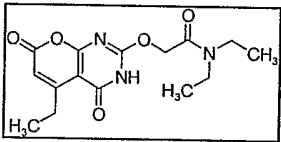
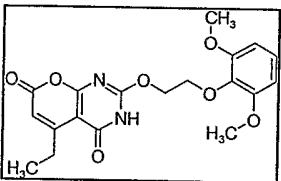
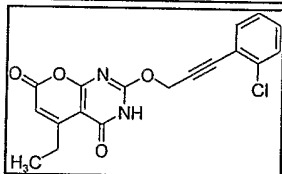
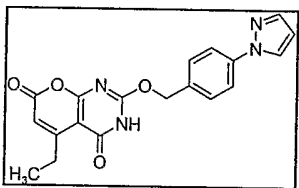
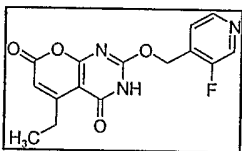
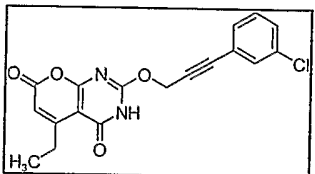
307.2

594		C	320.2
595		B	295.2
596		B	343.2
597		C	398.1
598		B	343.1
599		B	343.1
600		C	409.1
601		C	293.1

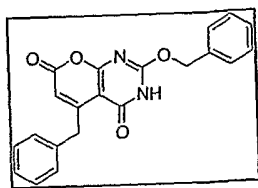
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603		B	327.2
604		B	387.2
605		C	309.2
606		C	321
607		B	281.2
608		B	384.2
609		C	376.1

610		C	335
611		C	324.2
612		C	364.2
613		B	412.1
614		B	347.1
615		B	337.1
616		B	379.2
617		B	397.2
618		B	343.2



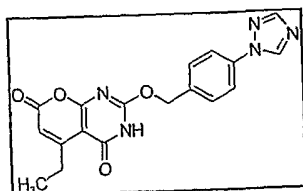
619		B	342.2
620		C	322.2
621		B	322.2
622		B	389.2
623		A	357.2
624		B	365.2
625		B	318.2
626		A	358

627



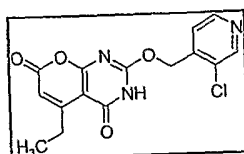
C 361.2

628



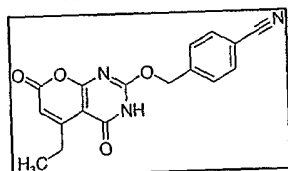
C 366.2

629



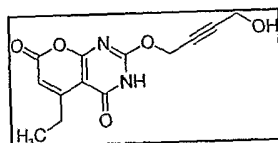
B 334.2

630



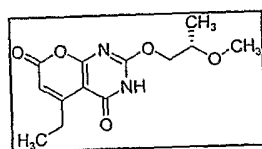
C 324.2

631



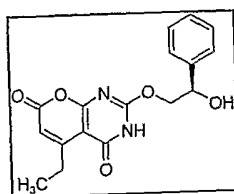
B 277

632



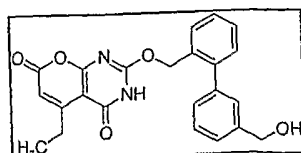
B 281.2

633



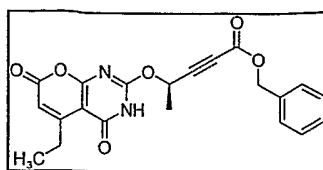
B 329.2

634



B 405

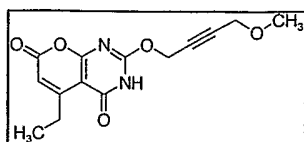
635



C

395

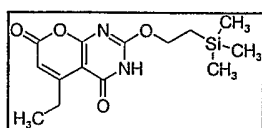
636



B

291

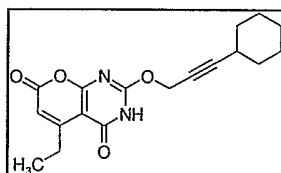
637



B

309.2

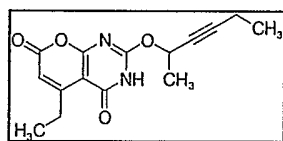
638



B

329

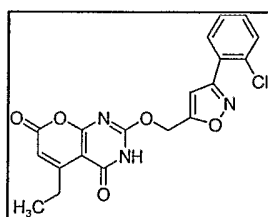
639



B

283

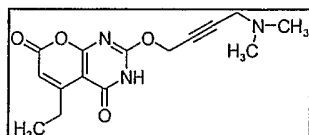
640



B

400.1

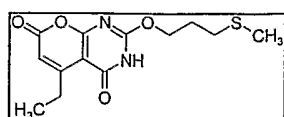
641



A

304

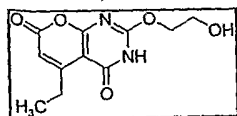
642



B

297.2

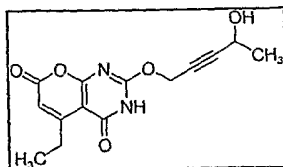
643



B

253.1

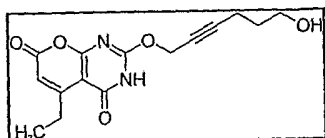
644



A

291

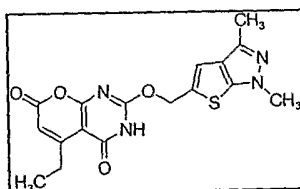
645



A

305

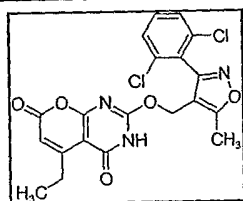
646



C

373.2

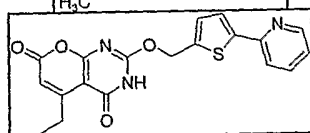
647



B

448.2

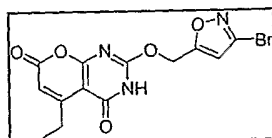
648



B

382.2

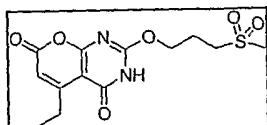
649



B

368

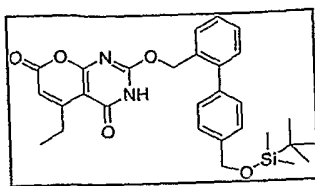
650



B

329.2

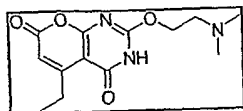
651



B

520

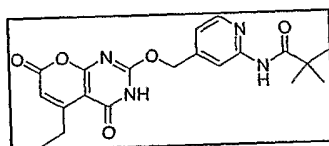
652



A

280.1

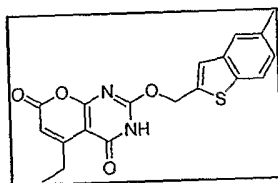
653



C

399.2

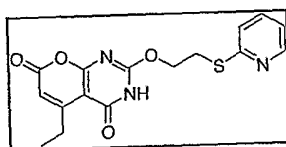
654



A

M+Na 391.2

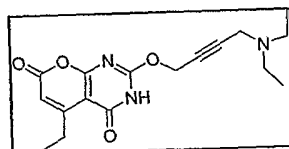
655



B

346.2

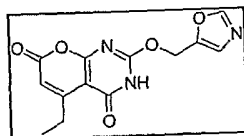
656



C

332

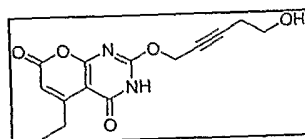
657



C

290

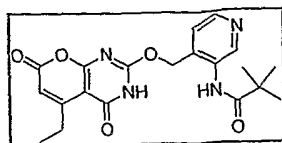
658



B

291

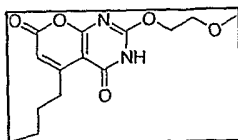
659



C

399.2

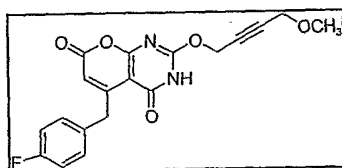
660



C

317.2
(M+Na)

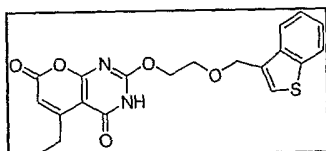
661



B

371.2

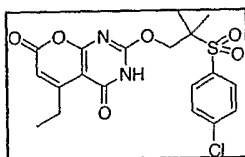
662



A

399.2

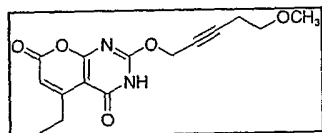
663



C

439.2

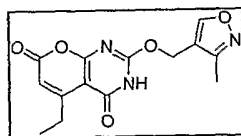
664



B

305

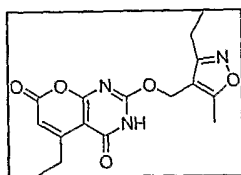
665



C

304

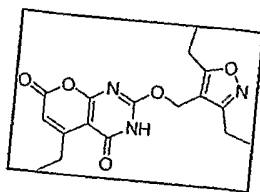
666



A

332

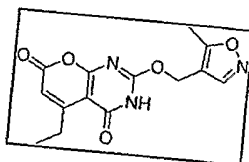
667



B

346

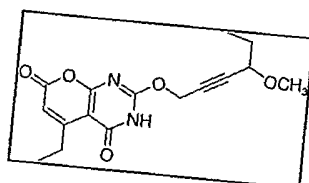
668



C

304

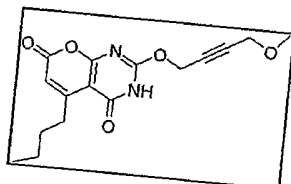
669



B

319

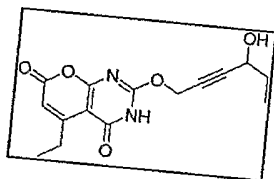
670



A

319.2

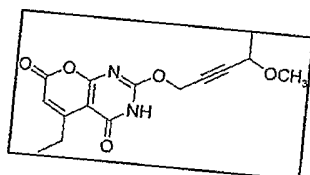
671



A

305

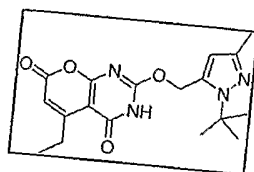
672



B

305

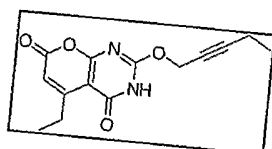
673



B

359

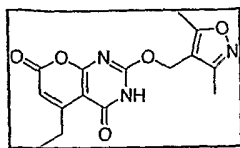
674



A

303

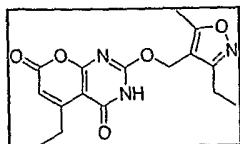
675



B

346

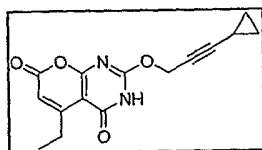
676



B

360

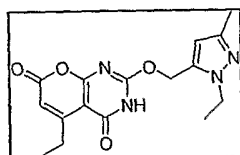
677



A

315

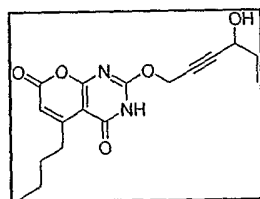
678



B

331

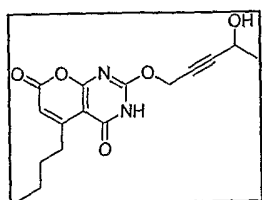
679



A

333

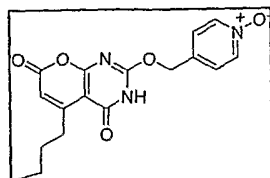
680



A

319

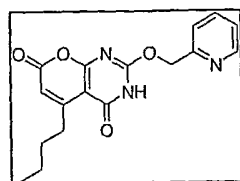
681



C

344.2

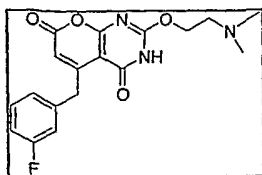
682



C

328.2

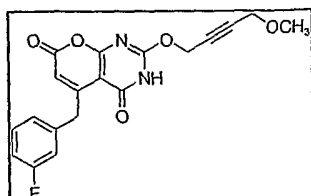
683



C

360.2

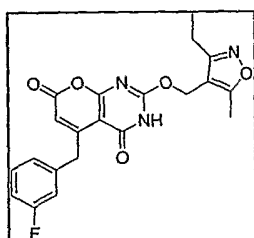
684



A

371.2

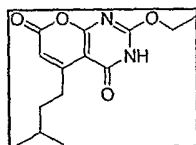
685



B

412.2

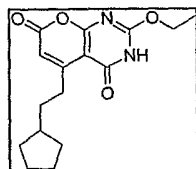
686



B

279.2

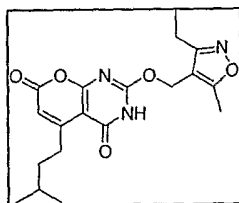
687



B

305.2

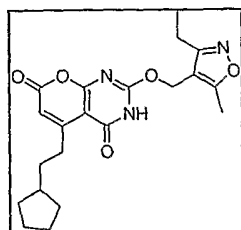
688



B

374.2

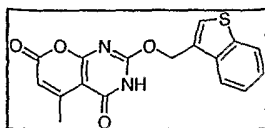
689



B

400.2

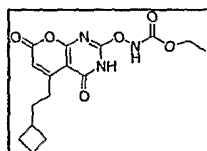
690



C

241.1

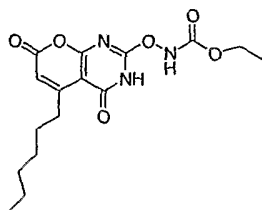
691



A

350.2

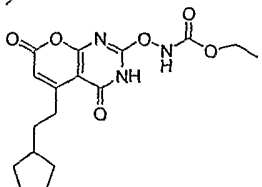
692



A

352.2

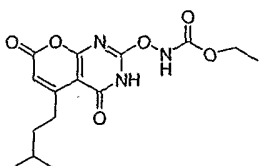
693



B

364.2

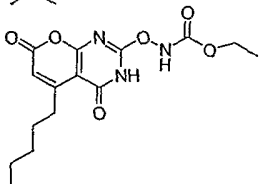
694



C

338.2

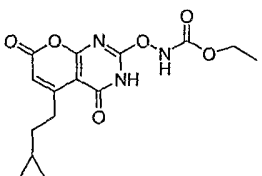
695



A

338.2

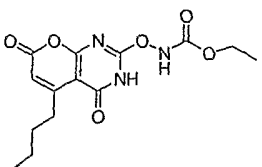
696



B

336.2

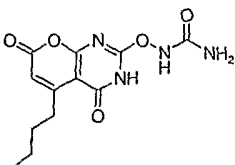
697



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324.2

698

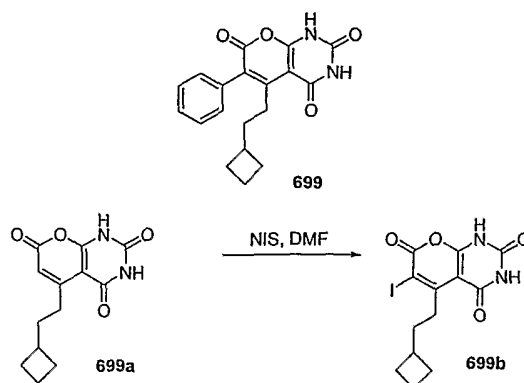


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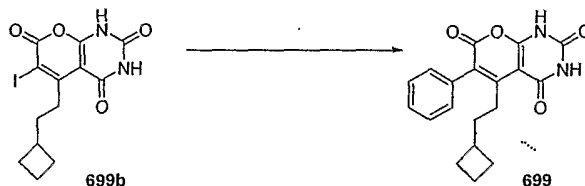
295.2

Experimentals for compounds 699-710 are described below:

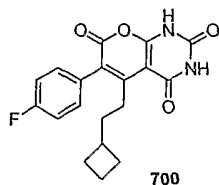
Preparative example 699



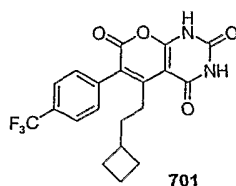
Compound **699a** (0.925 g, 3.53 mmol) was taken in DMF (10 mL) in a
 5 round bottomed flask equipped with a magnetic stirring bar. *N*-Iodosuccinimide (1.59 g, 7.05 mmol) was added portionwise and the reaction mixture was heated to 50°C overnight. After cooling to ambient temperature, H₂O (25 mL) was added. The product was filtered, washed with water followed by ether to give a white powdery mixture (> 95% yield). The product
 10 **699b** was used as such for the next step without any further purification.



