NITROGEN-CONTAINING HETEROCYCLIC COMPOUNDS AND METHODS OF USE THEREOF

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 quinolizinyl- 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.

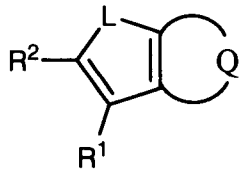
WO 2004/110375 describes combination therapies for the treatment of diabetes comprising the administration of a combination of an anti-obesity agent and an anti-diabetic agent. However, WO 2004/110375 fails to describe nicotinic acid receptor agonists, or combinations of one or more nicotinic acid receptor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

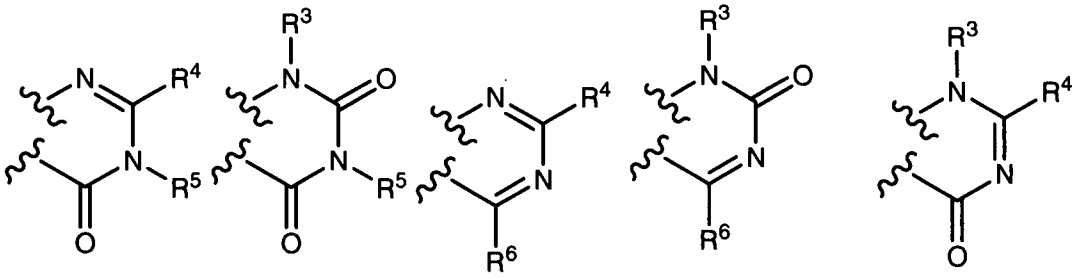
In one embodiment, the present invention is directed to a compound of Formula (I):



(I)

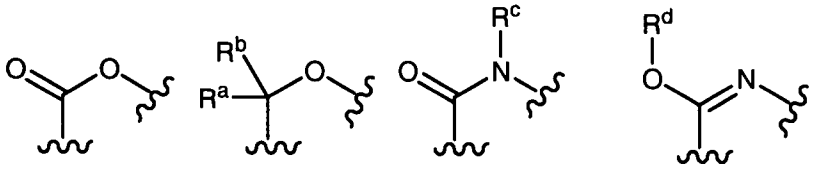
and pharmaceutically acceptable salts, solvates, esters, and tautomers thereof, wherein:

Q is selected from the group consisting of:



(a) , (b) , (c) , (d) and (e) ;

L is selected from the group consisting of:



(f) , (g) , (h) , and (i) ;

R^1 is selected from the group consisting of H, alkyl, arylalkyl, -alkylene-S-alkyl, alkenyl, alkynyl, haloalkyl, wherein an alkyl group can be optionally substituted with one or more of the following groups, which can be the same or different: -OH, cycloalkyl, -C(O)-alkyl, -alkylene-C(O)-O-alkyl, -O-R^{10}, -alkylene-O-alkyl, aryl, -alkylene-aryl, heteroaryl, -alkylene-heteroaryl, halogen, -$(CH_2)_n$-$N(R^7)_2$, -alkylene-cycloalkyl, or -alkylene-cycloalkenyl,

wherein the cycloalkyl or the cycloalkyl portion of said -alkylene-cycloalkyl of R^1 is unsubstituted or substituted with one or more X groups, said aryl or the aryl portion of said -alkylene-aryl of R^1 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 the 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, haloalkyl, -O-cycloalkyl, -O-alkynyl, -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, -N_3, and -O-C(O)-alkyl;

R^5 is selected from the group consisting of H, alkyl, -OH, haloalkyl, arylalkyl, -O-alkyl, -O-aryl, cycloalkyl, heterocyclyl, -O-cycloalkyl, -O-heterocyclyl, -O-arylalkyl or -alkylene-O-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 the 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)$_2$,

wherein the 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,

wherein the 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;

R^8 is selected from the group consisting of aryl, -OH, and heterocyclyl,

wherein the 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, 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

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, cycloalkyl, arylalkyl, haloalkyl, -alkylene-O-alkyl, -alkylene-aryl, -alkenylene-aryl, -alkylene-heteroaryl, alkenyl, -C(O)-alkyl, alkynyl, and -alkylene-cycloalkyl,

wherein an the alkynyl portion of an –O-alkynyl group can be optionally subsituted with –OH or alkoxy; the cycloalkyl portion of an –O-cycloalkyl group can be optionally substituted with an –alkylene-O-alkylene-aryl

group; 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 the 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 a heterocyclyl;

each R^{12} is independently selected from the group consisting of alkyl, aryl, and heteroaryl,

wherein the aryl of R^{12} is unsubstituted or substituted with one or more Y groups and said heteroaryl of R^{12} is unsubstituted or substituted with one or more Z groups; or wherein both R^{12} groups, together with the carbon atom to which they are attached, combine to form a heterocyclyl group;

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

wherein the 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,

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;

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, $-NO_2$, -OH, $-S(O_2)$-alkyl, $-S(O_2)$-aryl,

$-S(O_2)-NH_2$, $-S(O_2)-NH$-alkyl, $-S(O_2)-NH$-aryl, $-S(O_2)-N(alkyl)_2$, $-S(O_2)-N(aryl)_2$, $-S(O_2)-N(alkyl)(aryl)$, and aryl;

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 R^2, R^3 and R^5 are each H, then R^1 is not $-CH_3$.

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

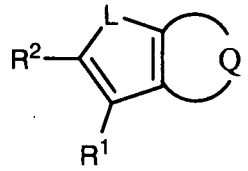
sequestrants, inorganic cholesterol sequestrants, AcylCoA:Cholesterol *O*-acyltransferase inhibitors, cholesteryl ester transfer protein inhibitors, fish oils containing Omega 3 fatty acids, natural water soluble fibers, plant stanols and/or fatty acid esters of plant stanols (e.g., Omacor® from Pronova 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, niacin or niacin receptor agonists, 5HT transporter inhibitors, NE transporter inhibitors, CB_1 antagonists/inverse agonists, ghrelin antagonists, H_3 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, 5HT2c agonists, Mc4r agonists, monoamine reuptake inhibitors, serotonin reuptake inhibitors, GLP-1 agonists, phentermine, topiramate, phytopharm compound 57, ghrelin antibodies, Mc3r agonists, ACC2 inhibitors, β3 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, 11β 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, 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, 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 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.

The present invention provides compound of Formula (I):



(I)

and pharmaceutically acceptable salts, solvates, estesr, and tautomers thereof, wherein L, Q, R^1 and R^2 are defined above for the compound of formula (I).

In one embodiment, R^1 is alkyl.

In another embodiment, R^1 is haloalkyl.

In another embodiment, R^1 is arylalkyl.

In still another embodiment, R^1 is -alkylene-S-alkyl.

In yet another embodiment, R^1 is -alkylene-cycloalkyl.

In another embodiment, R^1 is -alkylene-cyclopropyl, -alkylene-cyclobutyl, -alkylene-cyclopentyl or -alkylene-cyclohexyl.

In a further embodiment, R^1 is -alkylene-cycloalkenyl.

In another embodiment, R^1 is a straight chain alkyl having from 1 to 6 carbon atoms.

In one embodiment, R^1 is methyl.

In another embodiment, R^1 is ethyl.

In another embodiment, R^1 is n-propyl.

In still another embodiment, R^1 is n-butyl.

In one embodiment, R^1 is n-pentyl.

In another embodiment, R^1 is n-hexyl.

In yet another embodiment, R^1 is a branched chain alkyl having from 3 to 6 carbon atoms.

In a further embodiment, R^1 is isopropyl.

In one embodiment, R^1 is isobutyl.

In another embodiment, R^1 is isopentyl.

In another embodiment, R^1 is sec-butyl.

In still another embodiment, R^1 is tert-butyl.

In yet another embodiment, R^1 is haloalkyl, having from 1 to 3 F atoms.

In another embodiment, R^1 is $-(CH_2)_3CF_3$.

In one embodiment, R^2 is –H.

In another embodiment, R^2 is –CN.

In another embodiment, R^2 is -NHC(O)-alkyl.

In still another embodiment, R^2 is $-NHC(O)CH_3$.

In one embodiment, R^3 is –H.

In another embodiment, R^3 is –OH.

In another embodiment, R^3 is alkyl.

In another embodiment, R^3 is haloalkyl.

In still another embodiment, R^3 is -O-alkyl.

In yet another embodiment, R^3 is cycloalkyl.

In a further embodiment, R^3 is heterocyclyl.

In one embodiment, R^3 is -O-arylalkyl.

In another embodiment, R^3 is -alkylene-O-alkyl.

In one embodiment, R^3 is $-OCH_3$.

In another embodiment, R^3 is cyclobutyl.

In another embodiment, R^3 is ethyl.

In still another embodiment, R^3 is *N*-morpholinyl.

In one embodiment, R^3 is –O-benzyl.

In another embodiment, R^3 is $-CH_2CH_2OCH_3$.

In yet another embodiment, R^3 is $-OCH_2CH_3$.

In another embodiment, R^3 is $-CH_2F$.

In one embodiment, R^3 is $-CH_2CH_2F$.

In another embodiment, R^3 is –OH.

In one embodiment, R^4 is $-CF_3$.

In another embodiment, R^4 is –H.

In another embodiment, R^4 is -O-cycloalkyl.

In another embodiment, R^4–O-alkynyl.

In still another embodiment, R^4 is -O-alkynylene-cycloalkyl.

In yet another embodiment, R^4 is haloalkyl.

In a further embodiment, R^4 is $-O\text{-}N{=}C(R^7)_2$.

In one embodiment, R^4 is is $-CH_2F$.

In another embodiment, R^4 is $-CH(F)_2$.

In another embodiment, R^4 is $-CF_3$.

In another embodiment, R^4 is $-OCH_2C{\equiv}CCH_2CH_3$.

In another embodiment, R^4 is $-OCH_2C{\equiv}C(CH_2)_3CH_3$.

In still another embodiment, R^4 is $-OCH_2C{\equiv}CCH_2CH_2CH_3$.

In yet another embodiment, R^4 is $-OCH_2C{\equiv}C$-cyclopropyl.

In a further embodiment, R^4 is $-OCH_2C{\equiv}CCH(OCH_3)CH_3$.

In one embodiment, R^4 is $-OCH_2C{\equiv}CCH(OH)CH_3$.

In another embodiment, R^4 is $-OCH_2C{\equiv}CCH(OH)CH_2CH_3$.

In another embodiment, R^4 is $-OCH_2C{\equiv}CCH_2CH_2OCH_3$.

In still another embodiment, R^4 is $-OCH_2C{\equiv}CCH_2CH_2OH$.

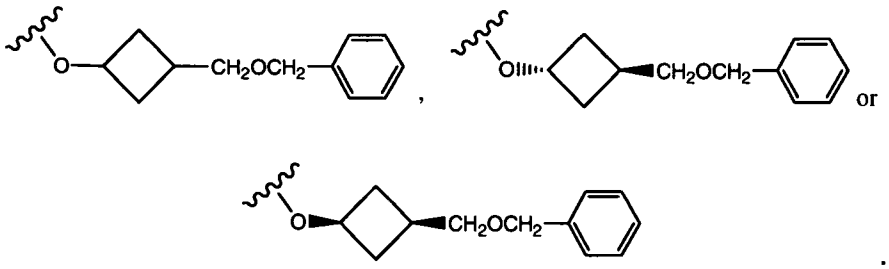
In yet another embodiment, R^4 is $-OCH_2C{\equiv}C(CH_2)_3OH$.

In a further embodiment, R^4 is $-OCH(CH_3)C{\equiv}CCH_2CH_3$.

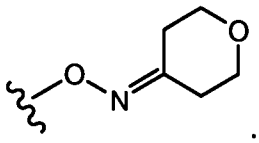
In another embodiment, R^4 is $-OCH_2C{\equiv}C$-cyclohexyl.

In one embodiment, R^4 is –O-cyclobutyl.

In another embodiment, R^4 is:



In one embodiment, R^4 is:



In one embodiment, R^5 is –H.

In another embodiment, R^5 is –OH.

In another embodiment, R^5 is alkyl.

In another embodiment, R^5 is haloalkyl.

In still another embodiment, R^5 is -O-alkyl.

In yet another embodiment, R^5 is cycloalkyl.

In a further embodiment, R^5 is heterocyclyl.

In one embodiment, R^5 is -O-arylalkyl.

In another embodiment, R^5 is -alkylene-O-alkyl.

In one embodiment, R^5 is $-OCH_3$.

In another embodiment, R^5 is cyclobutyl.

In another embodiment, R^5 is ethyl.

In still another embodiment, R^5 is *N*-morpholinyl.

In one embodiment, R^5 is –O-benzyl.

In another embodiment, R^5 is $-CH_2CH_2OCH_3$.

In yet another embodiment, R^5 is $-OCH_2CH_3$.

In another embodiment, R^5 is $-CH_2F$.

In one embodiment, R^5 is $-CH_2CH_2F$.

In another embodiment, R^5 is –OH.

In one embodiment, R^6 is alkoxy.

In another embodiment, R^6 is -O-alkylene-O-alkyl.

In another embodiment, R^6 is -O-arylalkyl.

In still another embodiment, R^6 is –O-haloalkyl.

In yet another embodiment, R^6 is $-OCH_2$-(4-methoxyphenyl).

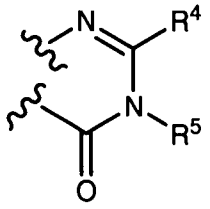
In one embodiment, R^6 is $-OCH_2F$.

In another embodiment, R^6 is $-OCH_2CH_2F$.

In another embodiment, R^6 is $-OCH_2CH_3$

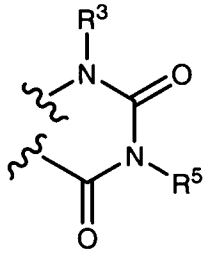
In still another embodiment, R^6 is $-OCH_2CH_2OCH_3$.