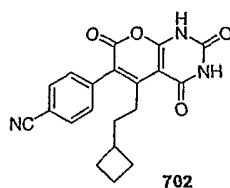
Compound **699b** (0.1 g, 0.258 mmol) was taken in 5 mL DME/H₂O (4:1) in a 10 mL round bottomed flask. PdCl₂(PPh₃)₂ (0.018 g, 0.0258 mmol), Na₂CO₃ (0.082 g, 0.774 mmol), and phenylboronic acid (0.057 g, 0.464 mmol)
 15 was added, and the reaction mixture was allowed to reflux (80 °C) for 6 h. After cooling, the mixture was concentrated and purified by flash chromatography (CH₂Cl₂ to 5% MeOH/CH₂Cl₂) to yield compound **699**.



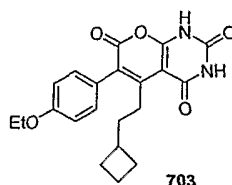
Compound **700** was prepared in the same manner as in example **699**.



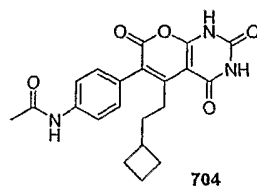
Compound **701** was prepared in the same manner as in example **699**.



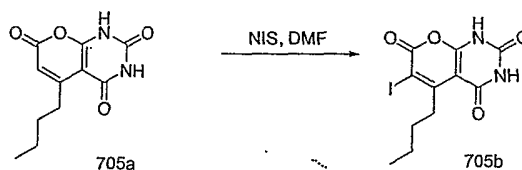
Compound **702** was prepared in the same manner as in example **699**.



5 Compound **703** was prepared in the same manner as in example **699**.

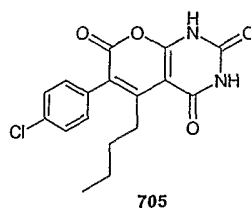


Compound **704** was prepared in the same manner as in example **699**.

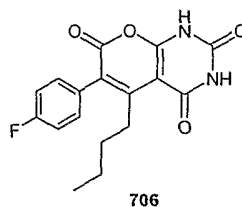


Compound **705b** was prepared in the same manner as in example

10 **699b**.

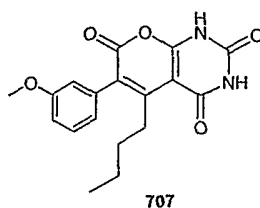


Compound **705** was prepared in the same manner of compound **699**.

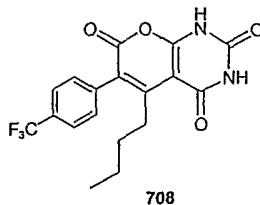


The compound **706** was prepared in the same manner of compound

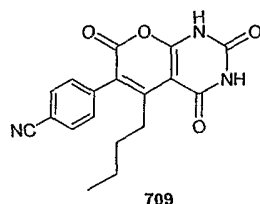
15 **699**.



The compound **707** was prepared in the same manner of compound **699**.

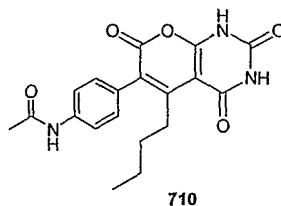


The compound **708** was prepared in the same manner of compound **699**.



5

The compound **709** was prepared in the same manner of compound **699**.



The compound **710** was prepared in the same manner of compound **699**.

Compound #	MOL. STRUCTURE	NA EC50 camp nM	Electrospray LCMS [M+1] ⁺
699		C	339.2
700		C	357.2
701		C	407.2

702		C	364.2
703		C	383.2
704		C	396.2
705		C	347.2
706		C	331.2
707		C	343.2
708		B	381.2
709		C	338.2
710		C	370.2

ASSAY:

The nicotinic acid receptor agonist activity of the inventive compounds was determined by following the inhibition of forskolin-stimulated cAMP

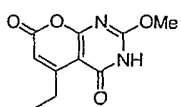
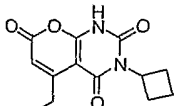
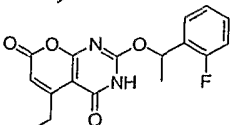
accumulation in cells using the MesoScale Discovery cAMP detection kit following the manufacturer's protocol. Briefly, Chinese Hamster Ovary (CHO) cells expressing recombinant human nicotinic acid receptor (NAR) were harvested enzymatically, washed 1X in phosphate buffered saline (PBS) and resuspended in PBS containing 0.5 mM IBMX at 3×10^6 cells/mL. Ten μL of cell suspension was added to each well of a 384-well plate which contained 10 μL of test compounds. Test compounds were diluted with PBS containing 6 μM of forskolin. Plates were incubated for 30 minutes at room temperature after the addition of cells. Lysis buffer containing cAMP-Tag was added to each well (10 μL /well) as per the manufacturer's protocol. Plates were then incubated from 45 minutes to overnight. Prior to reading, 10 μL of read buffer was added to each well, and the plate was read in a Sector 6000 plate imager. The signal was converted to cAMP concentration using a standard curve run on each plate. Compound EC_{50} values were determined from concentration gradients of test compounds.

Compounds of Formula (I) of the present invention, and salts, solvates, or esters thereof, have cAMP EC_{50} values of less than about 10,000 nM, preferably about 1000 nM or less, more preferably about 500 nM or less, even more preferably about 100 nM or less.

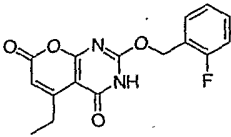
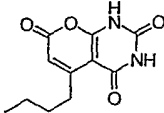
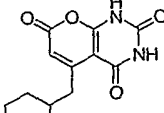
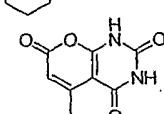
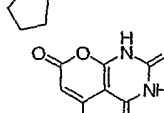
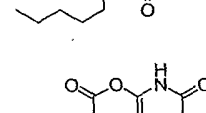
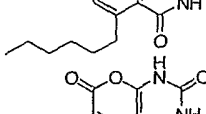
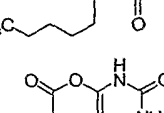
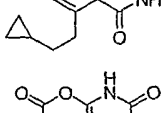
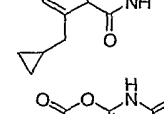
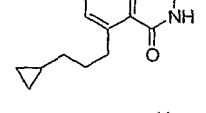
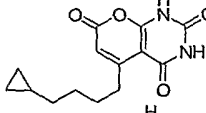
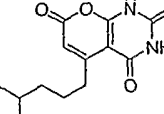
Examples 1, 5, 10, 29, 39, 71, 101-116, and 118-135 have cAMP EC_{50} values of 100 nM or less.

The activity of a non-limiting list of illustrative inventive compounds as measured by the above-described assay is shown in the following Table:

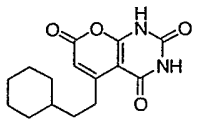
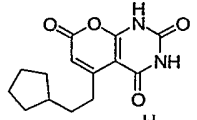
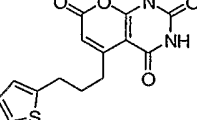
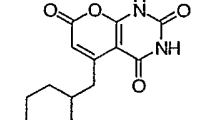
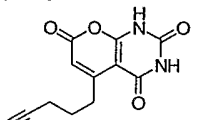
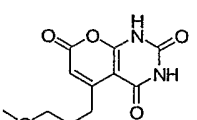
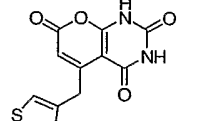
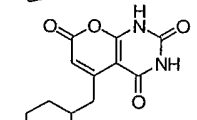
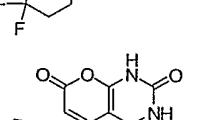
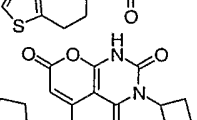
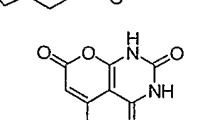
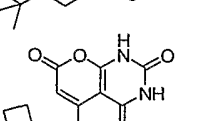
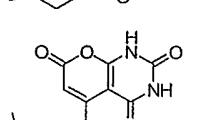
Table of Activity

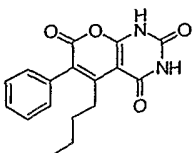
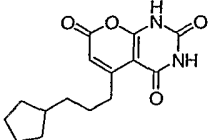
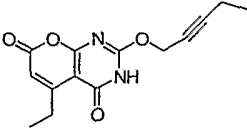
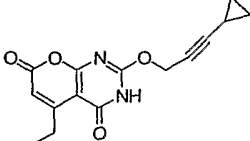
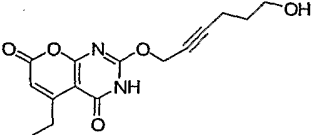
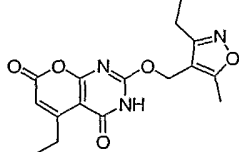
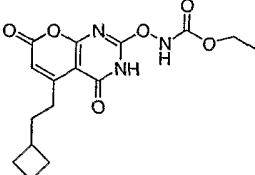
COMPOUND NUMBER	MOL. STRUCTURE	NA EC_{50} camp nM
11		125.0
35		9.0
90		475.3

172

74		183.0
102		31.0
103		74.3
104		47.0
107		18.7
108		28.0
112		14.4
116		12.6
117		155.0
118		4.2
119		10.1
122		5.3
123		4.3

173

124		78.5
125		1.2
126		26.5
127		57.3
128		6.3
129		106.5
135		4.8
223		26.45
229		47.4
241		12.95
262		49.9
266		1.2
268		2.1

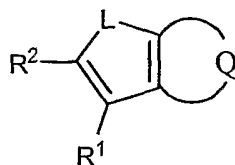
292		300
297		56.75
512		95.5
589		33.8
645		26.2
666		63.3
691		47.5

The activity of several other compounds of the present invention is shown earlier in this specification as A, B or C. It will be appreciated by those skilled in the art that the herein-described inventive compounds exhibit excellent nicotinic acid receptor agonist activity. While the present invention has been described with in conjunction with the specific embodiments set forth above, many alternatives, modifications and other variations thereof will be apparent to those of ordinary skill in the art. All such alternatives, modifications and variations are intended to fall within the spirit and scope of the present invention.

CLAIMS

WE CLAIM:

1. A compound of Formula (I):

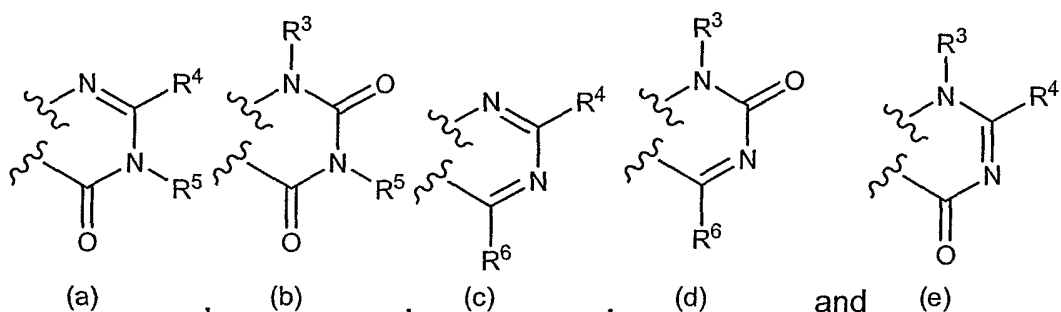


5

(I)

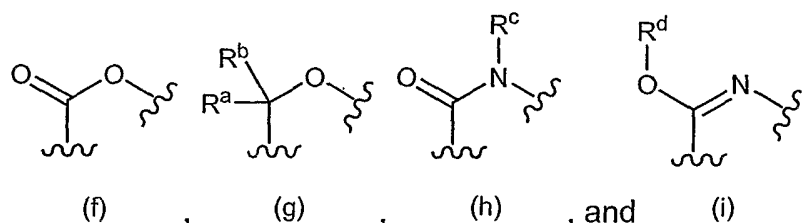
or a pharmaceutically acceptable salt, solvate, ester, or tautomer thereof,
wherein:

Q is selected from the group consisting of:



10

L is selected from the group consisting of:



R¹ is selected from the group consisting of H, alkyl, alkenyl, alkynyl,

haloalkyl, alkyl substituted with one or more hydroxyl groups,

cycloalkyl, -C(O)-alkyl, -alkylene-C(O)-O-alkyl, -O-R¹⁰,

15

-alkylene-O-alkyl, aryl, -alkylene-aryl, heteroaryl, -alkylene-heteroaryl,

halogen, -(CH₂)_n-N(R⁷)₂, -alkylene-cycloalkyl, and

-alkylene-cycloalkenyl,

wherein said cycloalkyl or the cycloalkyl portion of said

-alkylene-cycloalkyl of R¹ is unsubstituted or substituted with one

20

or more X groups, said aryl or the aryl portion of said

-alkylene-aryl of R¹ is unsubstituted or substituted with one or

more Y groups, and said heteroaryl or the heteroaryl portion of

said -alkylene-heteroaryl of R^1 is unsubstituted or substituted with one or more Y groups;

R^2 is selected from the group consisting of H, halogen, alkyl, haloalkyl, alkyl substituted with one or more -OH, -C(O)-alkyl, -C(O)-O-alkyl, -C(O)-OH, -O- R^{10} , -alkylene-O-alkyl, unsubstituted aryl, aryl substituted with one or more Y groups, unsubstituted heteroaryl, heteroaryl substituted with one or more Y groups, and halogen; or

R^1 and R^2 together with the ring carbon atoms to which they are shown attached, form a 5- or 6-membered cycloalkenyl ring or a 5- or 6-membered heterocyclic ring having 1 or 2 heteroatoms;

R^3 is selected from the group consisting of H, alkyl, alkyl substituted with one or more hydroxyl groups, -alkylene-O-alkyl, cycloalkyl, -alkylene-cycloalkyl, -alkylene-C(O)-O-alkyl, -alkylene-O-C(O)-alkyl, alkenyl, aryl, and heteroaryl,

wherein said cycloalkyl or the cycloalkyl portion of said -alkylene-cycloalkyl of R^3 is unsubstituted or substituted with one or more X groups, said aryl of R^3 is unsubstituted or substituted with one or more Y groups, and said heteroaryl of R^3 is unsubstituted or substituted with one or more Y groups;

R^4 is selected from the group consisting of H, halogen, alkyl, -O- R^{10} , -C(O)-O-alkyl, -S(O)_m- R^9 , -N(R^7)₂, -N(R^7)-NH-C(O)-alkyl, -N(R^7)-NH-C(O)-O-alkyl, -O-N=C(R^{12})₂, -N(R^7)-N=C(R^{12})₂, -C(O)-alkyl, unsubstituted heterocyclyl, heterocyclyl substituted with one or more X groups, -O-N(R^7)-C(O)-O-alkyl, -C(O)-N(R^7)₂, -CN, -N₃, and -O-C(O)-alkyl;

R^5 is selected from the group consisting of H, alkyl, -alkylene-C(O)- R^8 , -alkylene-C(O)-N(R^{11})₂, -alkylene-C(=N-O-alkyl)-aryl, cycloalkyl, -alkylene-cycloalkyl, -alkylene-C(O)-O-alkyl, -alkylene-O-C(O)-alkyl, -alkylene-C(O)-heterocyclyl, and alkenyl,

wherein said cycloalkyl or the cycloalkyl portion of said -alkylene-cycloalkyl of R^5 is unsubstituted or substituted with one or more X groups, and the aryl portion of said -alkylene-C(=N-O-alkyl)-aryl of R^5 is unsubstituted or substituted with one or more Y groups;

R^6 is selected from the group consisting of H, alkyl, alkenyl, alkyl substituted with one or more hydroxyl groups, -alkylene-O-alkyl, -O- R^{10} , halogen, aryl, heteroaryl, and -N(R^7)₂,

5 wherein said aryl of R^6 is unsubstituted or substituted with one or more Y groups, and said heteroaryl of R^6 is unsubstituted or substituted with one or more Z groups;

each R^7 is independently selected from the group consisting of H, alkyl, cycloalkyl, aryl, -C(O)-alkyl, and -C(O)-aryl,

10 wherein said cycloalkyl of R^7 is unsubstituted or substituted with one or more X groups, and the aryl portion of said -C(O)-aryl or said aryl of R^7 is unsubstituted or substituted with one or more Y groups; or

two R^7 groups, together with the N atom to which they are bonded form a heterocyclyl;

15 R^8 is selected from the group consisting of aryl, -OH, and heterocyclyl, wherein said heterocyclyl of R^8 is unsubstituted or substituted with one or more X groups, and said aryl of R^8 is unsubstituted or substituted with one or more Y groups;

R^9 is selected from the group consisting of alkyl, -alkylene-cycloalkyl, 20 alkenyl, -N(R^{11})₂, and -alkylene-aryl, wherein the cycloalkyl portion of said -alkylene-cycloalkyl of R^9 is unsubstituted or substituted with one or more X groups, and the aryl portion of said -alkylene-aryl of R^9 is unsubstituted or substituted with one or more Y groups, and

25 with the proviso that when R^9 is -N(R^{11})₂, m is 1 or 2;

R^{10} is selected from the group consisting of H, alkyl, -alkylene-aryl, -alkenylene-aryl, -alkylene-heteroaryl, alkenyl, -C(O)-alkyl, alkynyl, and -alkylene-cycloalkyl,

30 wherein the cycloalkyl portion of said -alkylene-cycloalkyl of R^{10} is unsubstituted or substituted with one or more X groups, the aryl portion of said -alkylene-aryl or -alkenylene-aryl of R^{10} is unsubstituted or substituted with one or more Y groups, and the heteroaryl portion of said -alkylene-heteroaryl of R^{10} is unsubstituted or substituted with one or more Z groups;

each R¹¹ is independently selected from the group consisting of H, alkyl, and aryl,

wherein said aryl of R¹¹ is unsubstituted or substituted with one or more Y groups; or

5 two R¹¹ groups, together with the N atom to which they are attached, form a heterocyclyl;

each R¹² is independently selected from the group consisting of alkyl, aryl, and heteroaryl,

10 wherein said aryl of R¹² is unsubstituted or substituted with one or more Y groups and said heteroaryl of R¹² is unsubstituted or substituted with one or more Z groups;

R^a and R^b are each independently selected from the group consisting of H, alkyl, aryl, and heteroaryl,

15 wherein said aryl of R^a and R^b is unsubstituted or substituted with one or more Y groups, and said heteroaryl of R^a and R^b is unsubstituted or substituted with one or more Z groups;

R^c is selected from the group consisting of H, alkyl, alkylene-aryl, and -C(O)-alkyl,

20 wherein the aryl portion of said alkylene-aryl of R^c is unsubstituted or substituted with one or more Y groups;

R^d is selected from the group consisting of H, alkyl, and alkylene-aryl,

wherein the aryl portion of said alkylene-aryl of R^d is unsubstituted or substituted with one or more Y groups;

25 each X is independently selected from the group consisting of halogen, alkyl, haloalkyl, -O-alkyl, -O-haloalkyl, and -OH;

each Y is independently selected from the group consisting of halogen, alkyl, haloalkyl, -O-alkyl, -O-haloalkyl, -CN, -NO₂, -OH, -S(O₂)-alkyl, -S(O₂)-aryl, -S(O₂)-NH₂, -S(O₂)-NH-alkyl, -S(O₂)-NH-aryl, -S(O₂)-N(alkyl)₂, -S(O₂)-N(aryl)₂, -S(O₂)-N(alkyl)(aryl), and aryl;

30 each Z is independently selected from the group consisting of alkyl, haloalkyl, halogen, -O-alkyl, -O-haloalkyl, -CN, -OH, aryl, and N-oxide;

n is 0, 1, 2, or 3;

m is 0, 1, or 2; and

with the proviso that when L is (f), and R², R³ and R⁵ are each H, then R¹ is not -CH₃.

2. The compound of Claim 1, or a pharmaceutically acceptable salt,
5 solvate, ester, or tautomer thereof, wherein:

R¹ is selected from the group consisting of -(C₁-C₆)alkyl, -(C₁-C₆)alkenyl,
-(C₁-C₆)alkynyl, -(C₁-C₆)haloalkyl, -(C₁-C₆)alkyl substituted with one
hydroxyl group, -(C₃-C₇)cycloalkyl, -(C₁-C₆)alkylene-O-(C₁-C₆)alkyl,
-(C₁-C₆)alkylene-(C₆-C₁₀)aryl, -(C₁-C₆)alkylene-(C₂-C₁₀)heteroaryl,
10 -(C₁-C₆)alkylene-C(O)-O-(C₁-C₆)alkyl, -(CH₂)_n-N(R⁷)₂,
-(C₁-C₆)alkylene-(C₃-C₇)cycloalkyl, and
-(C₁-C₆)alkylene-(C₃-C₇)cycloalkenyl

wherein said -(C₃-C₇)cycloalkyl or the (C₃-C₇)cycloalkyl portion of
said -(C₁-C₆)alkylene-(C₃-C₇)cycloalkyl is unsubstituted or
15 substituted with one or more X groups, the (C₆-C₁₀)aryl portion
of said -(C₁-C₆)alkylene-(C₆-C₁₀)aryl is unsubstituted or
substituted with one or more Y groups, and the
(C₂-C₁₀)heteroaryl portion of said -(C₁-C₆)alkylene-
(C₂-C₁₀)heteroaryl is unsubstituted or substituted with one or
20 more Z groups;

R² is H, halogen, unsubstituted aryl, aryl substituted with one or more Y
groups, unsubstituted heteroaryl, or heteroaryl substituted with one or
more Y groups;

R¹ and R² together with the ring carbon atoms to which they are shown
25 attached, form a 5- or 6-membered cycloalkenyl ring;

R³ is selected from the group consisting of H, (C₁-C₆)alkyl,
-(C₃-C₆)alkylene-O-(C₁-C₆)alkyl, (C₃-C₇)cycloalkyl,
-(C₁-C₆)alkylene-(C₃-C₇)cycloalkyl, -(C₁-C₆)alkylene-C(O)-O-alkyl, and
(C₁-C₆)alkenyl,

30 wherein said (C₃-C₇)cycloalkyl or the (C₃-C₇)cycloalkyl portion of
said -(C₃-C₆)alkylene-(C₃-C₇)cycloalkyl of R³ is unsubstituted or
substituted with one or more X groups;

R^4 is selected from the group consisting of halogen, $-O-R^{10}$,
 $-C(O)-O-(C_1-C_6)alkyl$, $-S(O)_m-R^9$, $-N(R^7)_2$, $-O-N=C(R^{12})_2$,
 $-N(R^7)-NH-C(O)-O-(C_1-C_6)alkyl$ and $-C(O)-(C_1-C_6)alkyl$;

R^5 is selected from the group consisting of H, $-(C_1-C_6)alkyl$,
 5 $-(C_1-C_6)alkylene-C(O)-R^8$,
 $-(C_1-C_6)alkylene-C(=N-O-(C_1-C_6)alkyl)-(C_6-C_{10})aryl$, $(C_3-C_7)cycloalkyl$,
 $-(C_1-C_6)alkylene-(C_3-C_7)cycloalkyl$,
 $-(C_1-C_6)alkylene-C(O)-O-(C_1-C_6)alkyl$, and $(C_2-C_6)alkenyl$

wherein said $(C_3-C_7)cycloalkyl$ or the $(C_3-C_7)cycloalkyl$ portion of

10 said $-(C_1-C_6)alkylene-(C_3-C_7)cycloalkyl$ of R^5 is unsubstituted or
 substituted with one or more X groups, and the $(C_6-C_{10})aryl$
 portion of said

$-(C_1-C_6)alkylene-C(=N-O-(C_1-C_6)alkyl)-(C_6-C_{10})aryl$ of R^5 is
 unsubstituted or substituted with one or more Y groups;

15 R^6 is selected from the group consisting of $-OR^{10}$, halogen, and $-N(R^7)_2$;
 each R^7 is independently selected from the group consisting of H,
 $(C_1-C_6)alkyl$, $(C_3-C_7)cycloalkyl$, and $(C_6-C_{10})aryl$,

wherein said $(C_3-C_7)cycloalkyl$ of R^7 is unsubstituted or substituted
 with one or more X groups, and said $(C_6-C_{10})aryl$ of R^7 is

20 unsubstituted or substituted with one or more Y groups;

R^8 is selected from the group consisting of unsubstituted $(C_6-C_{10})aryl$,
 $(C_6-C_{10})aryl$ substituted with one or more Y groups, $-OH$, unsubstituted
 $(C_2-C_{10})heterocyclyl$, and $(C_2-C_{10})heterocyclyl$ substituted with one or
 more X groups;

25 R^9 is selected from the group consisting of $(C_1-C_6)alkyl$,
 $-(C_1-C_6)alkylene-(C_3-C_7)cycloalkyl$, $(C_2-C_6)alkenyl$, and
 $-(C_1-C_6)alkylene-(C_6-C_{10})aryl$,

wherein the $(C_3-C_7)cycloalkyl$ portion of said

30 $-(C_1-C_6)alkylene-(C_3-C_7)cycloalkyl$ of R^9 is unsubstituted or
 substituted with one or more X groups, and the $(C_6-C_{10})aryl$
 portion of said $-(C_1-C_6)alkylene-(C_6-C_{10})aryl$ of R^9 is
 unsubstituted or substituted with one or more groups Y;

R^{10} is selected from the group consisting of H, $(C_1-C_6)alkyl$,
 $-(C_1-C_6)alkylene-(C_6-C_{10})aryl$, $-(C_2-C_6)alkenylene-(C_6-C_{10})aryl$,

-(C₁-C₆)alkylene-(C₂-C₁₀)heteroaryl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, and
-(C₁-C₆)alkylene-(C₃-C₇)cycloalkyl,

wherein the (C₃-C₇)cycloalkyl portion of said

5 -(C₁-C₆)alkylene-(C₃-C₇)cycloalkyl of R¹⁰ is unsubstituted or
substituted with one or more X groups, the (C₆-C₁₀)aryl portion
of said -(C₁-C₆)alkylene-(C₆-C₁₀)aryl or -(C₂-C₆)alkenylene-
(C₆-C₁₀)aryl of R¹⁰ is unsubstituted or substituted with one or
more Y groups, and the (C₂-C₁₀)heteroaryl portion of said
10 -(C₁-C₆)alkylene-(C₂-C₁₀)heteroaryl of R¹⁰ is unsubstituted or
substituted with one or more Z groups;

each R¹² is independently a (C₁-C₆)alkyl;

R^a and R^b are each independently a (C₁-C₆)alkyl;

R^c is H;

R^d is selected from the group consisting of H, (C₁-C₆)alkyl, and

15 -(C₁-C₆)alkylene-(C₆-C₁₀)aryl,

wherein the (C₆-C₁₀)aryl portion of said

 -(C₁-C₆)alkylene-(C₆-C₁₀)aryl of R^d is unsubstituted or
substituted with one or more Y groups;

each X is independently selected from the group consisting of F, Cl, Br,

20 (C₁-C₆)alkyl, (C₁-C₆)haloalkyl, -O-(C₁-C₆)alkyl, -O-(C₁-C₆)haloalkyl, and
-OH;

each Y is independently selected from the group consisting of F, Br, Cl,

(C₁-C₆)alkyl, (C₁-C₆)haloalkyl, -O-(C₁-C₆)alkyl, -O-(C₁-C₆)haloalkyl,
-CN, -NO₂, -OH, , -S(O₂)-(C₁-C₆)alkyl, -S(O₂)-(C₆-C₁₀)aryl, -S(O₂)-NH₂,

25 -S(O₂)-NH-(C₁-C₆)alkyl, -S(O₂)-NH-(C₆-C₁₀)aryl,

-S(O₂)-N((C₁-C₆)alkyl)₂, -S(O₂)-N((C₆-C₁₀)aryl)₂,

-S(O₂)-N((C₁-C₆)alkyl)((C₆-C₁₀)aryl), and (C₆-C₁₀)aryl; and

each Z is independently selected from the group consisting of (C₁-C₆)alkyl,

(C₁-C₆)haloalkyl, F, Br, and Cl, -O-(C₁-C₆)alkyl, -CN, -OH, (C₆-C₁₀)aryl,

30 and N-oxide.

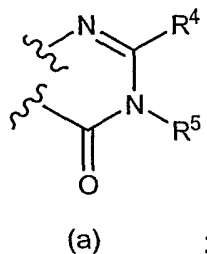
3. The compound of Claim 2, or a pharmaceutically acceptable salt,
solvate, ester, or tautomer thereof, wherein:

- R^1 is selected from the group consisting of $-\text{CH}_3$, $-\text{CH}_2\text{CH}_3$, $-\text{CH}_2\text{CH}_2\text{CH}_3$,
 $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$,
 $-\text{CH}_2\text{CH}_2\text{CH}(\text{CH}_3)_2$, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}(\text{CH}_3)_2$, $-\text{CH}(\text{CH}_3)_2$,
 $-\text{CH}_2\text{CH}_2\text{CH}=\text{CH}_2$, $-\text{CH}_2\text{CH}_2\text{CH}=\text{CHCH}_3$, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}=\text{CH}_2$,
5 $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}=\text{CH}_2$, $-\text{CH}_2\text{-OH}$, $-\text{CH}(\text{CH}_3)\text{-OH}$, cyclobutyl,
 $-\text{CH}_2\text{-C(O)-O-CH}_2\text{CH}_3$, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{-O-CH}_3$, $-\text{CH}_2\text{CF}_3$, $-\text{CHBrCH}_3$,
 $-\text{CH}_2\text{CH}_2\text{CF}_3$, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CF}_3$, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CF}_3$, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{Cl}$,
 $-\text{CH}_2\text{-(2-thiophenyl)}$, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{-(2-thiophenyl)}$, $-\text{CH}_2\text{-cyclopropyl}$,
 $-\text{CH}_2\text{CH}_2\text{-cyclopropyl}$, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{-cyclopropyl}$,
10 $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{-cyclopropyl}$, $-\text{CH}_2\text{-cyclobutyl}$, $-\text{CH}_2\text{CH}_2\text{-cyclobutyl}$,
 $-\text{CH}_2\text{CH}_2\text{CH}_2\text{-cyclobutyl}$, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{-cyclobutyl}$,
 $-\text{CH}_2\text{-cyclopentyl}$, $-\text{CH}_2\text{CH}_2\text{-cyclopentyl}$, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{-cyclopentyl}$,
 $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{-cyclopentyl}$, $-\text{CH}_2\text{-cyclohexyl}$, $-\text{CH}_2\text{-(4-methylcyclohexyl)}$,
 $-\text{CH}_2\text{CH}_2\text{-cyclohexyl}$, $-\text{CH}_2\text{-cycloheptyl}$, $-\text{CH}_2\text{-(2-cyclopentenyl)}$,
15 $-\text{CH}_2\text{CH}_2\text{C}\equiv\text{CH}$, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{C}\equiv\text{CH}$, $-\text{CH}_2\text{-phenyl}$,
 $-\text{CH}_2\text{-(2-fluorophenyl)}$, $-\text{CH}_2\text{-(3-fluorophenyl)}$, and $-\text{CH}_2\text{-NH(3-methoxyphenyl)}$;
- R^2 is selected from the group consisting of H, F, Cl, Br, unsubstituted aryl,
aryl substituted with one or more Y groups, unsubstituted heteroaryl, or
20 heteroaryl substituted with one or more Y groups; or
- R^1 and R^2 together with the ring carbon atoms to which they are shown
attached, form a cyclopentenyl or cyclohexenyl ring;
- R^3 is selected from the group consisting of H, $-\text{CH}_2\text{-cyclopropyl}$,
 $-\text{CH}_2\text{-C(O)-O-CH}_3$, cyclopropyl, cyclobutyl, cyclopentyl, cyclopentyl,
25 $-\text{CH}_3$, $-\text{CH}_2\text{CH}_3$, $-\text{CH}_2\text{CH}_2\text{CH}_3$, $-\text{CH}_2\text{CH}=\text{CH}_2$, and $-\text{CH}_2\text{-O-CH}_3$;
- R^4 is selected from the group consisting of Cl, $-\text{O-R}^{10}$, $-\text{C(O)-O-CH}_3$,
 $-\text{S(O)}_2\text{-CH}_3$, $-\text{S(O)-CH}_3$, $-\text{S(O)-CH}_2\text{CH}_3$, $-\text{S(O)-CH}(\text{CH}_3)_2$,
 $-\text{S(O)-C}(\text{CH}_3)_3$, $-\text{S(O)-CH}_2\text{-cyclopropyl}$, $-\text{S(O)-CH}_2\text{-phenyl}$,
 $-\text{S(O)-CH}(\text{CH}_3)\text{-phenyl}$, $-\text{S-CH}_2\text{-CH}=\text{CH}_2$, $-\text{N(R}^7)_2$, $-\text{O-N=C}(\text{CH}_3)_2$,
30 $-\text{NH-NH-C(O)-O-CH}_3$, and $-\text{C(O)-CH}_3$,
- wherein the phenyl portion of said $-\text{S(O)-CH}_2\text{-phenyl}$ or
 $-\text{S(O)-CH}(\text{CH}_3)\text{-phenyl}$ of R^4 is unsubstituted or substituted with
one or more groups Y;

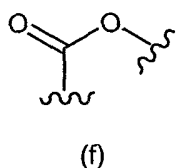
- R^5 is selected from the group consisting of H, $-\text{CH}_3$, $-\text{CH}_2\text{CH}_3$,
 $-\text{CH}_2\text{CH}_2\text{CH}_3$, $-\text{CH}_2\text{-C(O)-phenyl}$, $-\text{CH}_2\text{-C(O)-OH}$,
 $-\text{CH}_2\text{-C(=N-O-CH}_3\text{)-phenyl}$, cyclopropyl, cyclobutyl, cyclopentyl,
 $-\text{CH}_2\text{-C(O)-piperidyl}$, $-\text{CH}_2\text{-cyclopropyl}$, $-\text{CH}_2\text{-C(O)-O-CH}_3$, and
5 $-\text{CH}_2\text{-CH=CH}_3$,
wherein the phenyl portion of said $-\text{CH}_2\text{-C(O)-phenyl}$ is
unsubstituted or substituted with one or more Y groups;
 R^6 is selected from the group consisting of $-\text{O-R}^{10}$, Cl, and $-\text{N(R}^7\text{)}_2$;
each R^7 is independently selected from the group consisting of H,
10 cyclobutyl, unsubstituted phenyl, and phenyl substituted with one or
more Y groups;
 R^{10} is selected from the group consisting of H, $-\text{CH}_3$, $-\text{CH}_2\text{-cyclopropyl}$,
 $-\text{CH}_2\text{-CH=CH}_3$, $-\text{CH}_2\text{C}\equiv\text{C-CH}_3$, $-\text{CH}_2\text{-phenyl}$, $-\text{CH(CH}_3\text{)-phenyl}$,
 $-\text{CH(CH}_2\text{CH}_3\text{)-phenyl}$, $-\text{CH(CH}_2\text{CH}_2\text{CH}_3\text{)-phenyl}$,
15 $-\text{CH(CH(CH}_3\text{)}_2\text{)-phenyl}$, $-\text{CH(CH}_2\text{CH=CH}_2\text{)-phenyl}$, $-\text{CH}_2\text{-pyridyl}$,
 $-\text{CH(CH}_3\text{)-thiazolyl}$, and $-\text{CH}_2\text{-pyrimidinyl}$,
wherein the phenyl portion of said $-\text{CH}_2\text{-phenyl}$, $-\text{CH(CH}_3\text{)-phenyl}$,
 $-\text{CH(CH}_2\text{CH}_3\text{)-phenyl}$, $-\text{CH(CH}_2\text{CH}_2\text{CH}_3\text{)-phenyl}$,
 $-\text{CH(CH(CH}_3\text{)}_2\text{)-phenyl}$, or $-\text{CH(CH}_2\text{CH=CH}_2\text{)-phenyl}$ of R^{10} is
20 unsubstituted or substituted with one or more groups Y, and the
pyridyl, thiazolyl, or pyrimidinyl portion of said $-\text{CH}_2\text{-pyridyl}$,
 $-\text{CH}_2\text{-thiazolyl}$, or $-\text{CH}_2\text{-pyrimidinyl}$ portion of R^{10} is unsubstituted
or substituted with one or more groups Z;
 R^a and R^b are each $-\text{CH}_3$;
25 R^c is H;
 R^d is selected from the group consisting of H, $-\text{CH}_3$, and $-\text{CH}_2\text{-phenyl}$,
wherein the phenyl portion of said $-\text{CH}_2\text{-phenyl}$ of R^d is
unsubstituted or substituted with one or more Y groups;
each Y is independently selected from the group consisting of F, Cl, Br,
30 $-\text{CH}_3$, $-\text{CF}_3$, $-\text{O-CH}_3$, $-\text{O-CF}_3$, $-\text{CN}$, $-\text{OH}$, and phenyl; and
each Z is independently selected from the group consisting of $-\text{CH}_3$, $-\text{CF}_3$,
F, Br, and Cl, $-\text{O-CH}_3$, $-\text{CN}$, $-\text{OH}$, phenyl, and N-oxide.

4. The compound of Claim 1, or a pharmaceutically acceptable salt, solvate, ester, or tautomer thereof, wherein:

Q is:



5 L is:



R¹ is selected from the group consisting of -(C₁-C₆)alkyl, -(C₁-C₆)alkylene-O-(C₁-C₆)alkyl, unsubstituted (C₆-C₁₀)aryl, and (C₆-C₁₀)aryl substituted with one or more substituents Y;

10 R² is H or halogen;

R⁴ is selected from the group consisting of halogen, -O-R¹⁰, -C(O)-O-(C₁-C₆)alkyl, -S(O)_m-R⁹, -N(R⁷)₂, -O-N=C(R¹²)₂, -N(R⁷)-NH-C(O)-O-(C₁-C₆)alkyl, and -C(O)-(C₁-C₆)alkyl;

R⁵ is H or (C₁-C₆)alkyl;

15 each R⁷ is independently selected from the group consisting of H, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, unsubstituted (C₆-C₁₀)aryl, and (C₆-C₁₀)aryl substituted with one or more Y groups;

R⁹ is selected from the group consisting of (C₁-C₆)alkyl, -(C₁-C₆)alkylene-(C₃-C₆)cycloalkyl, (C₂-C₆)alkenyl, and -(C₁-C₆)alkylene-(C₆-C₁₀)aryl,

20 wherein the (C₆-C₁₀)aryl of said -(C₁-C₆)alkylene-(C₆-C₁₀)aryl of R⁹ is unsubstituted or substituted with one or more groups Y;

R¹⁰ is selected from the group consisting of H, (C₁-C₆)alkyl, -(C₁-C₆)alkylene-(C₆-C₁₀)aryl, -(C₁-C₆)alkenylene-(C₆-C₁₀)aryl, 25 -(C₁-C₆)alkylene-(C₂-C₁₀)heteroaryl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, and -(C₁-C₆)alkylene-(C₃-C₆)cycloalkyl,

wherein the aryl of said $-(C_1-C_6)alkylene-(C_6-C_{10})aryl$ or
 $-(C_1-C_6)alkenylene-(C_6-C_{10})aryl$ of R^{10} is unsubstituted or
substituted with one or more groups Y, and the
 $(C_2-C_{10})heteroaryl$ of said $-(C_1-C_6)alkylene-(C_2-C_{10})heteroaryl$ of
5 R^{10} is unsubstituted or substituted with one or more groups Z;
each R^{12} is independently selected from the group consisting of
 $(C_1-C_6)alkyl$, $(C_6-C_{10})aryl$, and $(C_2-C_{10})heteroaryl$,
wherein said $(C_6-C_{10})aryl$ is unsubstituted or substituted with one or
more Y group, and said $(C_2-C_{10})heteroaryl$ is unsubstituted or
10 substituted with one or more Z group;
each Y is independently selected from the group consisting of halogen,
 $(C_1-C_6)alkyl$, $(C_1-C_6)haloalkyl$, $-O-(C_1-C_6)haloalkyl$, $-O-(C_1-C_6)alkyl$,
 $-CN$, $-NO_2$, $-OH$, $-S(O_2)-(C_1-C_6)alkyl$, $-S(O_2)-(C_6-C_{10})aryl$, $-S(O_2)-NH_2$,
 $-S(O_2)-NH-(C_1-C_6)alkyl$, $-S(O_2)-NH-(C_6-C_{10})aryl$,
15 $-S(O_2)-N((C_1-C_6)alkyl)_2$, $-S(O_2)-N((C_6-C_{10})aryl)_2$,
 $-S(O_2)-N((C_1-C_6)alkyl)((C_6-C_{10})aryl)$, and $(C_6-C_{10})aryl$; and
each Z is independently selected from the group consisting of $(C_1-C_6)alkyl$,
 $(C_1-C_6)haloalkyl$, halogen, $-O-alkyl$, $-O-(C_1-C_6)haloalkyl$, $-CN$, $-OH$,
 $(C_6-C_{10})aryl$, and, and N-oxide.

20

5. The compound of Claim 4, or a pharmaceutically acceptable salt,
solvate, ester, or tautomer thereof, wherein:

R^1 is $-CH_2CH_3$, butyl, pentyl or $-CH_2CH_2CH_2-cyclopropyl$;

R^2 is H, Br, unsubstituted aryl, aryl substituted with one or more Y groups,
25 unsubstituted heteroaryl, or heteroaryl substituted with one or more Y
groups;

R^4 is selected from the group consisting of Cl, $-O-R^{10}$, $-C(O)-O-CH_3$,
 $-S(O)-CH_3$, $-S(O)-CH_2CH_3$, $-S(O)-CH(CH_3)_2$, $-S(O)-C(CH_3)_3$,
 $-S(O)-CH_2-cyclopropyl$, $-S-CH_2-CH=CH_2$, $-S(O)-CH_2-phenyl$,
30 $-S(O)-CH(CH_3)-phenyl$, $-N(R^7)_2$, $-O-N=C(CH_3)_2$, $-NH-NH-C(O)-O-CH_3$,
and $-C(O)-CH_3$,

wherein the phenyl portion of said $-S(O)-CH_2-phenyl$, or
 $-S(O)-CH(CH_3)-phenyl$ of R^4 is unsubstituted or substituted with
one or more groups Y;

R^5 is H or $-\text{CH}_2\text{CH}_3$;

each R^7 is independently selected from the group consisting of H and cyclobutyl;

R^{10} is selected from the group consisting of H, $-\text{CH}_3$, $-\text{CH}_2$ -cyclopropyl,
 5 $-\text{CH}_2$ - $\text{CH}=\text{CH}_2$, $-\text{CH}_2\text{C}\equiv\text{C}-\text{CH}_3$, $-\text{CH}_2$ -phenyl, $-\text{CH}(\text{CH}_3)$ -phenyl,
 $-\text{CH}(\text{CH}_2\text{CH}_3)$ -phenyl, $-\text{CH}(\text{CH}(\text{CH}_3)_2)$ -phenyl,
 $-\text{CH}(\text{CH}_2\text{CH}_2\text{CH}_3)$ -phenyl, $-\text{CH}(\text{CH}_2\text{CH}=\text{CH}_2)$ -phenyl, $-\text{CH}_2$ -pyridyl,
 $-\text{CH}(\text{CH}_3)$ -thiazolyl, $-\text{CH}_2$ -pyrimidinyl,

wherein the phenyl portion of said $-\text{CH}_2$ -phenyl,

10 $-\text{CH}(\text{CH}_3)$ -phenyl, $-\text{CH}(\text{CH}_2\text{CH}_3)$ -phenyl,
 $-\text{CH}(\text{CH}(\text{CH}_3)_2)$ -phenyl, $-\text{CH}(\text{CH}_2\text{CH}=\text{CH}_2)$ -phenyl, or
 $-\text{CH}(\text{CH}_2\text{CH}_2\text{CH}_3)$ -phenyl of R^{10} is unsubstituted or
 substituted with one or more groups Y, and the pyridyl,
 thiazolyl, or pyrimidinyl portion of said $-\text{CH}_2$ -pyridyl,
 15 $-\text{CH}(\text{CH}_3)$ -thiazolyl, or $-\text{CH}_2$ -pyrimidinyl of R^{10} is

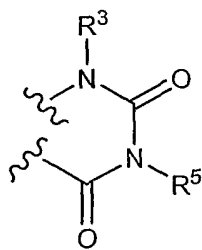
unsubstituted or substituted with one or more groups Z;

each Y is independently selected from the group consisting of F, Cl, Br,
 $-\text{CH}_3$, $-\text{CF}_3$, $-\text{O}-\text{CH}_3$, $-\text{O}-\text{CF}_3$, and phenyl; and

each Z is independently selected from the group consisting of $-\text{CH}_3$,
 20 phenyl, and N-oxide.