In one embodiment, Q is:



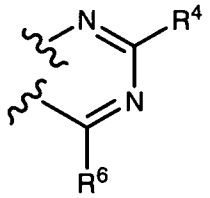
(a)

In another embodiment, Q is:



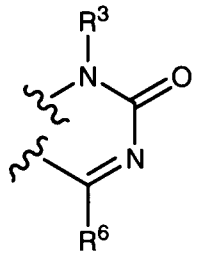
(b)

In another embodiment, Q is:



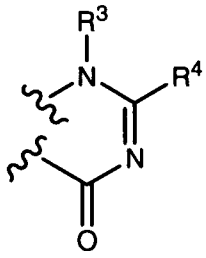
(c)

In still another embodiment, Q is:



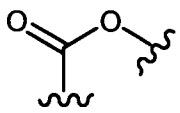
(d)

In yet another embodiment, Q is:



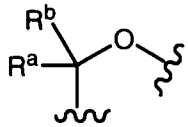
(e) .

In one embodiment, L is:



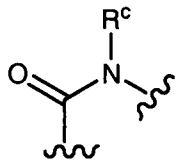
(f) .

In another embodiment, L is:



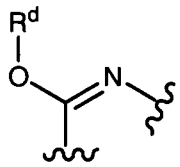
(g) .

In another embodiment, L is:



(h) .

In still another embodiment, L is:



(i) .

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

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)haloalkyl, -(C_1-C_6)alkyl substituted with one hydroxyl group, -(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(O)-O-(C_1-C_6)alkyl, -$(CH_2)_n$-N(R^7)$_2$, -(C_1-C_6)alkylene-(C_3-C_7)cycloalkyl, and -(C_1-C_6)alkylene-(C_3-C_7)cycloalkenyl

wherein the -(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, halogen, unsubstituted aryl, aryl substituted with one or more independently selected Y groups, unsubstituted heteroaryl, heteroaryl substituted with one or more independently selected Y groups; 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^3 is selected from the group consisting of H, (C_1-C_6)alkyl, -(C_3-C_6)alkylene-O-(C_1-C_6)alkyl, (C_3-C_7)cycloalkyl, -(C_1-C_6)alkylene-(C_3-C_7)cycloalkyl, -(C_1-C_6)alkylene-C(O)-O-alkyl, and (C_1-C_6)alkenyl,

wherein the (C_3-C_7)cycloalkyl or the (C_3-C_7)cycloalkyl portion of said -(C_3-C_6)alkylene-(C_3-C_7)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-(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, -(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 the (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 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;

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_7)cycloalkyl, and (C_6-C_{10})aryl,

wherein the (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 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;

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 -(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, -(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_7)cycloalkyl,

wherein the (C_3-C_7)cycloalkyl portion of said -(C_1-C_6)alkylene-(C_3-C_7)cycloalkyl of R^{10} 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 or -(C_2-C_6)alkenylene-(C_6-C_{10})aryl of R^{10} 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 of R^{10} is unsubstituted or substituted with one or more Z groups;

each R^{12} is independently a (C_1-C_6)alkyl;

R^a and R^b are each independently a (C_1-C_6)alkyl;

R^c is H;

R^d is selected from the group consisting of H, $(C_1$-$C_6)$alkyl, 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^d is unsubstituted or substituted with one or more Y groups;

each X is independently selected from the group consisting of F, Cl, Br, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, -O-$(C_1$-$C_6)$alkyl, -O-$(C_1$-$C_6)$haloalkyl, and –OH;

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, -$S(O_2)$-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, and N-oxide.

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

R^1 is selected from the group consisting of –CH_3, –CH_2CH_3, -$CH_2CH_2CH_3$, -$CH_2CH_2CH_2CH_3$, -$CH_2CH_2CH_2CH_2CH_3$, -$CH_2CH_2CH_2CH_2CH_2CH_3$, -$CH_2CH_2CH(CH_3)_2$, -$CH_2CH_2CH_2CH(CH_3)_2$, -$CH(CH_3)_2$, -CH_2CH_2CH=CH_2, -CH_2CH_2CH=$CHCH_3$, -$CH_2CH_2CH_2CH_2CH$=CH_2, -$CH_2CH_2CH_2CH$=CH_2, -CH_2-OH, -$CH(CH_3)$-OH, cyclobutyl, -CH_2-C(O)-O-CH_2CH_3, -$CH_2CH_2CH_2$-O-CH_3, -CH_2CF_3, -$CHBrCH_3$, -$CH_2CH_2CF_3$, -$CH_2CH_2CH_2CF_3$, -$CH_2CH_2CH_2CH_2CF_3$, -$CH_2CH_2CH_2Cl$, , -CH_2-(2-thiophenyl), -$CH_2CH_2CH_2$-(2-thiophenyl), -CH_2-cyclopropyl, -CH_2CH_2-cyclopropyl, -$CH_2CH_2CH_2$-cyclopropyl, -$CH_2CH_2CH_2CH_2$-cyclopropyl, -CH_2-cyclobutyl, -CH_2CH_2-cyclobutyl, -$CH_2CH_2CH_2$-cyclobutyl, -$CH_2CH_2CH_2CH_2$-cyclobutyl, -CH_2-cyclopentyl, -CH_2CH_2-cyclopentyl, -$CH_2CH_2CH_2$-cyclopentyl, -$CH_2CH_2CH_2CH_2$-cyclopentyl, -CH_2-cyclohexyl, -CH_2-(4-methylcyclohexyl), -CH_2CH_2-cyclohexyl, -CH_2-cycloheptyl, -CH_2-(2-cyclopentenyl, -$CH_2CH_2C{\equiv}CH$, -$CH_2CH_2CH_2C{\equiv}CH$, -CH_2-phenyl, -CH_2-(2-fluorophenyl), -CH_2-(3-fluorophenyl), and -CH_2-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, 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, -CH_2-cyclopropyl, -CH_2-C(O)-O-CH_3, cyclopropyl, cyclobutyl, cyclopentyl, cyclopentyl, -CH_3, -CH_2CH_3, -$CH_2CH_2CH_3$, -$CH_2CH{=}CH_2$, and -CH_2-O-CH_3;

R^4 is selected from the group consisting of Cl, -O-R^{10}, -C(O)-O-CH_3, -$S(O)_2$-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(O)-CH_2-phenyl, -S(O)-$CH(CH_3)$-phenyl, -S-CH_2-$CH{=}CH_2$, -$N(R^7)_2$, -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 selected from the group consisting of H, -CH_3, -CH_2CH_3, -$CH_2CH_2CH_3$, -CH_2-C(O)-phenyl, -CH_2-C(O)-OH, -CH_2-C(=N-O-CH_3)-phenyl, cyclopropyl, cyclobutyl, cyclopentyl, -CH_2-C(O)-piperidyl, -CH_2-cyclopropyl, -CH_2-C(O)-O-CH_3, and -CH_2-$CH{=}CH_3$,

wherein the phenyl portion of said -CH_2-C(O)-phenyl is unsubstituted or substituted with one or more Y groups;

R^6 is selected from the group consisting of –OR^{10}, Cl, and -$N(R^7)_2$;

each R^7 is independently selected from the group consisting of H, cyclobutyl, unsubstituted phenyl, and phenyl substituted with one or more Y groups;

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

wherein the phenyl portion of said -CH_2-phenyl, -$CH(CH_3)$-phenyl, -$CH(CH_2CH_3)$-phenyl, -$CH(CH_2CH_2CH_3)$-phenyl, -$CH(CH(CH_3)_2)$-phenyl,

or -CH($CH_2CH=CH_2$)-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_2-thiazolyl, or -CH_2-pyrimidinyl of R^{10} is unsubstituted or substituted with one or more groups Z;

R^a and R^b are each $-CH_3$;

R^c is H;

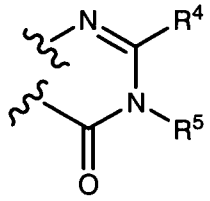
R^d is selected from the group consisting of H, -CH_3, and $-CH_2$-phenyl, wherein the phenyl portion of said $-CH_2$-phenyl of R^d is unsubstituted or substituted with one or more Y groups;

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

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

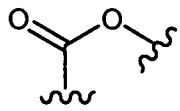
In another embodiment of the compounds of Formula (I),

Q is:



(a) ;

L is:



(f) ;

R^1 is selected from the group consisting of -(C_1-C_6)alkyl, -(C_1-C_6)alkylene-O-(C_1-C_6)alkyl, unsubstituted (C_6-C_{10})aryl, and (C_6-C_{10})aryl substituted with one or more substituents Y;

R^2 is H or halogen;

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 H or (C_1-C_6)alkyl;

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 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 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 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,

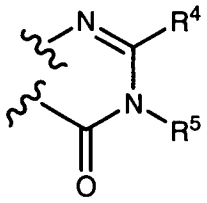
wherein the $(C_6$-$C_{10})$aryl is unsubstituted or substituted with one or more Y group, and said $(C_2$-$C_{10})$heteroaryl is unsubstituted or substituted with one or more Z group;

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, -$S(O_2)$-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.

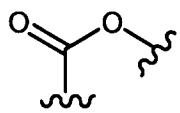
In another embodiment of the compounds of Formula (I),

Q is:



(a) ;

L is:



(f) ;

R^1 is $-CH_2CH_3$, butyl, pentyl, $-CH_2-CH_2-CH_2$-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;

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 $-C(O)-CH_3$,

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;

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,

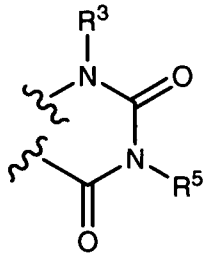
wherein the phenyl portion of said $-CH_2$-phenyl, $-CH(CH_3)$-phenyl, $-CH(CH_2CH_3)$-phenyl, $-CH(CH(CH_3)_2)$-phenyl, $-CH(CH_2CH=CH_2)$-phenyl, or $-CH(CH_2CH_2CH_3)$-phenyl, of R^{10} is unsubstituted or substituted with one or more groups Y, and the pyridyl, thiazolyl, or pyrimidinyl portion of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

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

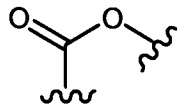
In another embodiment of the compounds of Formula (I),

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 the $-(C_3-C_7)$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 the 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 $(C_2$-$C_{10})$heterocyclyl and $(C_2$-$C_{10})$heterocyclyl substituted with one or more X groups;

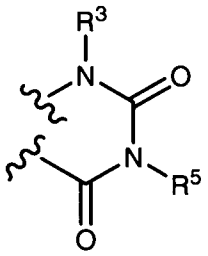
each X is independently selected from the group consisting of halogen, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, -O-$(C_1$-$C_6)$alkyl, -O-$(C_1$-$C_6)$haloalkyl, and –OH;

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, -$S(O_2)$-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, and N-oxide.

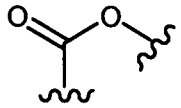
In another embodiment of the compounds of Formula (I),

Q is:



(b) ;

L is:



(f) ;

R^1 is selected from the group consisting of $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH_2CH_2CH_2CH_3$, $-CH_2CH_2CH_2CH_2CH_3$, $-CH_2CH_2CH_2CH_2CH_2CH_3$, $-CH_2CH_2CH(CH_3)_2$, $-CH_2CH_2CH_2CH(CH_3)_2$, $-CH(CH_3)_2$, $-CH_2$-C(O)-O-CH_2CH_3, $-CH_2CF_3$, $-CH_2CH_2CH=CH_2$, $-CH_2CH_2CH=CHCH_3$, $-CH_2CH_2CH_2CH_2CH=CH_2$, $-CH_2CH_2CH_2CH=CH_2$, $-CH_2OH$, $-CH(CH_3)OH$, $-CH_2N(R^7)_2$, cyclobutyl, $-CH_2CH_2CH_2$-O-CH_3, $-CH_2CH_2CF_3$, $-CH_2CH_2CH_2CF_3$, $-CH_2CH_2CH_2CH_2CF_3$, $-CH_2CH_2CH_2Cl$, , $-CH_2$-(2-thiophenyl), $-CH_2CH_2CH_2$-(2-thiophenyl), $-CH_2$-cyclopropyl, $-CH_2CH_2$-cyclopropyl, $-CH_2CH_2CH_2$-cyclopropyl, $-CH_2CH_2CH_2CH_2$-cyclopropyl, $-CH_2$-cyclopentyl, $-CH_2CH_2$-cyclopentyl, $-CH_2$-cyclohexyl, $-CH_2$-(4-methylcyclohexyl), $-CH_2CH_2$-cyclohexyl, $-CH_2$-cycloheptyl, $-CH_2$-(2-cyclopentenyl, $-CH_2CH_2C\equiv CH$, $-CH_2CH_2CH_2C\equiv CH$, $-CH_2$-phenyl, $-CH_2$-(2-fluorophenyl), $-CH_2$-(3-fluorophenyl), and $-CHBrCH_3$;

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^3 is selected from the group consisting of H, $-CH_2$-cyclopropyl, $-CH_2$-C(O)-O-CH_3, -cyclopropyl, cyclobutyl, cyclopentyl, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH_2CH=CH_2$, and $-CH_2$-O-CH_3;

R^5 is selected from the group consisting of H, $-CH_2$-cyclopropyl, $-CH_2$-C(O)-O-CH_3, $-CH_2$-C(O)-R^8, $-CH_2$-C(=N-O-CH_3)-phenyl, cyclopropyl, cyclobutyl, cyclopentyl, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, and $-CH_2CH=CH_2$;

each R^7 is independently H or phenyl,

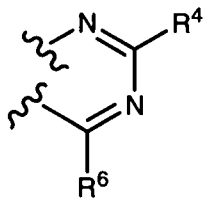
wherein the phenyl of R^7 is unsubstituted or substituted with one or more Y groups;

R^8 is selected from the group consisting of unsubstituted phenyl, phenyl substituted with one or more Y groups, -OH, and piperidyl; and

each Y is independently selected from the group consisting of F, $-CF_3$, $-OCH_3$, -CN, and –OH.