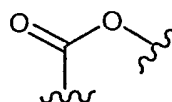
6. The compound of Claim 1, or a pharmaceutically acceptable salt, solvate, ester, or tautomer thereof, wherein:

Q is:



(b) ;

L is:



(f) ;

R^1 is selected from the group consisting of $-(C_1-C_6)alkyl$, $-(C_1-C_6)alkenyl$, $-(C_1-C_6)alkynyl$, $-(C_1-C_6)alkylene-C(O)-O-(C_1-C_6)alkyl$, $-(C_3-C_7)cycloalkyl$, $-(C_1-C_6)alkylene-O-(C_1-C_6)alkyl$, $-(C_1-C_6)alkylene-(C_6-C_{10})aryl$, $-(C_1-C_6)alkylene-(C_2-C_{10})heteroaryl$, $-(C_1-C_6)alkylene-(C_3-C_7)cycloalkyl$, $-(C_1-C_6)alkylene-(C_3-C_7)cycloalkenyl$, $(C_1-C_6)alkyl$ substituted with one or more hydroxyl groups, $-(CH_2)_n-N(R^7)_2$, and $-(C_1-C_6)haloalkyl$

wherein said $-(C_3-C_7)cycloalkyl$ or the $(C_3-C_7)cycloalkyl$ portion of said $-(C_1-C_6)alkylene-(C_3-C_7)cycloalkyl$ is unsubstituted or substituted with one or more X groups, the $(C_6-C_{10})aryl$ portion of said $-(C_1-C_6)alkylene-(C_6-C_{10})aryl$ is unsubstituted or substituted with one or more Y groups, and the $(C_2-C_{10})heteroaryl$ portion of said $-(C_1-C_6)alkylene-(C_2-C_{10})heteroaryl$ is unsubstituted or substituted with one or more Z groups;

R^2 is H;

R^3 is selected from the group consisting of H, $(C_1-C_6)alkyl$, $(C_3-C_6)cycloalkyl$, $-(C_1-C_6)alkylene-(C_3-C_6)cycloalkyl$, $-(C_1-C_6)alkylene-C(O)-O-(C_1-C_6)alkyl$, $(C_2-C_6)alkenyl$, and $-(C_1-C_6)alkylene-O-(C_1-C_6)alkyl$;

R^5 is selected from the group consisting of H, $-(C_1-C_6)alkyl$, $(C_2-C_6)alkenyl$, $-(C_1-C_6)alkylene-C(O)-R^8$, $-(C_1-C_6)alkylene-C(=N-O-(C_1-C_6)alkyl)-(C_6-C_{10})aryl$, $(C_3-C_6)cycloalkyl$, $-(C_1-C_6)alkylene-(C_3-C_6)cycloalkyl$, and $-(C_1-C_6)alkylene-C(O)-O-(C_1-C_6)alkyl$;

each R^7 is independently selected from the group consisting of H and aryl, wherein said aryl of R^7 is unsubstituted or substituted with one or more Y groups;

R^8 is selected from the group consisting of unsubstituted $(C_6-C_{10})aryl$, $(C_6-C_{10})aryl$ substituted with one or more Y groups, $-OH$, unsubstituted

(C₂-C₁₀)heterocyclyl and (C₂-C₁₀)heterocyclyl substituted with one or more X groups;

each X is independently selected from the group consisting of halogen, (C₁-C₆)alkyl, (C₁-C₆)haloalkyl, -O-(C₁-C₆)alkyl, -O-(C₁-C₆)haloalkyl, and -OH;

each Y is independently selected from the group consisting of halogen, (C₁-C₆)alkyl, (C₁-C₆)haloalkyl, -O-(C₁-C₆)haloalkyl, -O-(C₁-C₆)alkyl, -CN, -NO₂, -OH, -S(O₂)-(C₁-C₆)alkyl, -S(O₂)-(C₆-C₁₀)aryl, -S(O₂)-NH₂, -S(O₂)-NH-(C₁-C₆)alkyl, -S(O₂)-NH-(C₆-C₁₀)aryl, -S(O₂)-N((C₁-C₆)alkyl)₂, -S(O₂)-N((C₆-C₁₀)aryl)₂, -S(O₂)-N((C₁-C₆)alkyl)((C₆-C₁₀)aryl), and (C₆-C₁₀)aryl; and

each Z is independently selected from the group consisting of (C₁-C₆)alkyl, (C₁-C₆)haloalkyl, F, Br, and Cl, -O-(C₁-C₆)alkyl, -CN, -OH, (C₆-C₁₀)aryl, and N-oxide.

7. The compound of Claim 6, or a pharmaceutically acceptable salt, solvate, ester, or tautomer thereof, wherein:

R¹ is selected from the group consisting of -CH₃, -CH₂CH₃, -CH₂CH₂CH₃, -CH₂CH₂CH₂CH₃, -CH₂CH₂CH₂CH₂CH₃, -CH₂CH₂CH₂CH₂CH₂CH₃, -CH₂CH₂CH(CH₃)₂, -CH₂CH₂CH₂CH(CH₃)₂, -CH(CH₃)₂, -CH₂-C(O)-O-CH₂CH₃, -CH₂CF₃, -CH₂CH₂CH=CH₂, -CH₂CH₂CH=CHCH₃, -CH₂CH₂CH₂CH₂CH=CH₂, -CH₂CH₂CH₂CH=CH₂, -CH₂OH, -CH(CH₃)OH, -CH₂N(R⁷)₂, cyclobutyl, -CH₂CH₂CH₂-O-CH₃, -CH₂CH₂CF₃, -CH₂CH₂CH₂CF₃, -CH₂CH₂CH₂CH₂CF₃, -CH₂CH₂CH₂Cl, -CH₂-(2-thiophenyl), -CH₂CH₂CH₂-(2-thiophenyl), -CH₂-cyclopropyl, -CH₂CH₂-cyclopropyl, -CH₂CH₂CH₂-cyclopropyl, -CH₂CH₂CH₂CH₂-cyclopropyl, -CH₂-cyclopentyl, -CH₂CH₂-cyclopentyl, -CH₂-cyclohexyl, -CH₂-(4-methylcyclohexyl), -CH₂CH₂-cyclohexyl, -CH₂-cycloheptyl, -CH₂-(2-cyclopentenyl), -CH₂CH₂C≡CH, -CH₂CH₂CH₂C≡CH, -CH₂-phenyl, -CH₂-(2-fluorophenyl), -CH₂-(3-fluorophenyl), and -CHBrCH₃;

R² is H; or

R¹ and R² together with the ring carbon atoms to which they are shown attached, form a cyclopentenyl or cyclohexenyl ring;

R^3 is selected from the group consisting of H, $-\text{CH}_2\text{-cyclopropyl}$,
 $-\text{CH}_2\text{-C(O)-O-CH}_3$, $-\text{cyclopropyl}$, cyclobutyl , cyclopentyl , $-\text{CH}_3$,
 $-\text{CH}_2\text{CH}_3$, $-\text{CH}_2\text{CH}_2\text{CH}_3$, $-\text{CH}_2\text{CH=CH}_2$, and $-\text{CH}_2\text{-O-CH}_3$;

R^5 is selected from the group consisting of H, $-\text{CH}_2\text{-cyclopropyl}$,
 5 $-\text{CH}_2\text{-C(O)-O-CH}_3$, $-\text{CH}_2\text{-C(O)-R}^8$, $-\text{CH}_2\text{-C(=N-O-CH}_3\text{)-phenyl}$,
 cyclopropyl , cyclobutyl , cyclopentyl , $-\text{CH}_3$, $-\text{CH}_2\text{CH}_3$, $-\text{CH}_2\text{CH}_2\text{CH}_3$, and
 $-\text{CH}_2\text{CH=CH}_2$;

Each R^7 is independently H or phenyl,

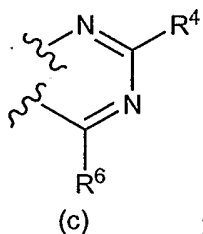
wherein said phenyl of R^7 is unsubstituted or substituted with one or
 10 more Y groups;

R^8 is selected from the group consisting of unsubstituted phenyl, phenyl
 substituted with one or more Y groups, $-\text{OH}$, and piperidyl; and
 each Y is independently selected from the group consisting of F, $-\text{CF}_3$,
 $-\text{OCH}_3$, $-\text{CN}$, and $-\text{OH}$.

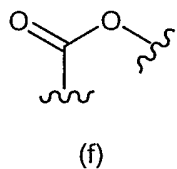
15

8. The compound of Claim 1, or a pharmaceutically acceptable salt,
 solvate, ester, or tautomer thereof, wherein:

Q is:



20 L is:



R^1 is selected from the group consisting of $-(\text{C}_1\text{-C}_6)\text{alkyl}$, $-(\text{C}_1\text{-C}_6)\text{alkenyl}$,
 $-(\text{C}_1\text{-C}_6)\text{alkynyl}$, $-(\text{C}_1\text{-C}_6)\text{alkylene-C(O)-O-(C}_1\text{-C}_6)\text{alkyl}$,
 $-(\text{C}_3\text{-C}_7)\text{cycloalkyl}$, $-(\text{C}_1\text{-C}_6)\text{alkylene-O-(C}_1\text{-C}_6)\text{alkyl}$,
 25 $-(\text{C}_1\text{-C}_6)\text{alkylene-(C}_6\text{-C}_{10})\text{aryl}$, $-(\text{C}_1\text{-C}_6)\text{alkylene-(C}_2\text{-C}_{10})\text{heteroaryl}$,
 $-(\text{C}_1\text{-C}_6)\text{alkylene-(C}_3\text{-C}_7)\text{cycloalkyl}$,
 $-(\text{C}_1\text{-C}_6)\text{alkylene-(C}_3\text{-C}_7)\text{cycloalkenyl}$, $-(\text{C}_1\text{-C}_6)\text{alkyl}$ substituted with one
 or more hydroxyl groups, $-(\text{CH}_2)_n\text{-N(R}^7)_2$, and $-(\text{C}_1\text{-C}_6)\text{haloalkyl}$

wherein said $-(C_3-C_7)$ cycloalkyl or the (C_3-C_7) cycloalkyl portion of said $-(C_1-C_6)$ alkylene- (C_3-C_7) cycloalkyl is unsubstituted or substituted with one or more X groups, the (C_6-C_{10}) aryl portion of said $-(C_1-C_6)$ alkylene- (C_6-C_{10}) aryl is unsubstituted or substituted with one or more Y groups, and the (C_2-C_{10}) heteroaryl portion of said $-(C_1-C_6)$ alkylene- (C_2-C_{10}) heteroaryl is unsubstituted or substituted with one or more Z groups;

R^2 is H; or

R^1 and R^2 together with the ring carbon atoms to which they are shown attached, form a 5- or 6-membered cycloalkenyl ring;

R^4 is selected from the group consisting of halogen, $-O-R^{10}$, $-C(O)-O-(C_1-C_6)$ alkyl, $-S(O)_m-R^9$, $-N(R^7)_2$, $-O-N=C(R^{12})_2$, $-N(R^7)-NH-C(O)-O-(C_1-C_6)$ alkyl, and $-C(O)-(C_1-C_6)$ alkyl;

R^6 is selected from the group consisting of $-O-R^{10}$, halogen, and $-N(R^7)_2$; each R^7 is independently selected from the group consisting of H, (C_1-C_6) alkyl, (C_3-C_6) cycloalkyl, unsubstituted (C_6-C_{10}) aryl, and (C_6-C_{10}) aryl substituted with one or more Y groups;

R^9 is selected from the group consisting of (C_1-C_6) alkyl, $-(C_1-C_6)$ alkylene- (C_3-C_6) cycloalkyl, (C_2-C_6) alkenyl, and $-(C_1-C_6)$ alkylene- (C_6-C_{10}) aryl,

wherein the (C_6-C_{10}) aryl portion of said $-(C_1-C_6)$ alkylene- (C_6-C_{10}) aryl of R^9 is unsubstituted or substituted with one or more groups Y;

R^{10} is selected from the group consisting of H, (C_1-C_6) alkyl, $-(C_1-C_6)$ alkylene- (C_6-C_{10}) aryl, $-(C_1-C_6)$ alkenylene- (C_6-C_{10}) aryl, $-(C_1-C_6)$ alkylene- (C_2-C_{10}) heteroaryl, (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, and $-(C_1-C_6)$ alkylene- (C_3-C_6) cycloalkyl

wherein the aryl portion of said $-(C_1-C_6)$ alkylene- (C_6-C_{10}) aryl or $-(C_1-C_6)$ alkenylene- (C_6-C_{10}) aryl of R^{10} is unsubstituted or substituted with one or more groups Y, and the (C_2-C_{10}) heteroaryl portion of said $-(C_1-C_6)$ alkylene- (C_2-C_{10}) heteroaryl of R^{10} is unsubstituted or substituted with one or more groups Z;

each R¹² is independently (C₁-C₆)alkyl;

each Y is independently selected from the group consisting of F, Br, Cl,

(C₁-C₆)alkyl, (C₁-C₆)haloalkyl, -O-(C₁-C₆)alkyl, -O-(C₁-C₆)haloalkyl,

-CN, -NO₂, -OH, , -S(O₂)-(C₁-C₆)alkyl, -S(O₂)-(C₆-C₁₀)aryl, -S(O₂)-NH₂,

5 -S(O₂)-NH-(C₁-C₆)alkyl, -S(O₂)-NH-(C₆-C₁₀)aryl,

-S(O₂)-N((C₁-C₆)alkyl)₂, -S(O₂)-N((C₆-C₁₀)aryl)₂,

-S(O₂)-N((C₁-C₆)alkyl)((C₆-C₁₀)aryl), and (C₆-C₁₀)aryl; and

each Z is independently selected from the group consisting of (C₁-C₆)alkyl,

(C₁-C₆)haloalkyl, F, Br, and Cl, -O-(C₁-C₆)alkyl, -CN, -OH, (C₆-C₁₀)aryl,

10 and N-oxide.

9. The compound of Claim 8, or a pharmaceutically acceptable salt, solvate, ester, or tautomer thereof, wherein:

R¹ is selected from the group consisting of -CH₃, -CH₂CH₃, -CH₂CH₂CH₃,

15 -CH₂CH₂CH₂CH₃, -CH₂CH₂CH₂CH₂CH₃, -CH₂CH₂CH₂CH₂CH₂CH₃,

-CH₂CH₂CH(CH₃)₂, -CH₂CH₂CH₂CH(CH₃)₂, -CH(CH₃)₂, -

CH₂-C(O)-O-CH₂CH₃, -CH₂-OH, -CH(CH₃)-OH, -CH₂CH₂CH=CH₂,

-CH₂CH₂CH=CHCH₃, -CH₂CH₂CH₂CH₂CH=CH₂,

-CH₂CH₂CH₂CH=CH₂, cyclobutyl, -CH₂CH₂CH₂-O-CH₃, -CH₂CH₂CF₃,

20 -CH₂CH₂CH₂CF₃, -CH₂CH₂CH₂CH₂CF₃, -CH₂CH₂CH₂Cl, , -CH₂-(2-

thiophenyl), -CH₂CH₂CH₂-(2-thiophenyl), -CH₂-cyclopropyl,

-CH₂CH₂-cyclopropyl, -CH₂CH₂CH₂-cyclopropyl,

-CH₂CH₂CH₂CH₂-cyclopropyl, -CH₂-cyclopentyl, -CH₂CH₂-cyclopentyl,

-CH₂-cyclohexyl, -CH₂-(4-methylcyclohexyl), -CH₂CH₂-cyclohexyl,

25 -CH₂-cycloheptyl, -CH₂-(2-cyclopentenyl), -CH₂CH₂C≡CH,

-CH₂CH₂CH₂C≡CH, -CH₂-phenyl, -CH₂-(2-fluorophenyl),

-CH₂-(3-fluorophenyl), -CHBrCH₃ and -CH₂CF₃;

R² is H; or

R¹ and R² together with the ring carbon atoms to which they are shown

30 attached, form a cyclopentenyl or cyclohexenyl ring

R⁴ is selected from the group consisting of Cl, -O-R¹⁰, -C(O)-O-CH₃,

-S(O)₂-CH₃, -S(O)-CH₃, -S(O)-CH₂CH₃, -S(O)-CH(CH₃)₂,

-S(O)-C(CH₃)₃, -S(O)-CH₂-cyclopropyl, -S-CH₂-CH=CH₂,

-S(O)-CH₂-phenyl, -S(O)-CH(CH₃)-phenyl, -N(R⁷)₂, -O-N=C(CH₃)₂,
-NH-NH-C(O)-O-CH₃, and -C(O)-CH₃,

wherein the phenyl portion of said -S(O)-CH₂-phenyl, or

-S(O)-CH(CH₃)-phenyl of R⁴ is unsubstituted or substituted with

5 one or more groups Y;

R⁶ is selected from the group consisting of -O-R¹⁰, -N(R⁷)₂, and Cl;

each R⁷ is independently selected from the group consisting of H,

unsubstituted phenyl, phenyl substituted with one or more Y groups,
and cyclobutyl;

10 R¹⁰ is selected from the group consisting of H, CH₃, -CH₂-cyclopropyl,

-CH₂-C≡C-CH₃, -CH₂-CH=CH₂, -CH₂-phenyl, -CH(CH₃)-phenyl,

-CH(CH₂CH₃)-phenyl, -CH(CH(CH₃)₂)-phenyl,

-CH(CH₂CH₂CH₃)-phenyl, -CH(CH₂CH=CH₂)-phenyl, -CH₂-pyridyl,

-CH(CH₃)-thiazolyl, -CH₂-pyrimidinyl,

15 wherein the phenyl portion of said -CH₂-phenyl, -CH(CH₃)-phenyl,

-CH(CH₂CH₃)-phenyl, -CH(CH₂CH=CH₂)-phenyl, or

-CH(CH₂CH₂CH₃)-phenyl, of R¹⁰ is unsubstituted or substituted

with one or more groups Y, and the pyridyl, thiazolyl, or

pyrimidinyl portion of said -CH₂-pyridyl, -CH(CH₃)-thiazolyl, or

20 -CH₂-pyrimidinyl of R¹⁰ is unsubstituted or substituted with one
or more groups Z;

each Y is independently selected from the group consisting of F, Cl, Br,

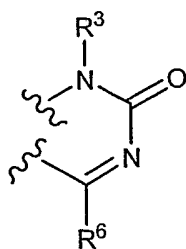
-CH₃, -CF₃, -O-CH₃, -O-CF₃, -CN, -OH, and phenyl; and

each Z is independently selected from the group consisting of -CH₃, F, Br,

25 and Cl, -O-CH₃, -CN, -OH, phenyl, and N-oxide.

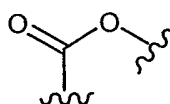
10. The compound of Claim 1, or a pharmaceutically acceptable salt,
solvate, ester, or tautomer thereof, wherein:

Q is:



(d) ;

L is:

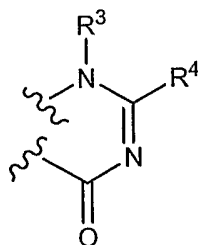


(f) ;

R¹ is -(C₁-C₆)alkyl;5 R² is H;R³ is H or -(C₂-C₆)alkenyl; andR⁶ is -OH or -O-(C₁-C₆)alkylene-(C₁-C₆)cycloalkyl.

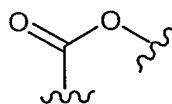
11. The compound of claim 1, or a pharmaceutically acceptable salt,
 10 solvate, ester, or tautomer thereof, wherein:

Q is:



(e) ;

L is:



(f) ;

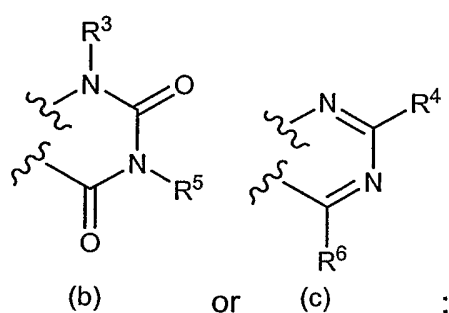
15 R¹ is -(C₁-C₆)alkyl or -(C₁-C₆)haloalkyl;R² is H;

R³ is selected from the group consisting of H,
 -(C₁-C₆)alkylene-(C₁-C₆)cycloalkyl,

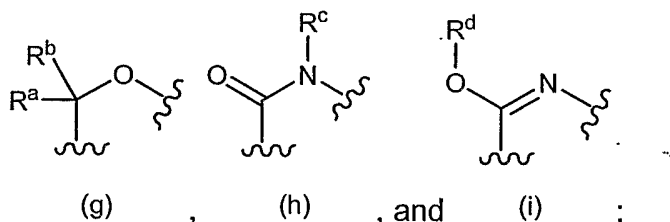
-(C₁-C₆)alkylene-C(O)-O-(C₁-C₆)alkyl, -(C₁-C₆)cycloalkyl, (C₁-C₆)alkyl, (C₂-C₆)alkenyl, and -(C₁-C₆)alkylene-O-(C₁-C₆)alkyl; and R⁴ is -O-N=C((C₁-C₆)alkyl)₂.

- 5 12. The compound of Claim 1, or a pharmaceutically acceptable salt, solvate, ester, or tautomer thereof, wherein:

Q is:



- 10 L is selected from the group consisting of:



R^a and R^b are each independently selected from the group consisting of H, (C₁-C₆)alkyl, (C₆-C₁₀)aryl, and (C₂-C₁₀)heteroaryl,

wherein said (C₆-C₁₀)aryl of R^a and R^b is unsubstituted or

- 15 substituted with one or more Y groups, and said (C₂-C₁₀)heteroaryl of R^a and R^b is unsubstituted or substituted with one or more Z groups;

R^c is selected from the group consisting of H, (C₁-C₆)alkyl, -(C₁-C₆)alkylene-(C₆-C₁₀)aryl, and -C(O)-(C₁-C₆)alkyl,

- 20 wherein the (C₆-C₁₀)aryl portion of said -(C₁-C₆)alkylene-(C₆-C₁₀)aryl of R^c is unsubstituted or substituted with one or more Y groups;

R^d is selected from the group consisting of H, (C₁-C₆)alkyl, and -(C₁-C₆)alkylene-(C₆-C₁₀)aryl,

wherein the (C₆-C₁₀)aryl portion of said

-(C₁-C₆)alkylene-(C₆-C₁₀)aryl of R^d is unsubstituted or substituted with one or more Y groups;

R¹ is (C₁-C₆)alkyl or or -(C₁-C₆)haloalkyl;

5 R² is H;

R³ is H;

R⁴ is -O-R¹⁰;

R⁵ is H or -(C₁-C₆)alkylene-cycloalkyl;

R⁶ is -O-R¹⁰;

10 R¹⁰ is H, (C₁-C₆)alkyl, or -(C₁-C₆)alkylene-(C₆-C₁₀)aryl; and

each Y is independently selected from the group consisting of F, Br, Cl,

(C₁-C₆)alkyl, (C₁-C₆)haloalkyl, -O-(C₁-C₆)alkyl, -O-(C₁-C₆)haloalkyl,

-CN, -NO₂, -OH, -S(O₂)-(C₁-C₆)alkyl, -S(O₂)-(C₆-C₁₀)aryl, -S(O₂)-NH₂,

-S(O₂)-NH-(C₁-C₆)alkyl, -S(O₂)-NH-(C₆-C₁₀)aryl,

15 -S(O₂)-N((C₁-C₆)alkyl)₂, -S(O₂)-N((C₆-C₁₀)aryl)₂,

-S(O₂)-N((C₁-C₆)alkyl)((C₆-C₁₀)aryl), and (C₆-C₁₀)aryl; and

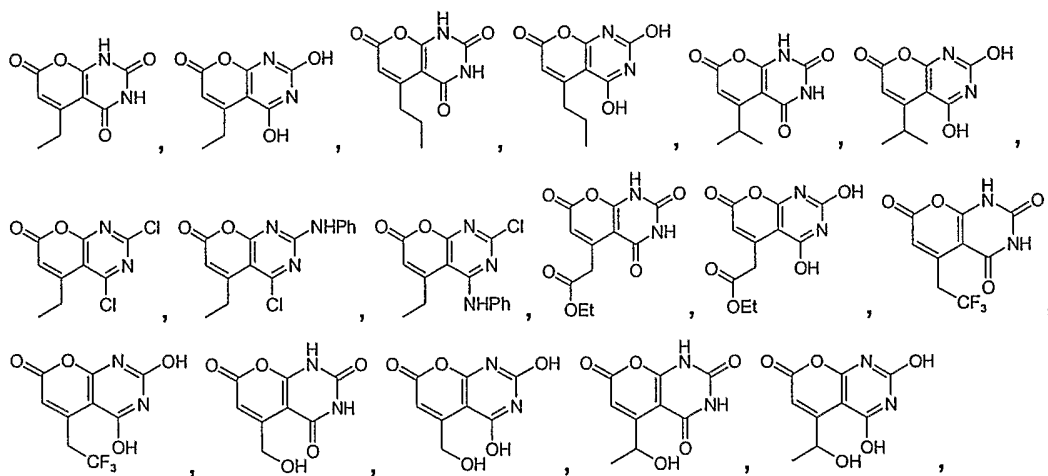
each Z is independently selected from the group consisting of (C₁-C₆)alkyl,

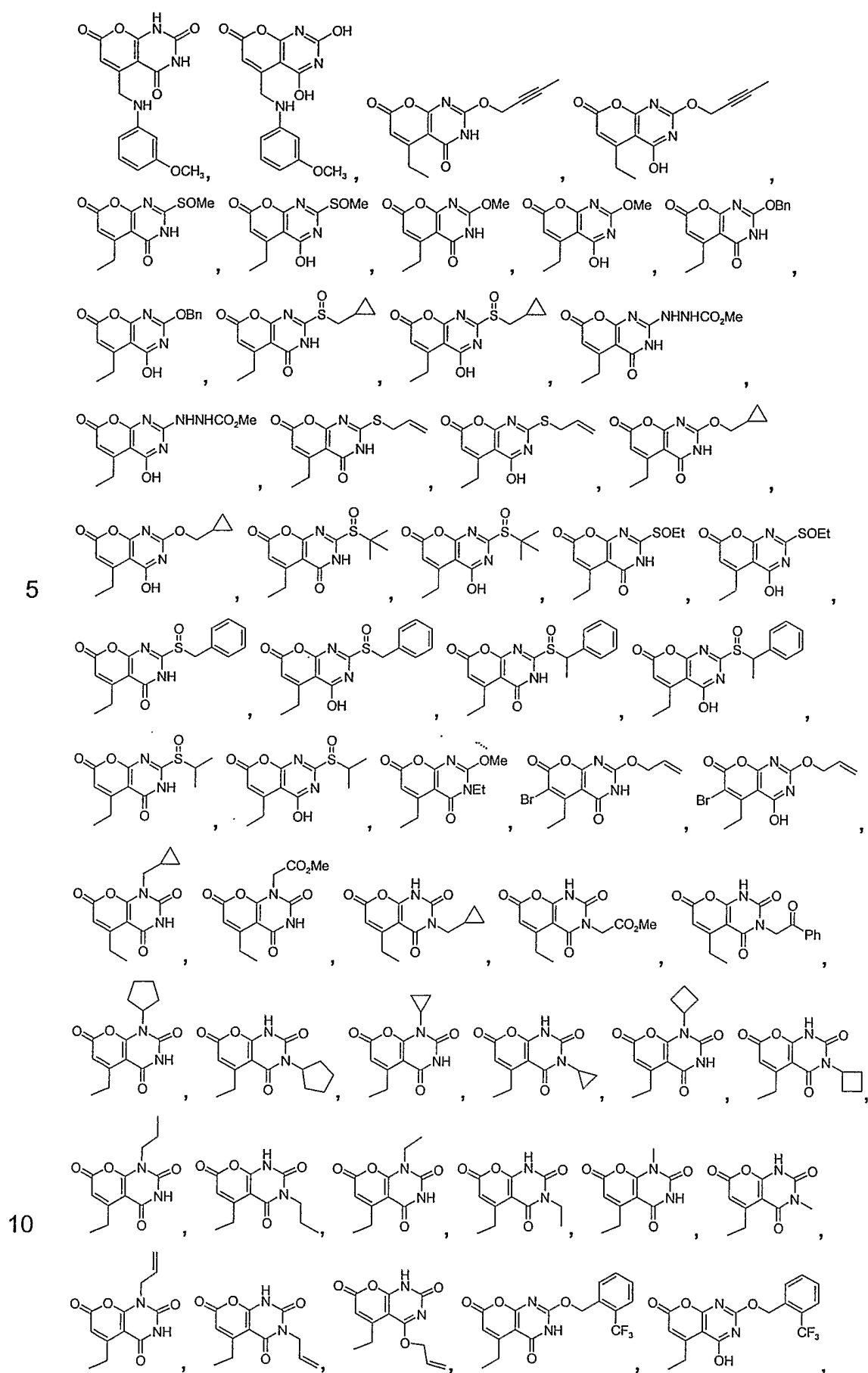
(C₁-C₆)haloalkyl, F, Br, and Cl, -O-(C₁-C₆)alkyl, -CN, -OH, (C₆-C₁₀)aryl,

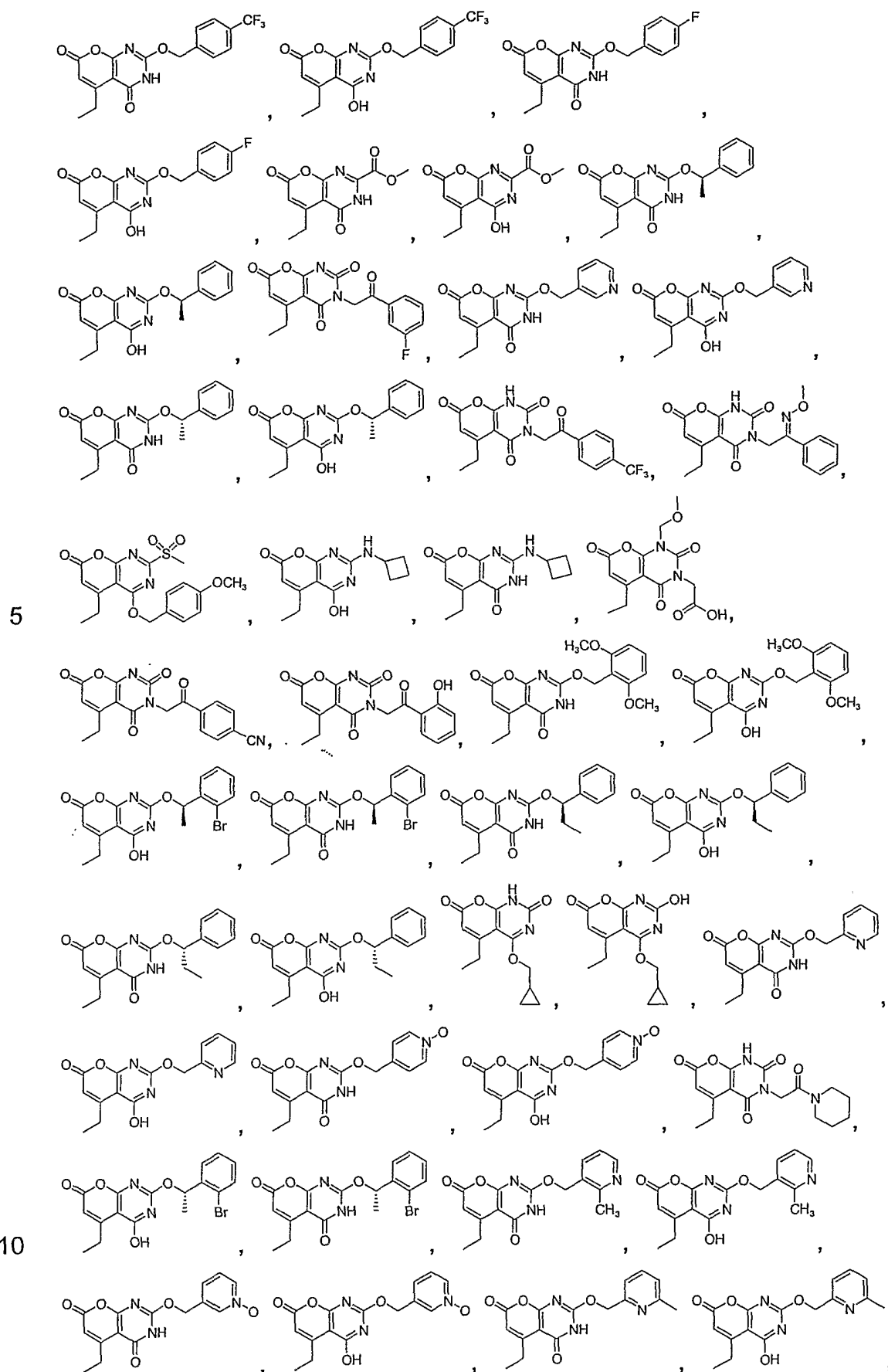
and N-oxide.