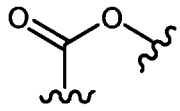
In another embodiment of the compounds of Formula (I),

Q is:



(c) ;

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 the -(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,

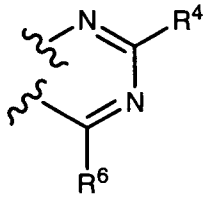
wherein the $(C_6$-$C_{10})$aryl portion of said -$(C_1$-$C_6)$alkylene-$(C_6$-$C_{10})$aryl or -$(C_1$-$C_6)$alkenylene-$(C_6$-$C_{10})$aryl of R^{10} is unsubstituted or substituted with one or more groups Y, and the $(C_2$-$C_{10})$heteroaryl portion of said -$(C_1$-$C_6)$alkylene-$(C_2$-$C_{10})$heteroaryl 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, -$S(O_2)$-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, and N-oxide.

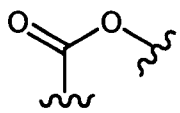
In another embodiment of the compounds of Formula (I),

Q is:



(c) ;

L is:



(f) ;

R^1 is selected from the group consisting of $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH_2CH_2CH_2CH_3$, $-CH_2CH_2CH_2CH_2CH_3$, $-CH_2CH_2CH_2CH_2CH_2CH_3$, $-CH_2CH_2CH(CH_3)_2$, $-CH_2CH_2CH_2CH(CH_3)_2$, $-CH(CH_3)_2$, $-CH_2$-C(O)-O-CH_2CH_3, $-CH_2$-OH, $-CH(CH_3)$-OH, $-CH_2CH_2CH=CH_2$, $-CH_2CH_2CH=CHCH_3$, $-CH_2CH_2CH_2CH_2CH=CH_2$, $-CH_2CH_2CH_2CH=CH_2$, cyclobutyl, $-CH_2CH_2CH_2$-O-CH_3, $-CH_2CH_2CF_3$, $-CH_2CH_2CH_2CF_3$, $-CH_2CH_2CH_2CH_2CF_3$, $-CH_2CH_2CH_2Cl$, , $-CH_2$-(2-thiophenyl), $-CH_2CH_2CH_2$-(2-thiophenyl), $-CH_2$-cyclopropyl, $-CH_2CH_2$-cyclopropyl, $-CH_2CH_2CH_2$-cyclopropyl, $-CH_2CH_2CH_2CH_2$-cyclopropyl, $-CH_2$-cyclopentyl, $-CH_2CH_2$-cyclopentyl, $-CH_2$-cyclohexyl, $-CH_2$-(4-methylcyclohexyl), $-CH_2CH_2$-cyclohexyl, $-CH_2$-cycloheptyl, $-CH_2$-(2-cyclopentenyl, $-CH_2CH_2C\equiv CH$, $-CH_2CH_2CH_2C\equiv CH$, $-CH_2$-phenyl, $-CH_2$-(2-fluorophenyl), $-CH_2$-(3-fluorophenyl), $-CHBrCH_3$ and $-CH_2CF_3$;

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, -O-R^{10}, -C(O)-O-CH_3, -$S(O)_2$-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,

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^6 is selected from the group consisting of -O-R^{10}, -N(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, and cyclobutyl;

R^{10} is selected from the group consisting of H, CH_3, $-CH_2$-cyclopropyl, $-CH_2$-C≡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, $-CH(CH_3)$-thiazolyl, $-CH_2$-pyrimidinyl,

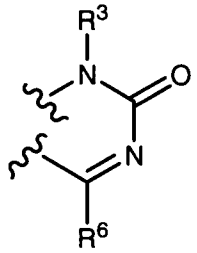
wherein the phenyl portion of said $-CH_2$-phenyl, $-CH(CH_3)$-phenyl, $-CH(CH_2CH_3)$-phenyl, $-CH(CH_2CH{=}CH_2)$-phenyl, or $-CH(CH_2CH_2CH_3)$-phenyl of R^{10} is unsubstituted or substituted with one or more groups Y, and the pyridyl, thiazolyl, or pyrimidinyl portion of said $-CH_2$-pyridyl, $-CH(CH_3)$-thiazolyl,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

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.

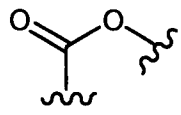
In another embodiment of the compounds of Formula (I),

Q is:



(d) ;

L is:



(f) ;

R^1 is $-(C_1\text{-}C_6)$alkyl;

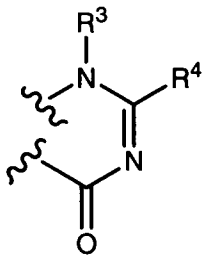
R^2 is H;

R^3 is H or $-(C_2\text{-}C_6)$alkenyl; and

R^6 is -OH or $-O-(C_1\text{-}C_6)$alkylene-$(C_1\text{-}C_6)$cycloalkyl.

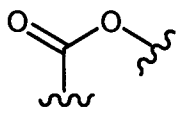
In another embodiment of the compounds of Formula (I),

Q is:



(e) ;

L is:



(f) ;

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

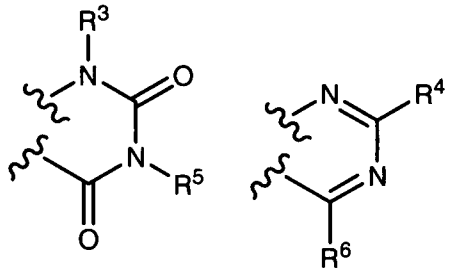
R^2 is H;

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, (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)$_2$.

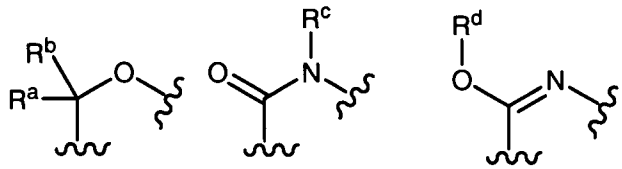
In another embodiment of the compounds of Formula (I),

Q is:



(b) or (c) ;

L is selected from the group consisting of:



(g) , (h) , and (i) ;

R^a and R^b are each independently selected from the group consisting of H, (C_1-C_6)alkyl, (C_6-C_{10})aryl, and (C_2-C_{10})heteroaryl,

wherein the (C_6-C_{10})aryl of R^a and R^b is unsubstituted or substituted with one or more Y groups, and said (C_2-C_{10})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, (C_1-C_6)alkyl, -(C_1-C_6)alkylene-(C_6-C_{10})aryl, and -C(O)-(C_1-C_6)alkyl,

wherein the (C_6-C_{10})aryl portion of said -(C_1-C_6)alkylene-(C_6-C_{10})aryl of R^c is unsubstituted or substituted with one or more Y groups;

R^d is selected from the group consisting of H, (C_1-C_6)alkyl, 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^d is unsubstituted or substituted with one or more Y groups;

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

R^2 is H;

R^3 is H;

R^4 is –O-R^{10};

R^5 is H or -(C_1-C_6)alkylene-(C_3-C_6)cycloalkyl;

R^6 is –O-R^{10};

R^{10} is H, (C_1-C_6)alkyl, or -(C_1-C_6)alkylene-(C_6-C_{10})aryl; and

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, -$S(O_2)$-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, and N-oxide.

In another embodiment of the Formula (I), R^1 is –CH_3, –CH_2CH_3, -$CH_2CH_2CH_3$, -$CH_2CH_2CH_2CH_3$, -$CH(CH_3)_2$, -CH_2-C(O)-O-CH_2CH_3, -CH_2CF_3, -CH_2-OH, -$CH(CH_3)$OH, -CH_2-N(R^7)$_2$, -CH_2-NH(3-methoxyphenyl), -$CH_2CH_2CH_2CH_2CH_3$, -$CH_2CH_2CH_2CH_2CH_2CH_3$, -$CH_2CH_2CH(CH_3)_2$, -$CH_2CH_2CH_2CH(CH_3)_2$, -$CH_2CH_2CH=CH_2$, -$CH_2CH_2CH=CHCH_3$, -$CH_2CH_2CH_2CH_2CH=CH_2$, -$CH_2CH_2CH_2CH=CH_2$, cyclobutyl, -$CH_2CH_2CH_2$-O-CH_3, -CH_2CF_3, -$CHBrCH_3$,

$-CH_2CH_2CF_3$, $-CH_2CH_2CH_2CF_3$, $-CH_2CH_2CH_2CH_2CF_3$, $-CH_2CH_2CH_2Cl$, , $-CH_2$-(2-thiophenyl), $-CH_2CH_2CH_2$-(2-thiophenyl), $-CH_2$-cyclopropyl, $-CH_2CH_2$-cyclopropyl, $-CH_2CH_2CH_2$-cyclopropyl, $-CH_2CH_2CH_2CH_2$-cyclopropyl, $-CH_2$-cyclopentyl, $-CH_2CH_2$-cyclopentyl, $-CH_2$-cyclohexyl, $-CH_2$-(4-methylcyclohexyl), $-CH_2CH_2$-cyclohexyl, $-CH_2$-cycloheptyl, $-CH_2$-(2-cyclopentenyl, $-CH_2CH_2C\equiv CH$, $-CH_2CH_2CH_2C\equiv CH$, $-CH_2$-phenyl, $-CH_2$-(2-fluorophenyl), $-CH_2$-(3-fluorophenyl), or $-CHBrCH_3$.

In another embodiment of the Formula (I), R^2 is H.

In another embodiment of the Formula (I), R^2 is Br.

In another embodiment, R^1 and R^2 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), R^3 is H, $-CH_2$-cyclopropyl, $-CH_2$-C(O)-O-CH_3, -cyclopropyl, cyclobutyl, cyclopentyl, $-CH_3$, $-CH_2CH_3$, $-CH_2$-CH_2CH_3, $-CH_2CH=CH_2$, or $-CH_2$-O-CH_3.

In another embodiment of the Formula (I), R^4 is Cl, -OH, -O-CH_3, -O-CH_2-cyclopropyl, $-CH_2$-C≡C-CH_3, -O-CH_2-phenyl, -O-CH(CH_3)-phenyl, -O-CH(CH_2CH_3)-phenyl, -O-CH($CH_2CH_2CH_3$)-phenyl, -O-CH(CH(CH_3)$_2$)-phenyl, -O-CH($CH_2CH=CH_2$)-phenyl, -O-CH_2-pyridyl, -O-CH_2-thiazolyl, -O-CH(CH_3)-thiazolyl, -O-CH_2-pyrimidinyl, -C(O)-O-CH_3, -S(O_2) -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(O)-CH_2-phenyl, -S(O)-CH(CH_3)-phenyl, -S(O)-N(R^{11})$_2$, -S(O_2)-N(R^{11})$_2$, -S-CH_2-$CH=CH_2$, -N(H)cyclobutyl, -N(H)phenyl, -NH-NH-C(O)-O-CH_3, -O-CH_2-$CH=CH_2$, -O-N=C(CH_3)$_2$, or -C(O)-CH_3, wherein 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), R^5 is H, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH_2$-C(O)-phenyl, $-CH_2$-C(O)-OH, $-CH_2$-C(=N-O-CH_3)-phenyl, cyclopropyl, cyclobutyl, cyclopentyl, $-CH_2$-C(O)-piperidyl, $-CH_2$-cyclopropyl, $-CH_2$-C(O)-O-CH_3, or $-CH_2$-$CH=CH_3$, wherein the phenyl of said

-CH_2-C(O)-phenyl of R^5 is unsubstituted or substituted with one or more Y groups as defined herein, said cyclopropyl, the cyclopropyl of said -CH_2-cyclopropyl, cyclobutyl, cyclopentyl, or the piperidyl of said -CH_2-C(O)-piperidyl of R^5 are unsubstituted or substituted with one or more X groups as defined herein.

In another embodiment of the compound of Formula (I), R^6 is -OH, Cl, -O-CH_3, -O-CH_2-cyclopropyl, -O-CH_2-CH=CH_3, -O-CH_2-phenyl, -O-CH(CH_3)-phenyl, -O-CH(CH_2CH_3)-phenyl, -O-CH($CH_2CH_2CH_3$)-phenyl, -O-CH(CH(CH_3)$_2$)-phenyl, -O-CH($CH_2CH=CH_2$)-phenyl, -O-CH_2-pyridyl, -O-CH_2-thiazolyl, -O-CH_2-pyrimidinyl, and -N(H)cyclobutyl, -N(H)phenyl, -NH-NH-C(O)-O-CH_3, wherein the phenyl of said -O-CH_2-phenyl, -O-CH(CH_3)-phenyl, -O-CH(CH_2CH_3)-phenyl, -O-CH($CH_2CH_2CH_3$)-phenyl, -O-CH(CH(CH_3)$_2$)-phenyl, or -O-CH($CH_2CH=CH_2$)-phenyl of R^6 is unsubstituted or substituted with one or more groups Y as defined herein, and the pyridyl, thiazolyl , or pyrimidinyl of said -O-CH_2-pyridyl, -O-CH_2-thiazolyl, or -O-CH_2-pyrimidinyl of R^6 is unsubstituted or substituted with one or more groups Z as defined herein.

In another embodiment of the compound of Formula (I), each R^7 is independently H, -CH_3, -CH_2CH_3, -$CH_2CH_2CH_3$, unsubstituted phenyl, phenyl substituted with one or more Y groups, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, -C(O)-CH_3, and -C(O)-phenyl. Alternatively, two groups R^7, together with the N atom to which they are attached, form an azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, pyrrolidinonyl, triazolyl, or pyrrolyl ring.

In another embodiment of the compound of Formula (I), R^8 is –CH_3, 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 –CH_3, -CH_2CH_3, -CH(CH_3)$_2$, -C(CH_3)$_3$, -CH_2-cyclopropyl, -CH_2-CH=CH_2 (allyl), -CH_2-phenyl, and -CH(CH_3)-phenyl.

In another embodiment of the compound of Formula (I), R^{10} is H, -$CH_2C{\equiv}CCH_3$, -CH_2-cyclopropyl, -$CH_2CH=CH_2$, -CH_2-phenyl, -CH(CH_3)-phenyl, -CH(CH_2CH_3)-phenyl, -CH(CH(CH_3)$_2$)-phenyl, -CH_2-pyridyl, -CH_2-thiazolyl, -CH(CH_3)-thiazolyl, -CH_2-pyrimidyl, -CH($CH_2CH=CH_2$)-phenyl, -CH($CH_2CH_2CH_3$)-phenyl, wherein the phenyl portion of -CH_2-phenyl, -CH(CH_3)-phenyl, -CH(CH_2CH_3)-phenyl,

-CH(CH(CH_3)$_2$)-phenyl, -CH(CH_2CH=CH_2)-phenyl, and -CH($CH_2CH_2CH_3$)-phenyl of R^{10} are unsubstituted or substituted with one or more Y groups, and the pyridyl, thiazolyl, and pyrimidyl portion of said -CH_2-pyridyl, -CH_2-thiazolyl, -CH(CH_3)-thiazolyl, -CH_2-pyrimidyl are unsubstituted or substituted with one or more Z groups.

In another embodiment of the compound of Formula (I), R^{11} is H, -CH_3, or phenyl, wherein the 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 azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, pyrrolidinonyl, triazolyl, or pyrrolyl ring.

In another embodiment of the compound of Formula (I), R^{12} is H, -CH_3, -CH_2CH_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 -CH_3.

In another embodiment of the compound of Formula (I), R^b is H or -CH_3.

In another embodiment of the compound of Formula (I), R^a and R^b are both –CH_3.

In another embodiment of the compound of Formula (I), R^c is H or -CH_3.

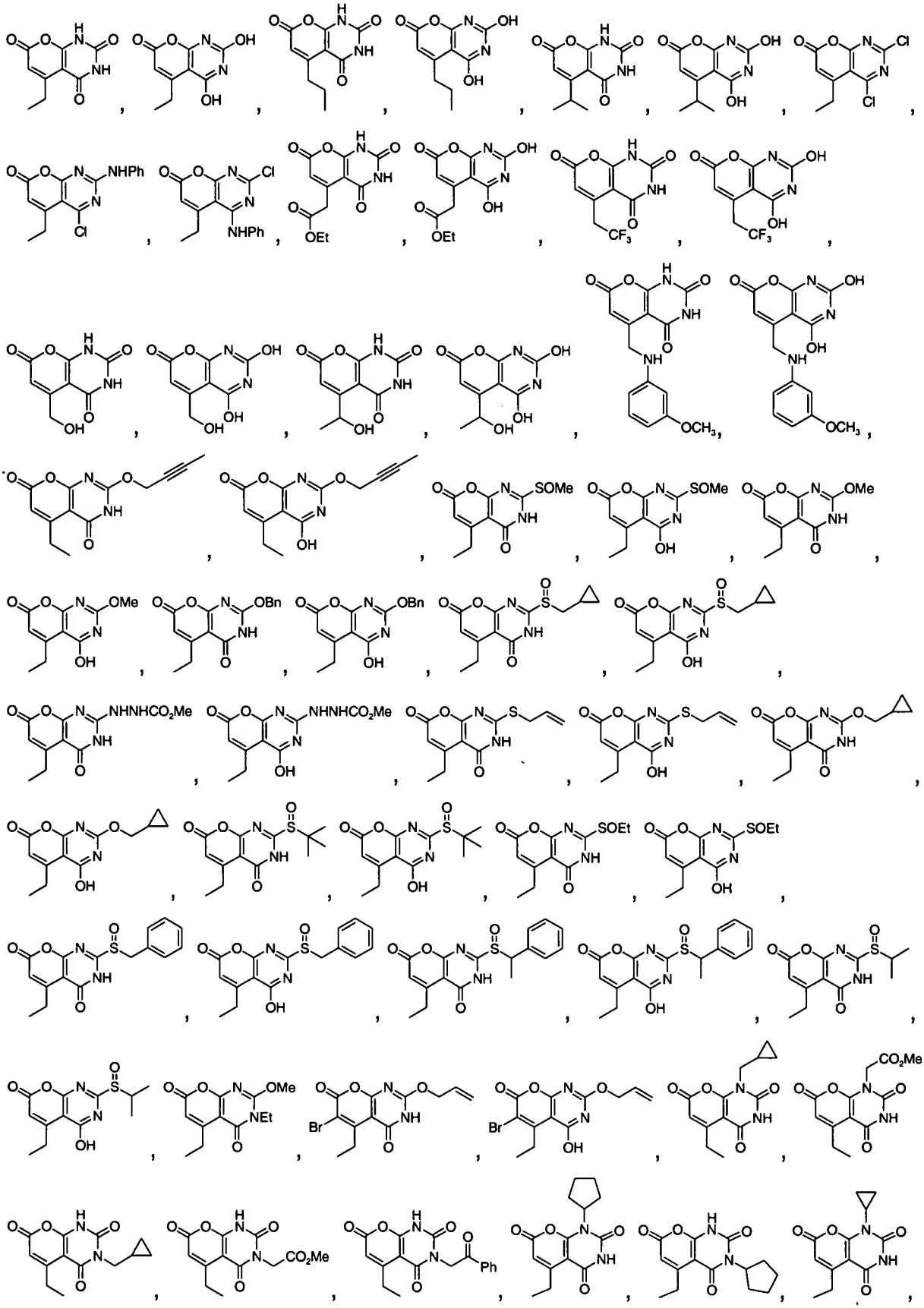
In another embodiment of the compound of Formula (I), R^d is H, -CH_3, or -CH_2-phenyl, wherein the phenyl portion of said –CH_2-phenyl of R^d is unsubstituted or substituted with one or more Y groups as defined herein.

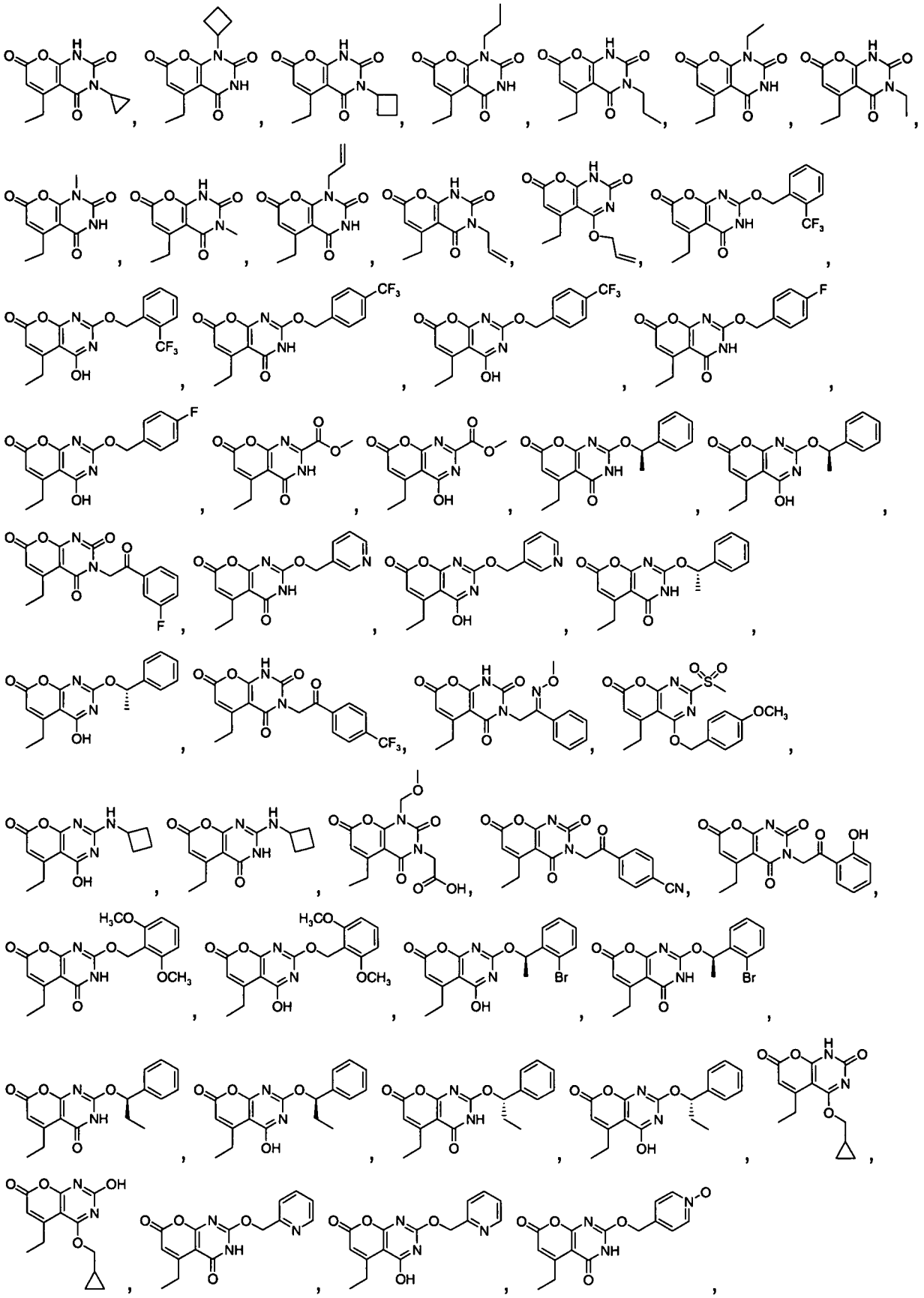
In another embodiment of the compound of Formula (I), each X is independently selected from the group consisting of –CH_3, -CF_3, F, Br, and Cl, -O-CH_3, , -O-CF_3, -CN, -OH, phenyl, and N-oxide;

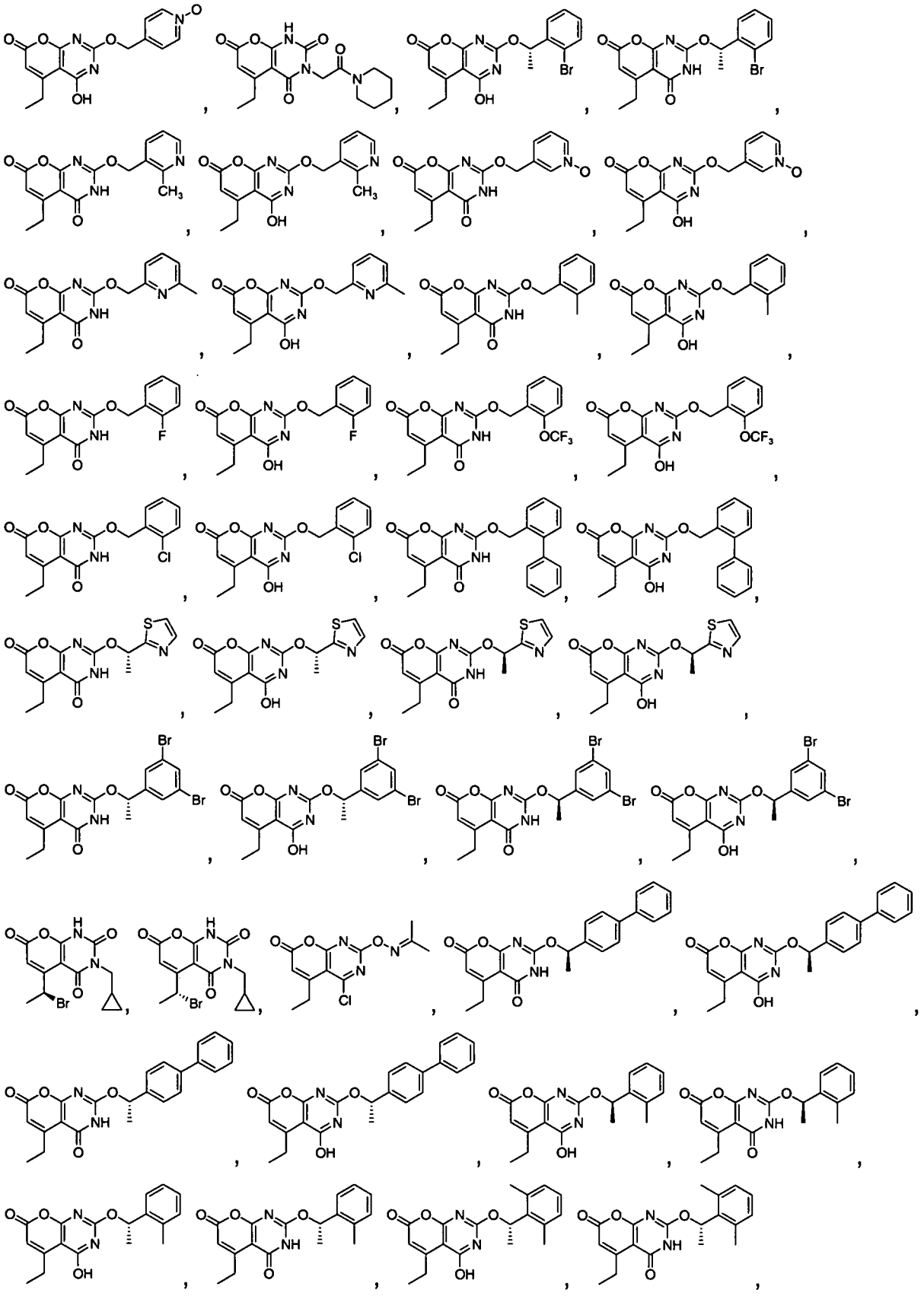
In another embodiment of the compound of Formula (I), each Y is independently selected from the group consisting of F, Cl, Br, -CH_3, -CF_3, -O-CH_3, -O-CF_3, -CN, -OH, and phenyl; and