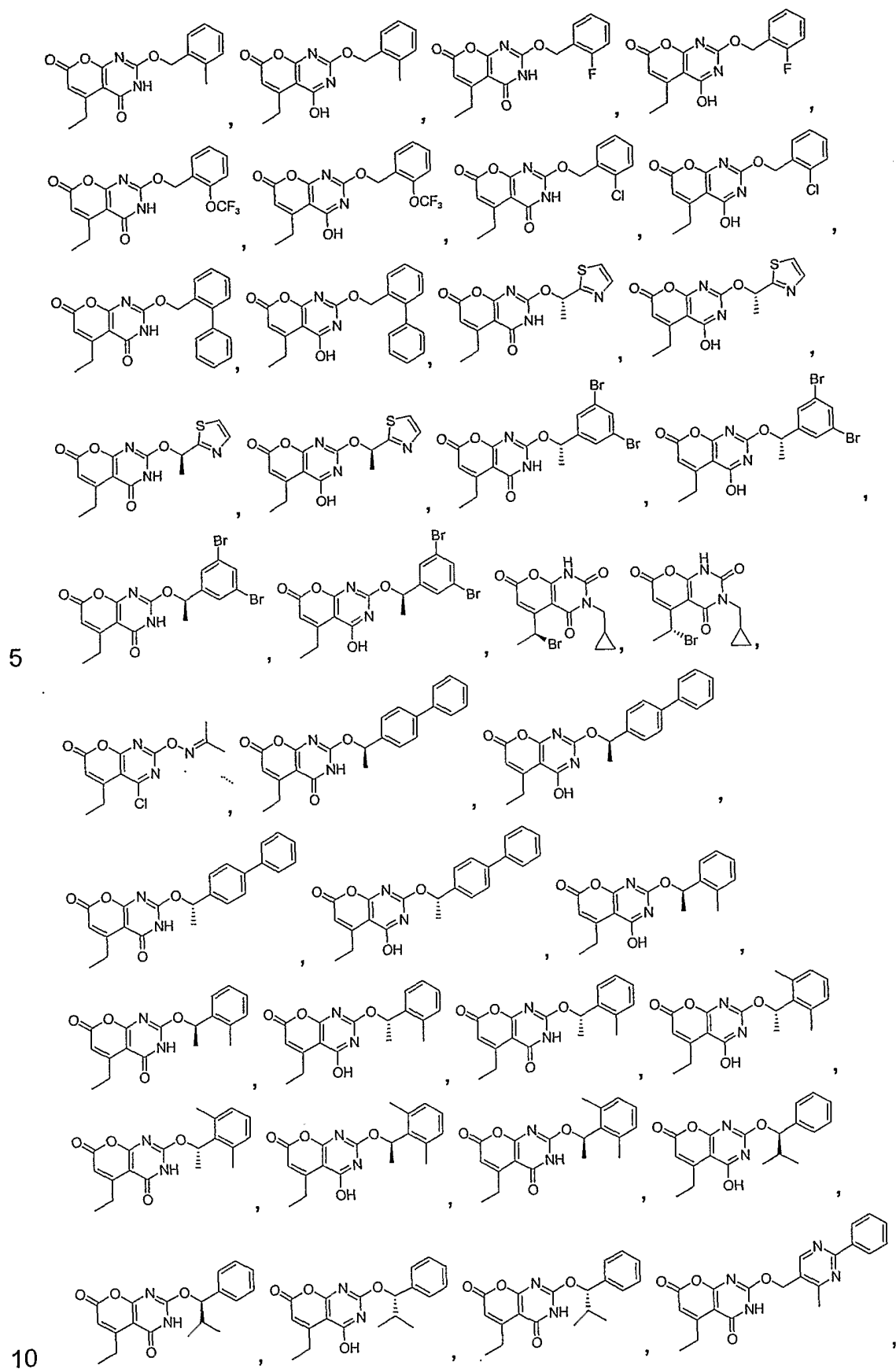
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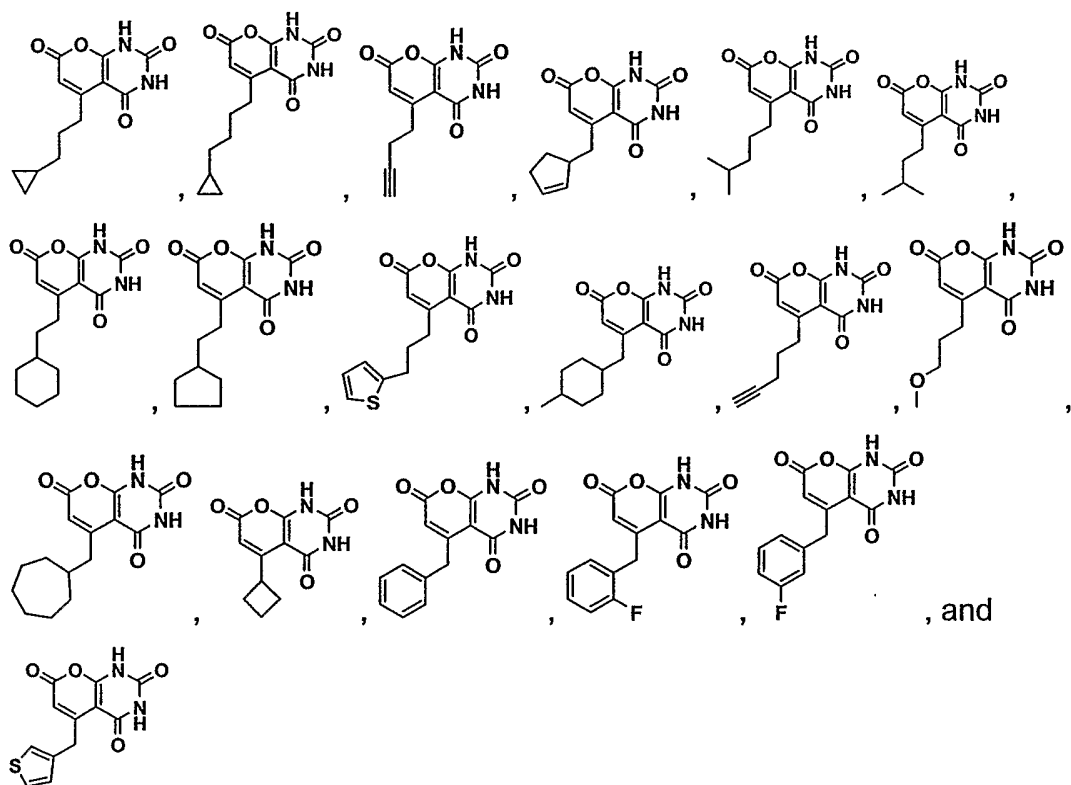
13. A compound, or a pharmaceutically acceptable salt, solvate, ester, or tautomer thereof, selected from the group consisting of:





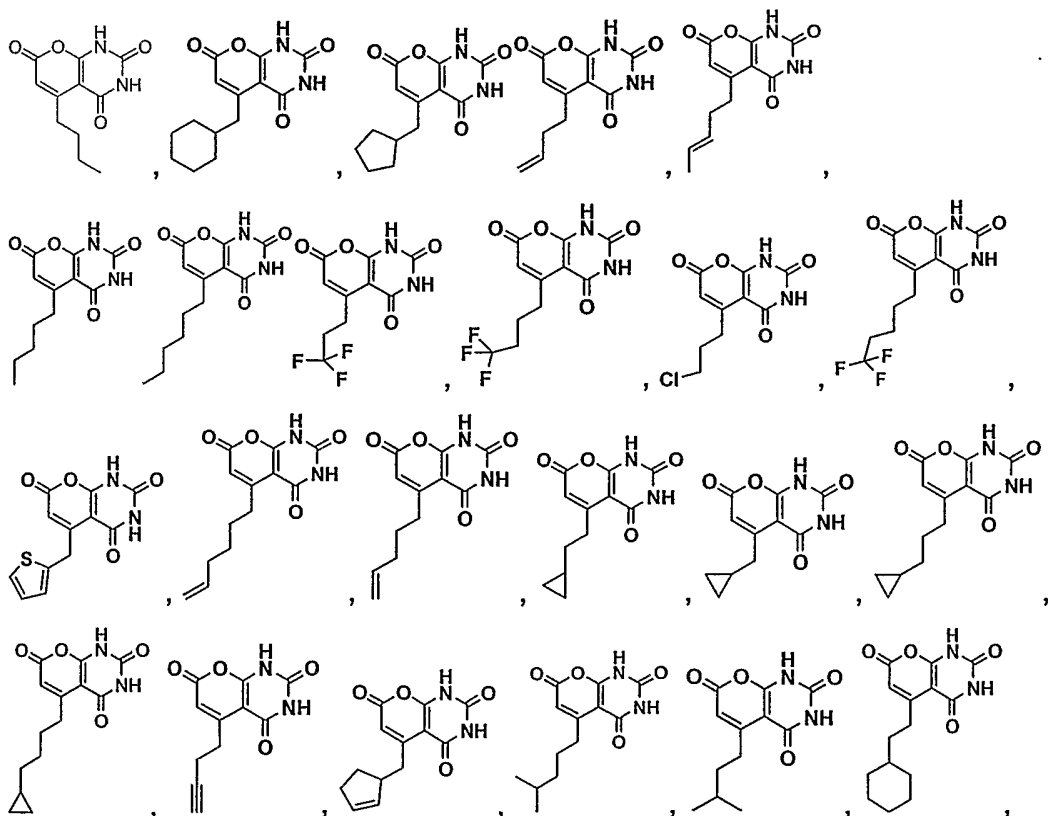


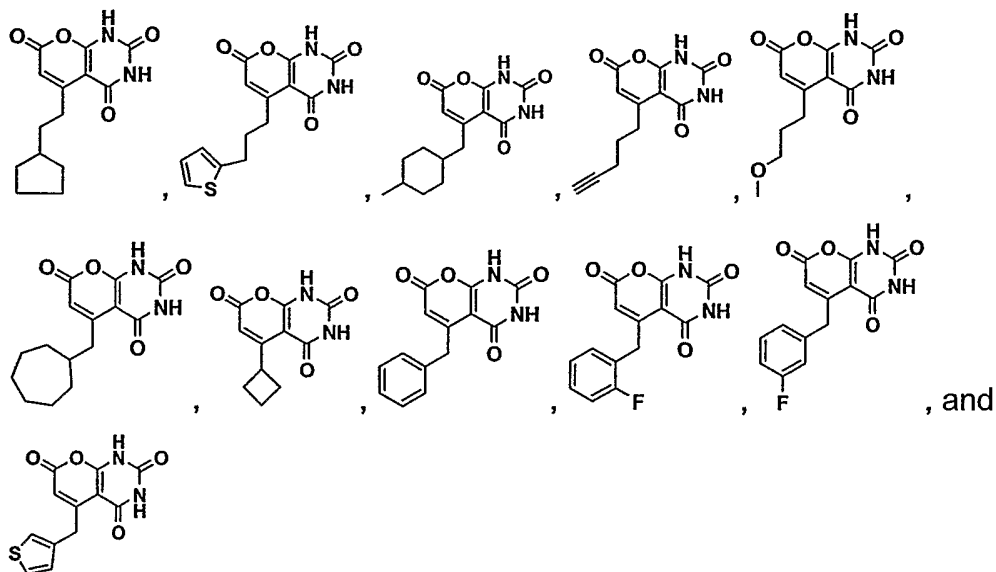




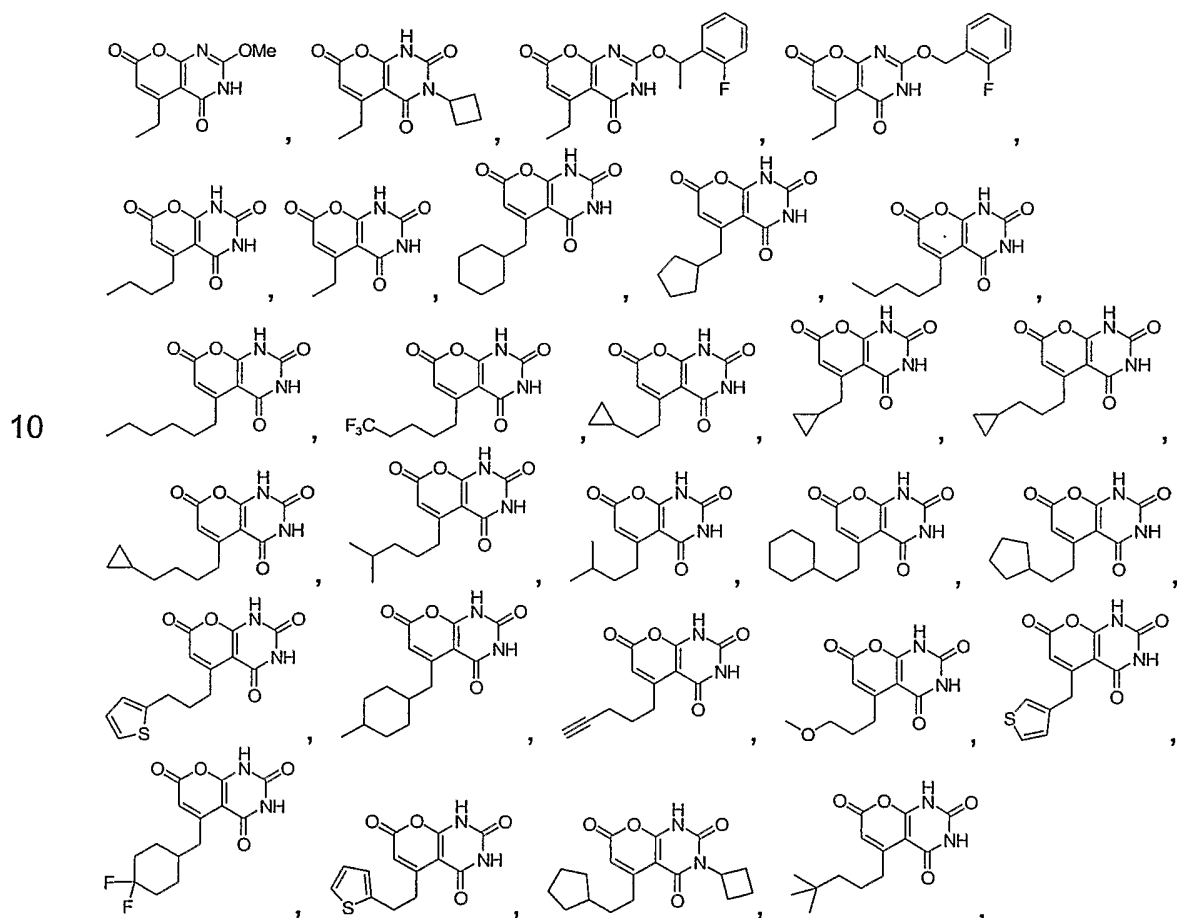
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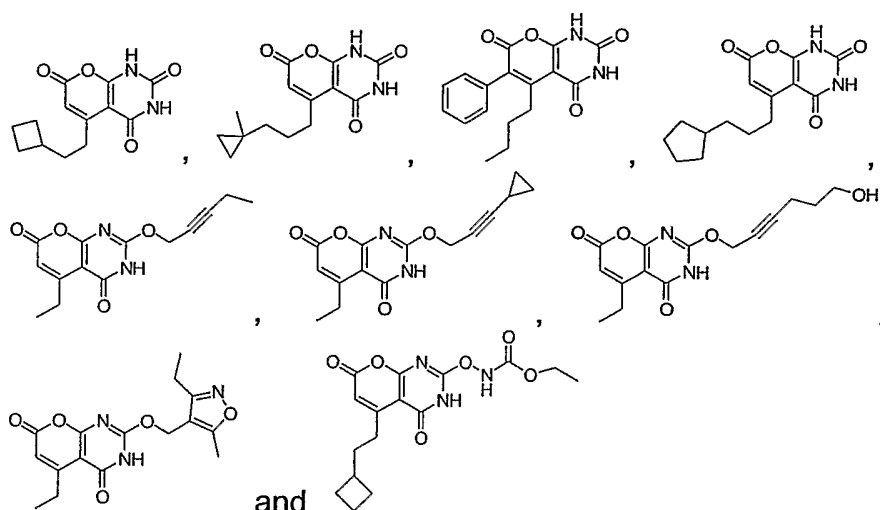
14. A compound, or a pharmaceutically acceptable salt, solvate, ester, or tautomer thereof, selected from the group consisting of:





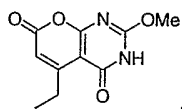
- 5 15. A compound, or a pharmaceutically acceptable salt, solvate, ester, or tautomer thereof, selected from the group consisting of:





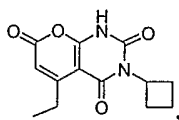
- 5 16. A purified compound of Claim 1, or a pharmaceutically acceptable salt, solvate, ester, or tautomer thereof.