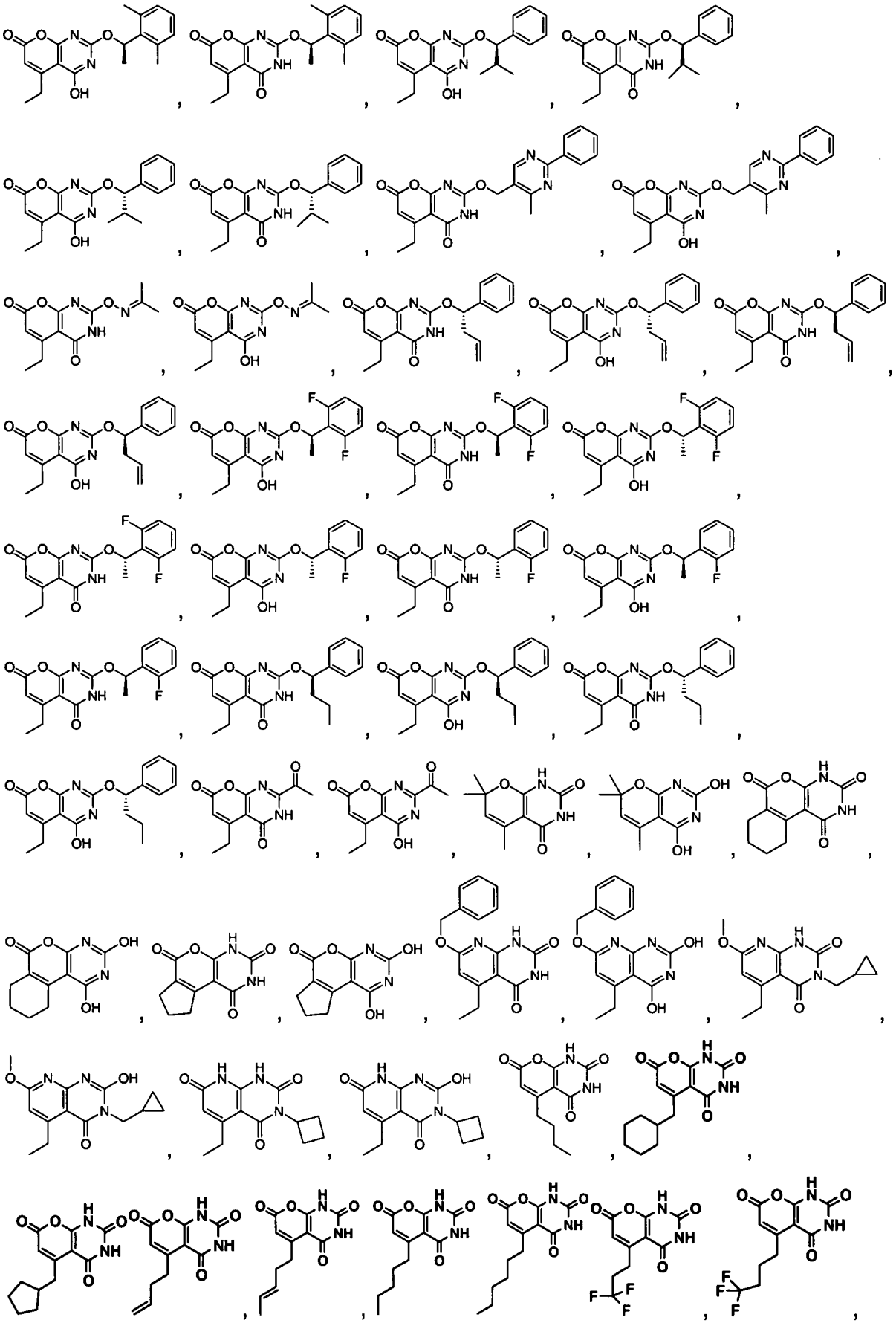
In another embodiment of the compound of Formula (I), each Z is independently selected from the group consisting of –CH_3, -CF_3, F, Br, and Cl, -O-CH_3, -O-CF_3, -CN, -OH, phenyl, and N-oxide.

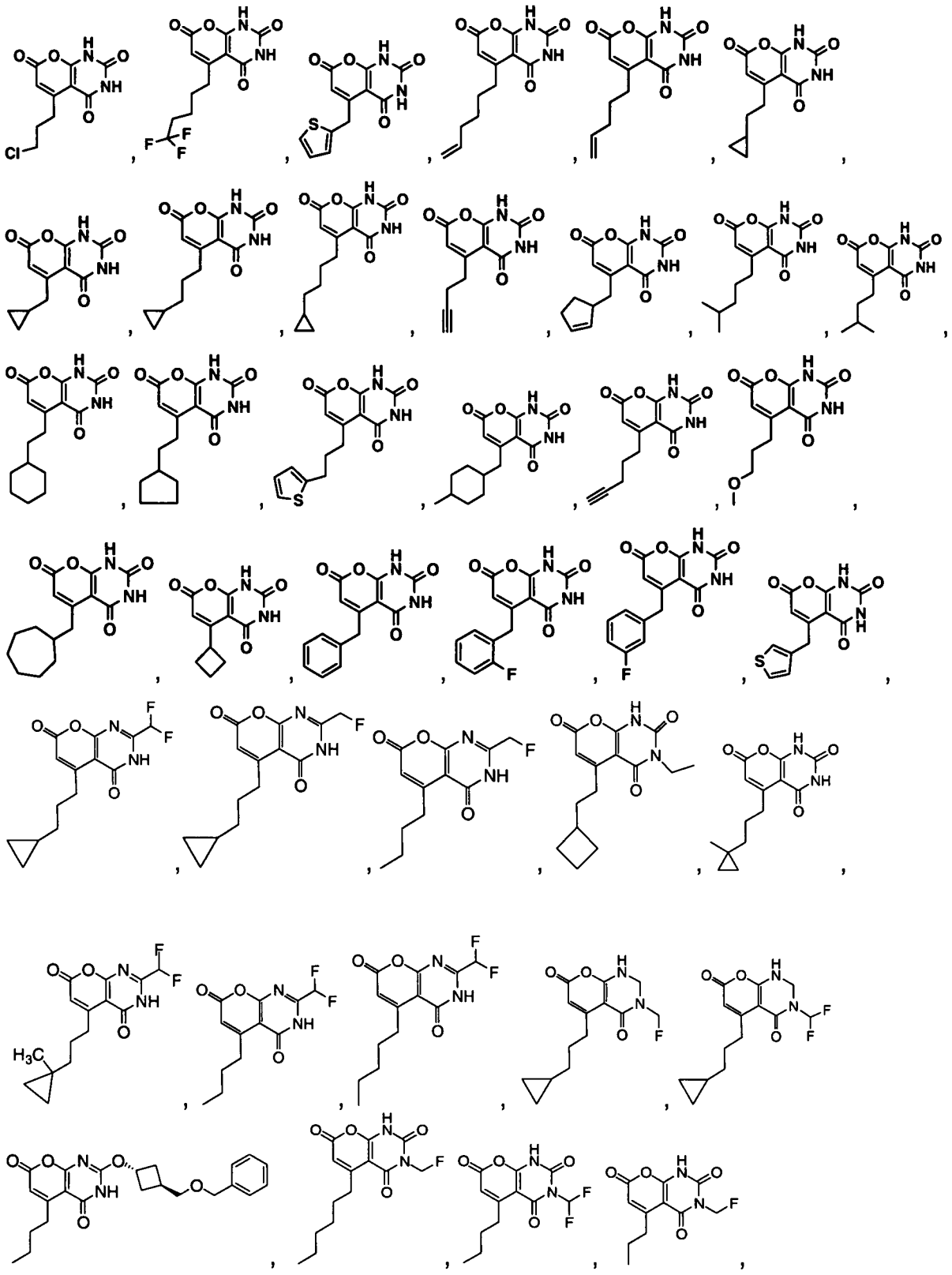
Non-limiting illustrative examples of the compounds of formula (I), include the following compounds:

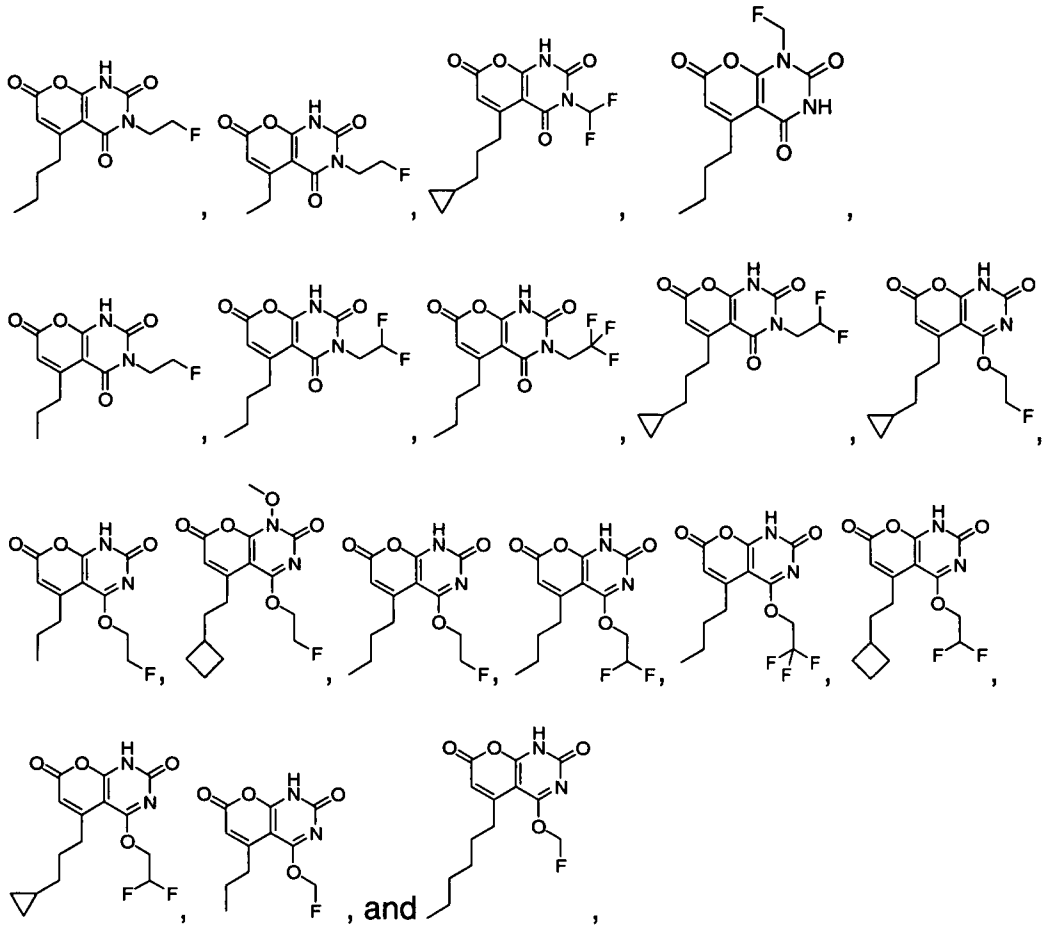






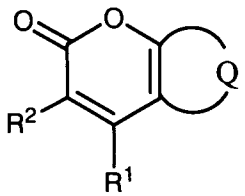






and pharmaceutically acceptable salts, solvates, esters, or tautomers thereof.

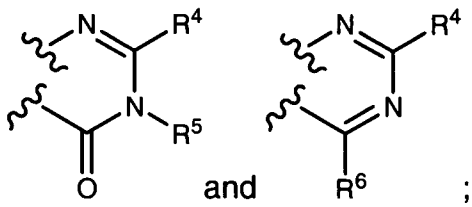
In one embodiment, the compounds of formula (I) have the formula (II):



(II)

and pharmaceutically acceptable salts, solvates, esters, and tautomers thereof, wherein:

Q is selected from the group consisting of:



;

R^1 is –H, alkyl, haloalkyl, arylalkyl, -alkylene-S-alkyl or -alkylene-cycloalkyl;

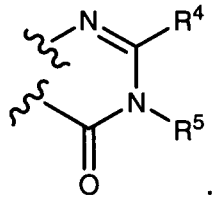
R^2 is –H, -CN, or -NHC(O)-alkyl;

R^4 is -O-cycloalkyl, –O-alkynyl, -O-alkynylene-cycloalkyl, haloalkyl or –O-N=C(R^{12})$_2$, wherein both R^{12} groups, together with the carbon atom to which they are attached, combine to form a heterocyclyl group, and wherein the alkynyl portion of an –O-alkynyl group can be optionally subsituted with –OH or alkoxy; and wherein the cycloalkyl portion of an –O-cycloalkyl group can be optionally substituted with an –alkylene-O-alkylene-aryl group;

R^5 is –H, -OH, alkyl, haloalkyl, arylalkyl, -O-alkyl, -O-aryl, cycloalkyl, heterocyclyl, -O-cycloalkyl, -O-heterocyclyl, -O-arylalkyl or -alkylene-O-alkyl; and

R^6 is alkoxy, -O-alkylene-O-alkyl, -O-arylalkyl or –O-haloalkyl.

The following embodiments refer to the compounds of formula (II), wherein Q is:



In one embodiment, R^1 is alkyl.

In another embodiment, R^1 is haloalkyl.

In another embodiment, R^1 is arylalkyl.

In still another embodiment, R^1 is -alkylene-S-alkyl.

In yet another embodiment, R^1 is -alkylene-cycloalkyl.

In another embodiment, R^1 is -alkylene-cyclopropyl, -alkylene-cyclobutyl, -alkylene-cyclopentyl or -alkylene-cyclohexyl.

In a further embodiment, R^1 is -alkylene-cycloalkenyl.

In another embodiment, R^1 is a straight chain alkyl having from 1 to 6 carbon atoms.

In one embodiment, R^1 is methyl.

In another embodiment, R^1 is ethyl.

In another embodiment, R^1 is n-propyl.

In still another embodiment, R^1 is n-butyl.

In one embodiment, R^1 is n-pentyl.

In another embodiment, R^1 is n-hexyl.

In yet another embodiment, R^1 is a branched chain alkyl having from 3 to 6 carbon atoms.

In a further embodiment, R^1 is isopropyl.

In one embodiment, R^1 is isobutyl.

In another embodiment, R^1 is isopentyl.

In another embodiment, R^1 is sec-butyl.

In still another embodiment, R^1 is tert-butyl.

In yet another embodiment, R^1 is haloalkyl, having from 1 to 3 F atoms.

In another embodiment, R^1 is $-(CH_2)_3CF_3$.

In one embodiment, R^4 is $-CF_3$.

In another embodiment, R^4 is –H.

In another embodiment, R^4 is -O-cycloalkyl.

In another embodiment, R^4–O-alkynyl.

In still another embodiment, R^4 is -O-alkynylene-cycloalkyl.

In yet another embodiment, R^4 is haloalkyl.

In a further embodiment, R^4 is $-O\text{-}N{=}C(R^7)_2$.

In one embodiment, R^4 is is $-CH_2F$.

In another embodiment, R^4 is $-CH(F)_2$.

In another embodiment, R^4 is $-CF_3$.

In another embodiment, R^4 is $-OCH_2C{\equiv}CCH_2CH_3$.

In another embodiment, R^4 is $-OCH_2C{\equiv}C(CH_2)_3CH_3$.

In still another embodiment, R^4 is $-OCH_2C{\equiv}CCH_2CH_2CH_3$.

In yet another embodiment, R^4 is $-OCH_2C{\equiv}C$-cyclopropyl.

In a further embodiment, R^4 is $-OCH_2C{\equiv}CCH(OCH_3)CH_3$.

In one embodiment, R^4 is $-OCH_2C{\equiv}CCH(OH)CH_3$.

In another embodiment, R^4 is $-OCH_2C{\equiv}CCH(OH)CH_2CH_3$.

In another embodiment, R^4 is $-OCH_2C{\equiv}CCH_2CH_2OCH_3$.

In still another embodiment, R^4 is $-OCH_2C{\equiv}CCH_2CH_2OH$.

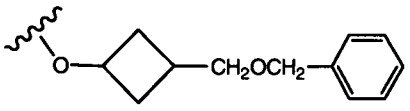
In yet another embodiment, R^4 is $-OCH_2C{\equiv}C(CH_2)_3OH$.

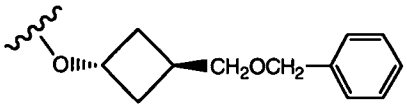
In a further embodiment, R^4 is $-OCH(CH_3)C{\equiv}CCH_2CH_3$.

In another embodiment, R^4 is $-OCH_2C{\equiv}C$-cyclohexyl.

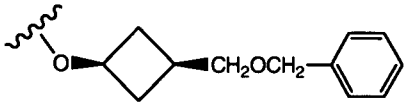
In one embodiment, R^4 is –O-cyclobutyl.

In another embodiment, R^4 is:



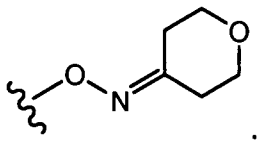
,


or



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In one embodiment, R^4 is:



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In one embodiment, R^5 is –H.

In another embodiment, R^5 is –OH.

In another embodiment, R^5 is alkyl.

In another embodiment, R^5 is haloalkyl.

In still another embodiment, R^5 is -O-alkyl.

In yet another embodiment, R^5 is cycloalkyl.

In a further embodiment, R^5 is heterocyclyl.

In one embodiment, R^5 is -O-arylalkyl.

In another embodiment, R^5 is -alkylene-O-alkyl.

In one embodiment, R^5 is $-OCH_3$.

In another embodiment, R^5 is cyclobutyl.

In another embodiment, R^5 is ethyl.

In still another embodiment, R^5 is *N*-morpholinyl.

In one embodiment, R^5 is –O-benzyl.

In another embodiment, R^5 is $-CH_2CH_2OCH_3$.

In yet another embodiment, R^5 is $-OCH_2CH_3$.

In another embodiment, R^5 is $-CH_2F$.

In one embodiment, R^5 is $-CH_2CH_2F$.

In another embodiment, R^5 is –OH.

In one embodiment, R^1 is alkyl and R^5 is –H.

In another embodiment, R^1 is haloalkyl and R^5 is –H.

In another embodiment, R^1 is arylalkyl and R^5 is –H.

In still another embodiment, R^1 is -alkylene-S-alkyl and R^5 is –H.

In yet another embodiment, R^1 is -alkylene-cycloalkyl and R^5 is –H.

In one embodiment, R^1 is alkyl and R^5 is –H.

In another embodiment, R^1 is haloalkyl and R^5 is –H

In another embodiment, R^1 is arylalkyl and R^5 is –H.

In still another embodiment, R^1 is -alkylene-S-alkyl and R^5 is –H.

In yet another embodiment, R^1 is -alkylene-cycloalkyl and R^5 is –H.

In one embodiment, R^1 is alkyl, R^5 is –H and R^4 is –O-alkynyl.

In another embodiment, R^1 is alkyl, R^5 is –H and R^4 is -O-alkynylene-cycloalkyl.

In another embodiment, R^1 is alkyl, R^5 is –H and R^4 is haloalkyl.

In still another embodiment, R^1 is alkyl, R^5 is –H and R^4 is –O-N=C$(R^7)_2$.

In one embodiment, R^1 is haloalkyl, R^5 is –H and R^4 is –O-alkynyl.

In another embodiment, R^1 is haloalkyl, R^5 is –H and R^4 is -O-alkynylene-cycloalkyl.

In another embodiment, R^1 is haloalkyl, R^5 is –H and R^4 is haloalkyl.

In still another embodiment, R^1 is haloalkyl, R^5 is –H and R^4 is –O-N=C$(R^7)_2$.

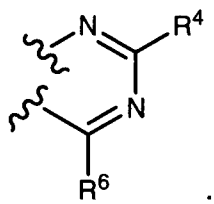
In one embodiment, R^1 is -alkylene-cycloalkyl, R^5 is –H and R^4 is –O-alkynyl.

In another embodiment, R^1 is -alkylene-cycloalkyl, R^5 is –H and R^4 is -O-alkynylene-cycloalkyl.

In yet another embodiment, R^1 is -alkylene-cycloalkyl, R^5 is –H and R^4 is haloalkyl.

In still another embodiment, R^1 is -alkylene-cycloalkyl, R^5 is –H and R^4 is –O-N=C$(R^7)_2$.

The following embodiments refer to the compounds of formula (II), wherein Q is:



.

In one embodiment, R^1 is alkyl.

In another embodiment, R^1 is haloalkyl.

In another embodiment, R^1 is arylalkyl.

In still another embodiment, R^1 is -alkylene-S-alkyl.

In yet another embodiment, R^1 is -alkylene-cycloalkyl.

In another embodiment, R^1 is -alkylene-cyclopropyl, -alkylene-cyclobutyl, -alkylene-cyclopentyl or -alkylene-cyclohexyl.

In a further embodiment, R^1 is -alkylene-cycloalkenyl.

In another embodiment, R^1 is a straight chain alkyl having from 1 to 6 carbon atoms.

In one embodiment, R^1 is methyl.

In another embodiment, R^1 is ethyl.

In another embodiment, R^1 is n-propyl.

In still another embodiment, R^1 is n-butyl.

In one embodiment, R^1 is n-pentyl.

In another embodiment, R^1 is n-hexyl.

In yet another embodiment, R^1 is a branched chain alkyl having from 3 to 6 carbon atoms.

In a further embodiment, R^1 is isopropyl.

In one embodiment, R^1 is isobutyl.

In another embodiment, R^1 is isopentyl.

In another embodiment, R^1 is sec-butyl.

In still another embodiment, R^1 is tert-butyl.

In yet another embodiment, R^1 is haloalkyl, having from 1 to 3 F atoms.

In another embodiment, R^1 is $-(CH_2)_3CF_3$.

In one embodiment, R^2 is –H.

In another embodiment, R^2 is –CN.

In another embodiment, R^2 is -NHC(O)-alkyl.

In still another embodiment, R^2 is $-NHC(O)CH_3$.

In one embodiment, R^4 is $-CF_3$.

In another embodiment, R^4 is –H.

In another embodiment, R^4 is -O-cycloalkyl.

In another embodiment, R^4–O-alkynyl.

In still another embodiment, R^4 is -O-alkynylene-cycloalkyl.

In yet another embodiment, R^4 is haloalkyl.

In a further embodiment, R^4 is $-O\text{-}N{=}C(R^7)_2$.

In one embodiment, R^4 is is $-CH_2F$.

In another embodiment, R^4 is $-CH(F)_2$.

In another embodiment, R^4 is $-CF_3$.

In another embodiment, R^4 is $-OCH_2C{\equiv}CCH_2CH_3$.

In another embodiment, R^4 is $-OCH_2C{\equiv}C(CH_2)_3CH_3$.

In still another embodiment, R^4 is $-OCH_2C{\equiv}CCH_2CH_2CH_3$.

In yet another embodiment, R^4 is $-OCH_2C{\equiv}C$-cyclopropyl.

In a further embodiment, R^4 is $-OCH_2C{\equiv}CCH(OCH_3)CH_3$.

In one embodiment, R^4 is $-OCH_2C{\equiv}CCH(OH)CH_3$.

In another embodiment, R^4 is $-OCH_2C{\equiv}CCH(OH)CH_2CH_3$.

In another embodiment, R^4 is $-OCH_2C{\equiv}CCH_2CH_2OCH_3$.

In still another embodiment, R^4 is $-OCH_2C{\equiv}CCH_2CH_2OH$.

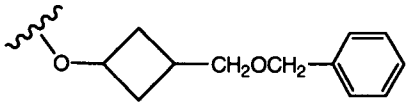
In yet another embodiment, R^4 is $-OCH_2C{\equiv}C(CH_2)_3OH$.

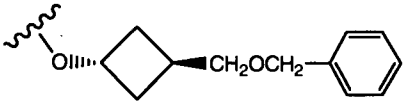
In a further embodiment, R^4 is $-OCH(CH_3)C{\equiv}CCH_2CH_3$.

In another embodiment, R^4 is $-OCH_2C{\equiv}C$-cyclohexyl.

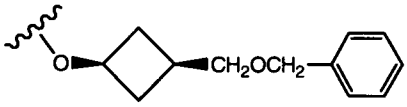
In one embodiment, R^4 is –O-cyclobutyl.

In another embodiment, R^4 is:



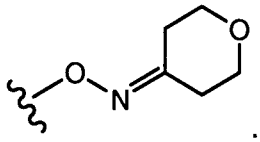
,


or



.

In one embodiment, R^4 is:



.

In one embodiment, R^6 is alkoxy.

In another embodiment, R^6 is -O-alkylene-O-alkyl.

In another embodiment, R^6 is -O-arylalkyl.

In still another embodiment, R^6 is –O-haloalkyl.

In yet another embodiment, R^6 is $-OCH_2$-(4-methoxyphenyl).

In one embodiment, R^6 is $-OCH_2F$.

In another embodiment, R^6 is $-OCH_2CH_2F$.

In another embodiment, R^6 is $-OCH_2CH_3$

In still another embodiment, R^6 is $-OCH_2CH_2OCH_3$.

In one embodiment, R^1 is alkyl and R^4 is –O-alkynyl.

In another embodiment, R^1 is alkyl and R^4 is -O-alkynylene-cycloalkyl.

In another embodiment, R^1 is alkyl and R^4 is haloalkyl.

In still another embodiment, R^1 is alkyl and R^4 is $-O-N=C(R^7)_2$.

In one embodiment, R^1 is haloalkyl and R^4 is –O-alkynyl.

In another embodiment, R^1 is haloalkyl and R^4 is -O-alkynylene-cycloalkyl.

In another embodiment, R^1 is haloalkyl and R^4 is haloalkyl.

In still another embodiment, R^1 is haloalkyl and R^4 is $-O-N=C(R^7)_2$.

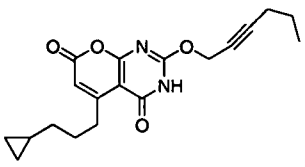
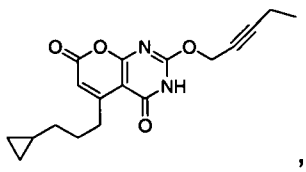
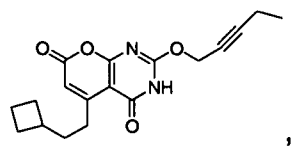
In one embodiment, R^1 is -alkylene-cycloalkyl and R^4 is –O-alkynyl.

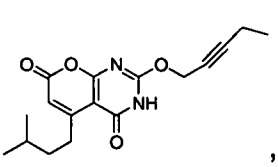
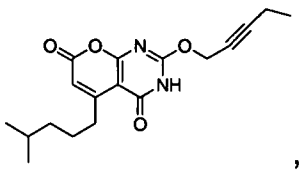
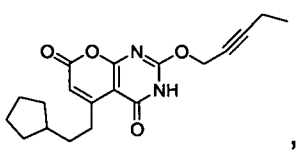
In another embodiment, R^1 is -alkylene-cycloalkyl and R^4 is -O-alkynylene-cycloalkyl.

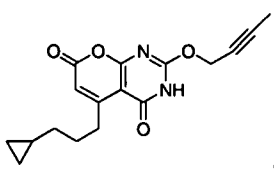
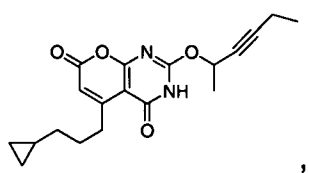
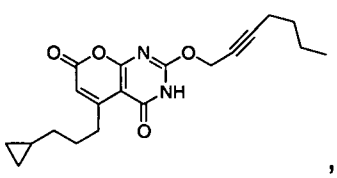
In yet another embodiment, R^1 is -alkylene-cycloalkyl and R^4 is haloalkyl.