17. A compound having the following structural formula:



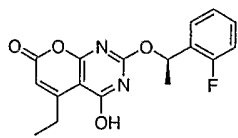
- 10 or a pharmaceutically acceptable salt, solvate, ester, or tautomer thereof.

18. A compound having the following structural formula:



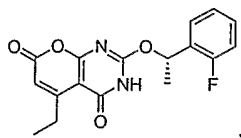
- or a pharmaceutically acceptable salt, solvate, ester, or tautomer thereof.

19. A compound having the following structural formula:



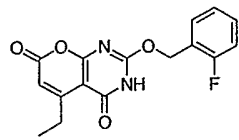
- or a pharmaceutically acceptable salt, solvate, ester, or tautomer thereof.

- 20 20. A compound having the following structural formula:



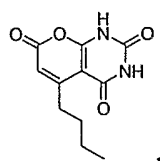
or a pharmaceutically acceptable salt, solvate, ester, or tautomer thereof.

21. A compound having the following structural formula:



5 or a pharmaceutically acceptable salt, solvate, ester, or tautomer thereof.

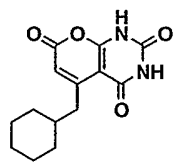
22. A compound having the following structural formula:



or a pharmaceutically acceptable salt, solvate, ester, or tautomer thereof.

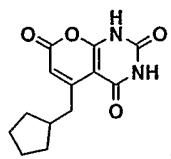
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23. A compound having the following structural formula:



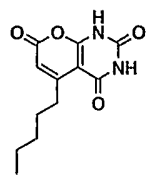
or a pharmaceutically acceptable salt, solvate, ester, or tautomer thereof.

15 24. A compound having the following structural formula:



or a pharmaceutically acceptable salt, solvate, ester, or tautomer thereof.

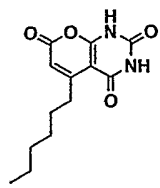
25. A compound having the following structural formula:



20

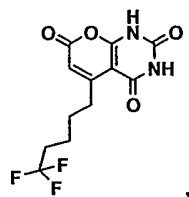
or a pharmaceutically acceptable salt, solvate, ester, or tautomer thereof.

26. A compound having the following structural formula:



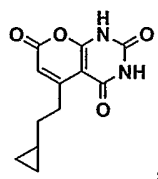
or a pharmaceutically acceptable salt, solvate, ester, or tautomer thereof.

- 5 27. A compound having the following structural formula:



or a pharmaceutically acceptable salt, solvate, ester, or tautomer thereof.

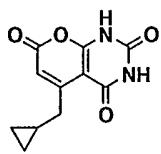
28. A compound having the following structural formula:



10

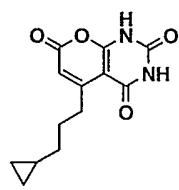
or a pharmaceutically acceptable salt, solvate, ester, or tautomer thereof.

29. A compound having the following structural formula:



15 or a pharmaceutically acceptable salt, solvate, ester, or tautomer thereof.

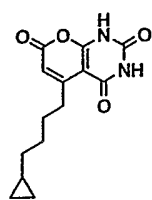
30. A compound having the following structural formula:



or a pharmaceutically acceptable salt, solvate, ester, or tautomer thereof.

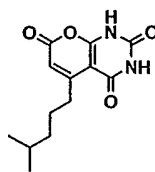
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31. A compound having the following structural formula:



or a pharmaceutically acceptable salt, solvate, ester, or tautomer thereof.

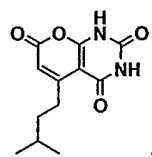
32. A compound having the following structural formula:



5

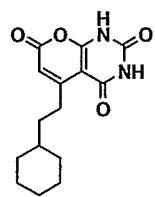
or a pharmaceutically acceptable salt, solvate, ester, or tautomer thereof.

33. A compound having the following structural formula:



10 or a pharmaceutically acceptable salt, solvate, ester, or tautomer thereof.

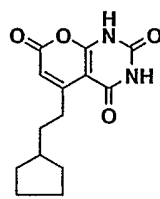
34. A compound having the following structural formula:



or a pharmaceutically acceptable salt, solvate, ester, or tautomer thereof.

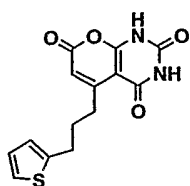
15

35. A compound having the following structural formula:



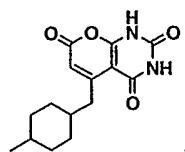
or a pharmaceutically acceptable salt, solvate, ester, or tautomer thereof.

20 36. A compound having the following structural formula:



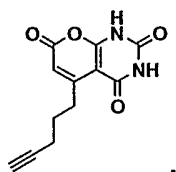
or a pharmaceutically acceptable salt, solvate, ester, or tautomer thereof.

37. A compound having the following structural formula:



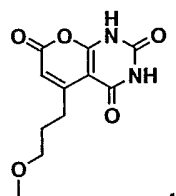
or a pharmaceutically acceptable salt, solvate, ester, or tautomer thereof.

38. A compound having the following structural formula:



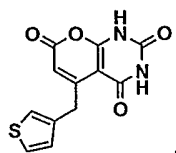
or a pharmaceutically acceptable salt, solvate, ester, or tautomer thereof.

39. A compound having the following structural formula:



or a pharmaceutically acceptable salt, solvate, ester, or tautomer thereof.

40. A compound having the following structural formula:



or a pharmaceutically acceptable salt, solvate, ester, or tautomer thereof.

41. A composition comprising:

at least one compound of Claim 1, or a pharmaceutically acceptable salt, solvate, ester, or tautomer thereof; and
at least one pharmaceutically acceptable carrier.

5 42. A composition comprising:

at least one compound of Claim 13, or a pharmaceutically acceptable salt, solvate, ester, or tautomer thereof; and
at least one pharmaceutically acceptable carrier.

10 43. The composition of Claim 41, further comprising at least one additional therapeutic agent selected from the group consisting of hydroxy-substituted azetidinone compounds, substituted β -lactam compounds, HMG CoA reductase inhibitor compounds, HMG CoA synthetase inhibitors, squalene synthesis inhibitors, squalene epoxidase inhibitors, sterol biosynthesis
15 inhibitors, nicotinic acid derivatives, bile acid sequestrants, aspirin, NSAID agents, Vytorin[®], ezetimibe, inorganic cholesterol sequestrants, AcylCoA:Cholesterol O-acyltransferase inhibitors, cholesteryl ester transfer protein inhibitors, fish oils containing Omega 3 fatty acids, natural water soluble fibers, plant stanols and/or fatty acid esters of plant stanols, anti-
20 oxidants, PPAR α agonists, PPAR γ -agonists, FXR receptor modulators, LXR receptor agonists, lipoprotein synthesis inhibitors, renin angiotensin inhibitors, microsomal triglyceride transport inhibitors, bile acid reabsorption inhibitors, PPAR δ agonists, triglyceride synthesis inhibitors, squalene epoxidase inhibitors, low density lipoprotein receptor inducers or activators, platelet
25 aggregation inhibitors, 5-LO or FLAP inhibitors, PPAR δ partial agonists, niacin or niacin receptor agonists, 5HT transporter inhibitors, NE transporter inhibitors, CB₁ antagonists/inverse agonists, ghrelin antagonists, H₃ antagonists/inverse agonists, MCH1R antagonists, MCH2R agonists/antagonists, NPY1 antagonists, NPY5 antagonists, NPY2 agonists,
30 NPY4 agonists, mGluR5 antagonists, leptins, leptin agonists/modulators, leptin derivatives, opioid antagonists, orexin receptor antagonists, BRS3 agonists, CCK-A agonists, CNTF, CNTF derivatives, CNTF agonists/modulators, 5HT_{2c} agonists, Mc4r agonists, monoamine reuptake

- inhibitors, serotonin reuptake inhibitors, GLP-1 agonists, phentermine, topiramate, phytopharm compound 57, ghrelin antibodies, Mc3r agonists, ACC inhibitors, β 3 agonists, DGAT1 inhibitors, DGAT2 inhibitors, FAS inhibitors, PDE inhibitors, thyroid hormone β agonists, UCP-1 activators,
- 5 UCP-2 activators, UCP-3 activators, acyl-estrogens, glucocorticoid agonists/antagonists, 11 β HSD-1 inhibitors, SCD-1 inhibitors, lipase inhibitors, fatty acid transporter inhibitors, dicarboxylate transporter inhibitors, glucose transporter inhibitors, phosphate transporter inhibitors, antidiabetic agents, anti-hypertensive agents, anti-dyslipidemic agents, DP receptor antagonists,
- 10 apolipoprotein-B secretion/microsomal triglyceride transfer protein (apo-B/MTP) inhibitors, sympathomimetic agonists, dopamine agonists, melanocyte-stimulating hormone receptor analogs, melanin concentrating hormone antagonists, leptons, galanin receptor antagonists, bombesin agonists, neuropeptide-Y antagonists, thyromimetic agents,
- 15 dehydroepiandrosterone, analogs of dehydroepiandrosterone, urocortin binding protein antagonists, glucagons-like peptide-1 receptor agonists, human agouti-related proteins (AGRP), neuromedin U receptor agonists, noradrenergic anorectic agents, appetite suppressants, hormone sensitive lipase antagonists, MSH-receptor analogs, α -glucosidase inhibitors, apo A1
- 20 milano reverse cholesterol transport inhibitors, fatty acid binding protein inhibitors (FABP), and fatty acid transporter protein inhibitors (FATP).

44. The composition of Claim 43, wherein said at least one additional therapeutic agent is a HMG CoA synthetase inhibitor selected from the group
- 25 consisting of lovastatin, simvastatin, pravastatin, atorvastatin, fluvastatin, cerivastatin, rivastatin, rosuvastatin calcium, and pitavastatin.

45. The composition of Claim 44, wherein said HMG CoA synthetase inhibitor is simvastatin.

30

46. The composition of Claim 43, wherein said at least one additional therapeutic agent is a cholesteryl ester transfer protein inhibitor.

47. The composition of Claim 46, wherein said cholesteryl ester transfer protein inhibitor is torcetrapib.
48. The composition of claim 43, wherein said at least one additional
5 therapeutical agent is Vytorin[®], ezetimibe, aspirin, ibuprofen or acetaminophen or combination thereof.
49. The use of a therapeutically effective amount of at least one compound of Claim 1, or a pharmaceutically acceptable salt, solvate, ester, or tautomer
10 thereof, for treating a disease, disorder, or condition in a patient in need thereof, wherein said disease, disorder, or condition is selected from the group consisting of metabolic syndrome, dyslipidemia, cardiovascular diseases, disorders of the peripheral and central nervous system, hematological diseases, cancer, inflammation, respiratory diseases,
15 gastroenterological diseases, diabetes, and non-alcoholic fatty liver disease.
50. The use of Claim 49, wherein said disease, disorder, or condition is dyslipidemia.
- 20 51. The use of Claim 49, further comprising administering at least one additional therapeutic agent selected from the group consisting of hydroxy-substituted azetidinone compounds, substituted β -lactam compounds, HMG CoA reductase inhibitor compounds, HMG CoA synthetase inhibitors, squalene synthesis inhibitors, squalene epoxidase inhibitors, sterol
25 biosynthesis inhibitors, nicotinic acid derivatives, bile acid sequestrants, inorganic cholesterol sequestrants, aspirin, NSAID agent, ezetimibe, Vytorin[®], AcylCoA:Cholesterol O-acyltransferase inhibitors, cholesteryl ester transfer protein inhibitors, fish oils containing Omega 3 fatty acids, natural water soluble fibers, plant stanols and/or fatty acid esters of plant stanols, Omacor[®],
30 anti-oxidants, PPAR α agonists, PPAR γ -agonists, FXR receptor modulators, LXR receptor agonists, lipoprotein synthesis inhibitors, renin angiotensin inhibitors, microsomal triglyceride transport protein inhibitors, bile acid reabsorption inhibitors, PPAR δ agonists, triglyceride synthesis inhibitors,

- squalene epoxidase inhibitors, low density lipoprotein receptor inducers or activators, platelet aggregation inhibitors, 5-LO or FLAP inhibitors, PPAR δ partial agonists, niacin or niacin receptor agonists, 5HT transporter inhibitors, NE transporter inhibitors, CB₁ antagonists/inverse agonists, ghrelin
- 5 antagonists, H₃ antagonists/inverse agonists, MCH1R antagonists, MCH2R agonists/antagonists, NPY1 antagonists, NPY5 antagonists, NPY2 agonists, NPY4 agonists, mGluR5 antagonists, leptins, leptin agonists/modulators, leptin derivatives, opioid antagonists, orexin receptor antagonists, BRS3 agonists, CCK-A agonists, CNTF, CNTF derivatives, CNTF
- 10 agonists/modulators, 5HT2c agonists, Mc4r agonists, monoamine reuptake inhibitors, serotonin reuptake inhibitors, GLP-1 agonists, phentermine, topiramate, phytopharm compound 57, ghrelin antibodies, Mc3r agonists, ACC inhibitors, β 3 agonists, DGAT1 inhibitors, DGAT2 inhibitors, FAS inhibitors, PDE inhibitors, thyroid hormone β agonists, UCP-1 activators,
- 15 UCP-2 activators, UCP-3 activators, acyl-estrogens, glucocorticoid agonists/antagonists, 11 β HSD-1 inhibitors, SCD-1 inhibitors, lipase inhibitors, fatty acid transporter inhibitors, dicarboxylate transporter inhibitors, glucose transporter inhibitors, phosphate transporter inhibitors, antidiabetic agents, anti-hypertensive agents, anti-dyslipidemic agents, DP receptor antagonists,
- 20 apolipoprotein-B secretion/microsomal triglyceride transfer protein (apo-B/MTP) inhibitors, sympathomimetic agonists, dopamine agonists, melanocyte-stimulating hormone receptor analogs, melanin concentrating hormone antagonists, leptons, galanin receptor antagonists, bombesin agonists, neuropeptide-Y antagonists, thyromimetic agents,
- 25 dehydroepiandrosterone, analogs of dehydroepiandrosterone, urocortin binding protein antagonists, glucagons-like peptide-1 receptor agonists, human agouti-related proteins (AGRP), neuromedin U receptor agonists, noradrenergic anorectic agents, appetite suppressants, hormone sensitive lipase antagonists, MSH-receptor analogs, α -glucosidase inhibitors, apo A1
- 30 milano reverse cholesterol transport inhibitors, fatty acid binding protein inhibitors (FABP), and fatty acid transporter protein inhibitors (FATP).

52. The use of Claim 51, wherein said at least one additional active ingredient is a HMG CoA synthetase inhibitor selected from the group

consisting of lovastatin, simvastatin, pravastatin, atorvastatin, fluvastatin, cerivastatin, rivastatin, rosuvastatin calcium, and pitavastatin.

53. The use of Claim 52, wherein said HMG CoA synthetase inhibitor is
5 simvastatin.

54. The use of claim 49 or 51, wherein said administration is oral, intravenous, subcutaneous or combination thereof.