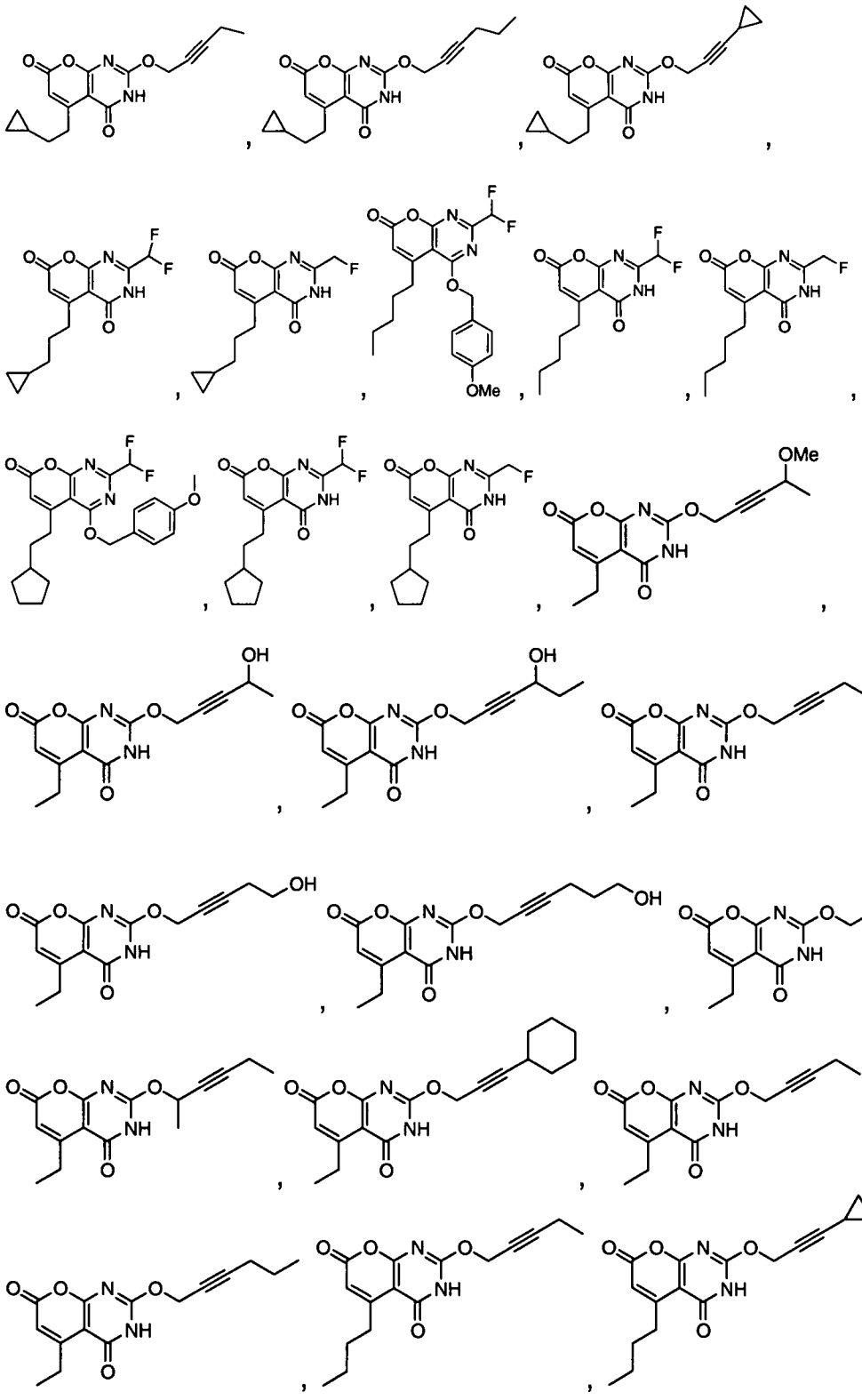
In still another embodiment, R^1 is -alkylene-cycloalkyl and R^4 is $-O-N=C(R^7)_2$.

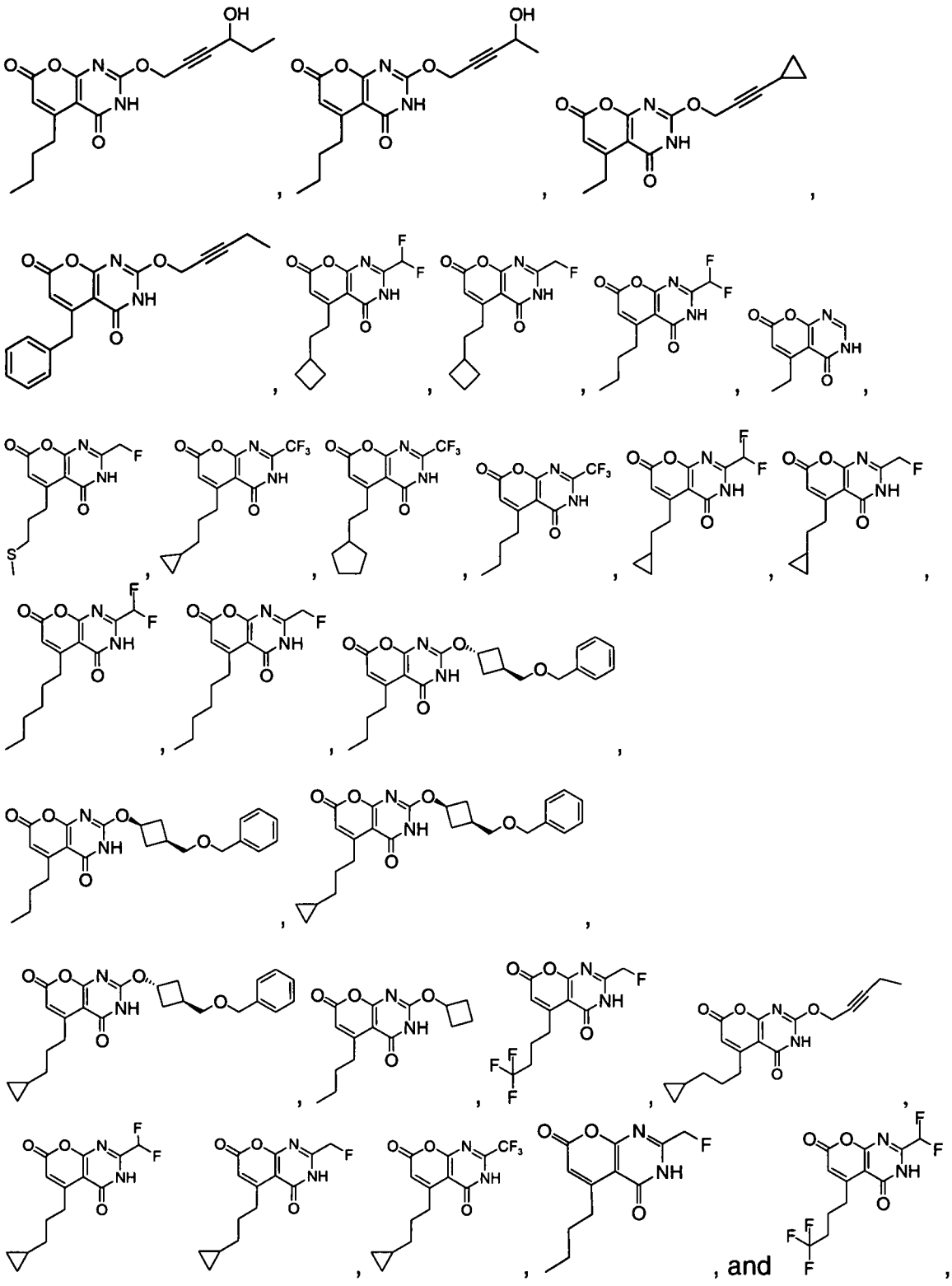
Non-limiting illustrative examples of the compounds of formula (II), include the following compounds:


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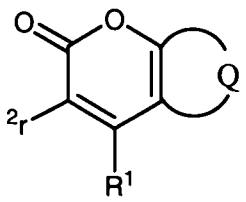

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and pharmaceutically acceptable salts, solvates, esters, or tautomers thereof.

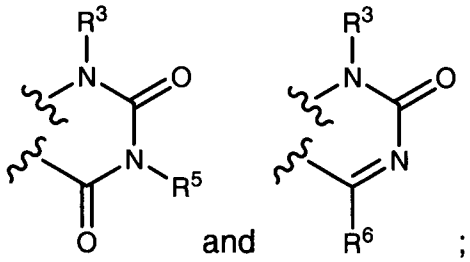
In one embodiment, the compounds of formula (I) have the formula (III):



(III)

and pharmaceutically acceptable salts, solvates, esters, or tautomers thereof, wherein:

Q is selected from the group consisting of:



;

R^1 is –H, alkyl, haloalkyl, arylalkyl, -alkylene-S-alkyl or -alkylene-cycloalkyl;

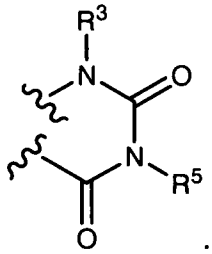
R^2 is –H, -CN, or -NHC(O)-alkyl;

R^3 is –H, -OH, alkyl, haloalkyl, arylalkyl, -O-alkyl, -O-aryl, cycloalkyl, heterocyclyl, -O-cycloalkyl, -O-heterocyclyl, -O-arylalkyl or -alkylene-O-alkyl;

R^5 is –H, -OH, alkyl, haloalkyl, arylalkyl, -O-alkyl, -O-aryl, cycloalkyl, heterocyclyl, -O-cycloalkyl, -O-heterocyclyl, -O-arylalkyl or -alkylene-O-alkyl; and

R^6 is alkoxy, -O-alkylene-O-alkyl, -O-arylalkyl or –O-haloalkyl.

The following embodiments refer to the compounds of formula (III), wherein Q is:



In one embodiment, R^1 is alkyl.

In another embodiment, R^1 is haloalkyl.

In another embodiment, R^1 is -alkylene-S-alkyl.

In still another embodiment, R^1 is -arylalkyl.

In yet another embodiment, R^1 is -alkylene.

In a further embodiment, R^1 is –cycloalkyl.

In one embodiment, R^1 is -alkylene-cycloalkenyl.

In another embodiment, R^1 is a straight chain alkyl having from 1 to 6 carbon atoms.

In one embodiment, R^1 is methyl.

In another embodiment, R^1 is ethyl.

In another embodiment, R^1 is n-propyl.

In still another embodiment, R^1 is n-butyl.

In one embodiment, R^1 is n-pentyl.

In another embodiment, R^1 is n-hexyl.

In yet another embodiment, R^1 is a branched chain alkyl having from 3 to 6 carbon atoms.

In a further embodiment, R^1 is isopropyl.

In one embodiment, R^1 is isobutyl.

In another embodiment, R^1 is isopentyl.

In another embodiment, R^1 is sec-butyl.

In still another embodiment, R^1 is tert-butyl.

In yet another embodiment, R^1 is haloalkyl, having from 1 to 3 F atoms.

In another embodiment, R^1 is $-(CH_2)_3CF_3$.

In one embodiment, R^2 is –H.

In another embodiment, R^2 is –CN.

In another embodiment, R^2 is -NHC(O)-alkyl.

In still another embodiment, R^2 is $-NHC(O)CH_3$.

In one embodiment, R^3 is –H.

In another embodiment, R^3 is –OH.

In another embodiment, R^3 is alkyl.

In another embodiment, R^3 is haloalkyl.

In still another embodiment, R^3 is -O-alkyl.

In yet another embodiment, R^3 is cycloalkyl.

In a further embodiment, R^3 is heterocyclyl.

In one embodiment, R^3 is -O-arylalkyl.

In another embodiment, R^3 is -alkylene-O-alkyl.

In one embodiment, R^3 is $-OCH_3$.

In another embodiment, R^3 is cyclobutyl.

In another embodiment, R^3 is ethyl.

In still another embodiment, R^3 is *N*-morpholinyl.

In one embodiment, R^3 is –O-benzyl.

In another embodiment, R^3 is $-CH_2CH_2OCH_3$.

In yet another embodiment, R^3 is $-OCH_2CH_3$.

In another embodiment, R^3 is $-CH_2F$.

In one embodiment, R^3 is $-CH_2CH_2F$.

In another embodiment, R^3 is –OH.

In one embodiment, R^5 is –H.

In another embodiment, R^5 is –OH.

In another embodiment, R^5 is alkyl.

In another embodiment, R^5 is haloalkyl.

In still another embodiment, R^5 is -O-alkyl.

In yet another embodiment, R^5 is cycloalkyl.

In a further embodiment, R^5 is heterocyclyl.

In one embodiment, R^5 is -O-arylalkyl.

In another embodiment, R^5 is -alkylene-O-alkyl.

In one embodiment, R^5 is $-OCH_3$.

In another embodiment, R^5 is cyclobutyl.

In another embodiment, R^5 is ethyl.

In still another embodiment, R^5 is *N*-morpholinyl.

In one embodiment, R^5 is –O-benzyl.

In another embodiment, R^5 is $-CH_2CH_2OCH_3$.

In yet another embodiment, R^5 is $-OCH_2CH_3$.

In another embodiment, R^5 is $-CH_2F$.

In one embodiment, R^5 is $-CH_2CH_2F$.

In another embodiment, R^5 is –OH.

In one embodiment, R^1 is alkyl, and each of R^2, R^3 and R^5 is -H.

In another embodiment, R^1 is alkyl, R^2 is –H, and one, but not both of R^3 and R^5 is -H.

In another embodiment, R^1 is alkyl, R^2 is –H, and one of R^3 and R^5 is –H and the other is alkyl.

In still another embodiment, R^1 is alkyl, R^2 is –H, and one of R^3 and R^5 is –H and the other is –O-alkyl.

In yet another embodiment, R^1 is alkyl, R^2 is –H, and one of R^3 and R^5 is –H and the other is –cycloalkyl.

In one embodiment, R^1 is alkyl, R^2 is –H, and one of R^3 and R^5 is –H and the other is –heterocyclyl.

In one embodiment, R^1 is alkyl, R^2 is –H, and one of R^3 and R^5 is –H and the other is –alkylene-O-alkyl.

In one embodiment, R^1 is –alkylene-cycloalkyl, and each of R^2, R^3 and R^5 is -H.

In another embodiment, R^1 is –alkylene-cycloalkyl, R^2 is –H, and one, but not both of R^3 and R^5 is -H.

In another embodiment, R^1 is –alkylene-cycloalkyl, R^2 is –H, and one of R^3 and R^5 is –H and the other is alkyl.

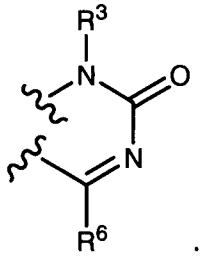
In still another embodiment, R^1 is –alkylene-cycloalkyl, R^2 is –H, and one of R^3 and R^5 is –H and the other is –O-alkyl.

In yet another embodiment, R^1 is –alkylene-cycloalkyl, R^2 is –H, and one of R^3 and R^5 is –H and the other is –cycloalkyl.

In one embodiment, R^1 is –alkylene-cycloalkyl, R^2 is –H, and one of R^3 and R^5 is –H and the other is –heterocyclyl.

In one embodiment, R^1 is –alkylene-cycloalkyl, R^2 is –H, and one of R^3 and R^5 is –H and the other is –alkylene-O-alkyl.

The following embodiments refer to the compounds of formula (III), wherein Q is:



In one embodiment, R^6 is alkoxy.

In another embodiment, R^6 is -O-alkylene-O-alkyl.

In another embodiment, R^6 is -O-arylalkyl.

In still another embodiment, R^6 is –O-haloalkyl.

In yet another embodiment, R^6 is $-OCH_2$-(4-methoxyphenyl).

In one embodiment, R^6 is $-OCH_2F$.

In another embodiment, R^6 is $-OCH_2CH_2F$.

In another embodiment, R^6 is $-OCH_2CH_3$

In still another embodiment, R^6 is $-OCH_2CH_2OCH_3$.

In one embodiment, R^1 is alkyl.

In another embodiment, R^1 is haloalkyl.

In another embodiment, R^1 is -alkylene-S-alkyl.

In still another embodiment, R^1 is -arylalkyl.

In yet another embodiment, R^1 is -alkylene.

In a further embodiment, R^1 is –cycloalkyl.

In one embodiment, R^1 is -alkylene-cycloalkenyl.

In another embodiment, R^1 is a straight chain alkyl having from 1 to 6 carbon atoms.

In one embodiment, R^1 is methyl.

In another embodiment, R^1 is ethyl.

In another embodiment, R^1 is n-propyl.

In still another embodiment, R^1 is n-butyl.

In one embodiment, R^1 is n-pentyl.

In another embodiment, R^1 is n-hexyl.

In yet another embodiment, R^1 is a branched chain alkyl having from 3 to 6 carbon atoms.

In a further embodiment, R^1 is isopropyl.

In one embodiment, R^1 is isobutyl.

In another embodiment, R^1 is isopentyl.

In another embodiment, R^1 is sec-butyl.

In still another embodiment, R^1 is tert-butyl.

In yet another embodiment, R^1 is haloalkyl, having from 1 to 3 F atoms.

In another embodiment, R^1 is $-(CH_2)_3CF_3$.

In one embodiment, R^2 is –H.

In another embodiment, R^2 is –CN.

In another embodiment, R^2 is -NHC(O)-alkyl.

In still another embodiment, R^2 is $-NHC(O)CH_3$.

In one embodiment, R^3 is –H.

In another embodiment, R^3 is –OH.

In another embodiment, R^3 is alkyl.

In another embodiment, R^3 is haloalkyl.

In still another embodiment, R^3 is -O-alkyl.

In yet another embodiment, R^3 is cycloalkyl.

In a further embodiment, R^3 is heterocyclyl.

In one embodiment, R^3 is -O-arylalkyl.

In another embodiment, R^3 is -alkylene-O-alkyl.

In one embodiment, R^3 is $-OCH_3$.

In another embodiment, R^3 is cyclobutyl.

In another embodiment, R^3 is ethyl.

In still another embodiment, R^3 is *N*-morpholinyl.

In one embodiment, R^3 is –O-benzyl.

In another embodiment, R^3 is $-CH_2CH_2OCH_3$.

In yet another embodiment, R^3 is $-OCH_2CH_3$.

In another embodiment, R^3 is $-CH_2F$.

In one embodiment, R^3 is $-CH_2CH_2F$.

In another embodiment, R^3 is –OH.

In one embodiment, R^6 is alkoxy, R^1 is alkyl, and each of R^2 and R^3 is -H.

In another embodiment, R^6 is alkoxy, R^1 is alkyl, R^2 is –H, and R^3 is alkyl.

In still another embodiment, R^6 is alkoxy, R^1 is alkyl, R^2 is –H, and R^3 is –O-alkyl.

In yet another embodiment, R^6 is alkoxy, R^1 is alkyl, R^2 is –H, and R^3 is –cycloalkyl.

In one embodiment, R^6 is alkoxy, R^1 is alkyl, R^2 is –H, and and R^3 is –heterocyclyl.

In one embodiment, R^6 is alkoxy, R^1 is alkyl, R^2 is –H, and R^3 is –alkylene-O-alkyl.

In one embodiment, R^6 is alkoxy, R^1 is –alkylene-cycloalkyl, and each of R^2 and R^3 is -H.

In another embodiment, R^6 is alkoxy, R^1 is –alkylene-cycloalkyl, R^2 is –H, and R^3 is alkyl.

In still another embodiment, R^6 is alkoxy, R^1 is –alkylene-cycloalkyl, R^2 is –H, and R^3 is –O-alkyl.

In yet another embodiment, R^6 is alkoxy, R^1 is –alkylene-cycloalkyl, R^2 is –H, and R^3 is –cycloalkyl.

In one embodiment, R^6 is alkoxy, R^1 is –alkylene-cycloalkyl, R^2 is –H, and R^3 is –heterocyclyl.

In one embodiment, R^6 is alkoxy, R^1 is –alkylene-cycloalkyl, R^2 is –H, and R^3 is –alkylene-O-alkyl.

In one embodiment, R^6 is -O-alkylene-O-alkyl, R^1 is alkyl, and each of R^2 and R^3 is -H.

In another embodiment, R^6 is -O-alkylene-O-alkyl, R^1 is alkyl, R^2 is –H, and R^3 is alkyl.

In still another embodiment, R^6 is -O-alkylene-O-alkyl, R^1 is alkyl, R^2 is –H, and R^3 is –O-alkyl.

In yet another embodiment, R^6 is -O-alkylene-O-alkyl, R^1 is alkyl, R^2 is –H, and R^3 is –cycloalkyl.

In one embodiment, R^6 is -O-alkylene-O-alkyl, R^1 is alkyl, R^2 is –H, and and R^3 is –heterocyclyl.

In one embodiment, R^6 is -O-alkylene-O-alkyl, R^1 is alkyl, R^2 is –H, and R^3 is –alkylene-O-alkyl.

In one embodiment, R^6 is -O-alkylene-O-alkyl, R^1 is –alkylene-cycloalkyl, and each of R^2 and R^3 is -H.

In another embodiment, R^6 is -O-alkylene-O-alkyl, R^1 is –alkylene-cycloalkyl, R^2 is –H, and R^3 is alkyl.

In still another embodiment, R^6 is -O-alkylene-O-alkyl, R^1 is –alkylene-cycloalkyl, R^2 is –H, and R^3 is –O-alkyl.

In yet another embodiment, R^6 is -O-alkylene-O-alkyl, R^1 is –alkylene-cycloalkyl, R^2 is –H, and R^3 is –cycloalkyl.

In one embodiment, R^6 is -O-alkylene-O-alkyl, R^1 is –alkylene-cycloalkyl, R^2 is –H, and R^3 is –heterocyclyl.

In one embodiment, R^6 is -O-alkylene-O-alkyl, R^1 is –alkylene-cycloalkyl, R^2 is –H, and R^3 is –alkylene-O-alkyl.

In one embodiment, R^6 is -O-arylalkyl, R^1 is alkyl, and each of R^2 and R^3 is -H.

In another embodiment, R^6 is -O-arylalkyl, R^1 is alkyl, R^2 is –H, and R^3 is alkyl.

In still another embodiment, R^6 is -O-arylalkyl, R^1 is alkyl, R^2 is –H, and R^3 is –O-alkyl.

In yet another embodiment, R^6 is -O-arylalkyl, R^1 is alkyl, R^2 is –H, and R^3 is –cycloalkyl.

In one embodiment, R^6 is -O-arylalkyl, R^1 is alkyl, R^2 is –H, and and R^3 is –heterocyclyl.

In one embodiment, R^6 is -O-arylalkyl, R^1 is alkyl, R^2 is –H, and R^3 is –alkylene-O-alkyl.

In one embodiment, R^6 is -O-arylalkyl, R^1 is –alkylene-cycloalkyl, and each of R^2 and R^3 is -H.

In another embodiment, R^6 is -O-arylalkyl, R^1 is –alkylene-cycloalkyl, R^2 is –H, and R^3 is alkyl.

In still another embodiment, R^6 is -O-arylalkyl, R^1 is –alkylene-cycloalkyl, R^2 is –H, and R^3 is –O-alkyl.

In yet another embodiment, R^6 is -O-arylalkyl, R^1 is –alkylene-cycloalkyl, R^2 is –H, and R^3 is –cycloalkyl.

In one embodiment, R^6 is -O-arylalkyl, R^1 is –alkylene-cycloalkyl, R^2 is –H, and R^3 is –heterocyclyl.

In one embodiment, R^6 is -O-arylalkyl, R^1 is –alkylene-cycloalkyl, R^2 is –H, and R^3 is –alkylene-O-alkyl.

In one embodiment, R^6 is -O-haloalkyl, R^1 is alkyl, and each of R^2 and R^3 is -H.

In another embodiment, R^6 is -O-haloalkyl, R^1 is alkyl, R^2 is –H, and R^3 is alkyl.

In still another embodiment, R^6 is -O-haloalkyl, R^1 is alkyl, R^2 is –H, and R^3 is –O-alkyl.

In yet another embodiment, R^6 is -O-haloalkyl, R^1 is alkyl, R^2 is –H, and R^3 is –cycloalkyl.

In one embodiment, R^6 is -O-haloalkyl, R^1 is alkyl, R^2 is –H, and and R^3 is –heterocyclyl.

In one embodiment, R^6 is -O-haloalkyl, R^1 is alkyl, R^2 is –H, and R^3 is –alkylene-O-alkyl.

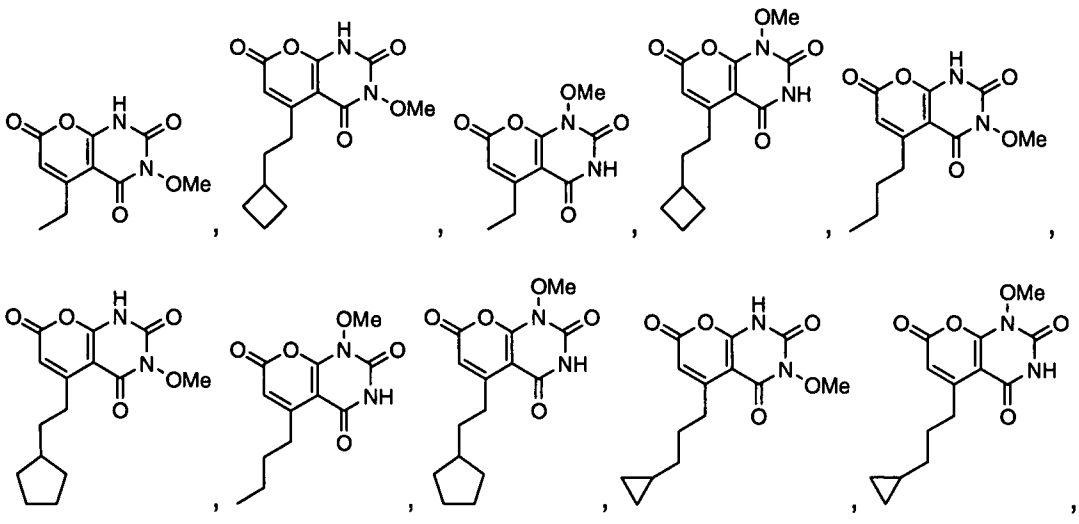
In one embodiment, R^6 is -O-haloalkyl, R^1 is –alkylene-cycloalkyl, and each of R^2 and R^3 is -H.

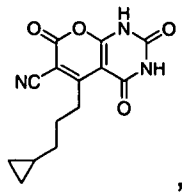
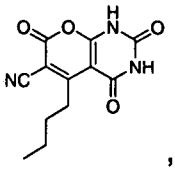
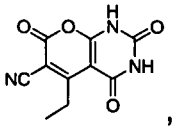
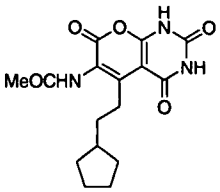
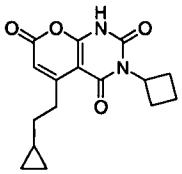
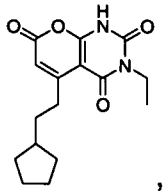
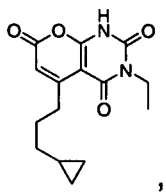
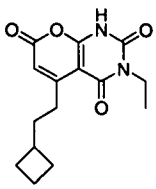
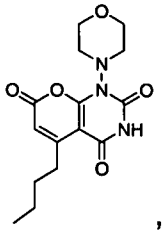
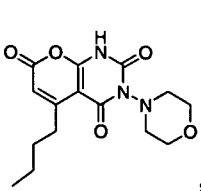
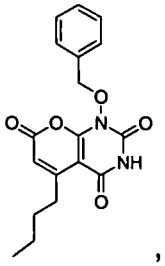
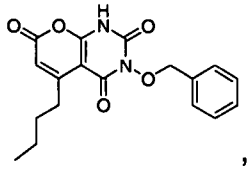
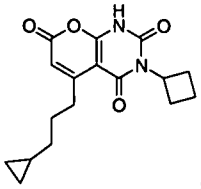
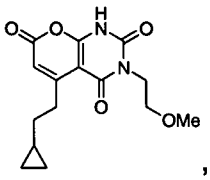
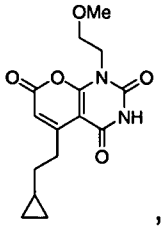
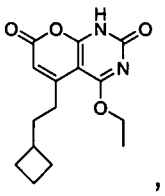
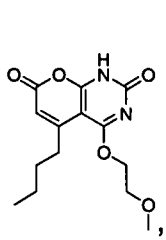
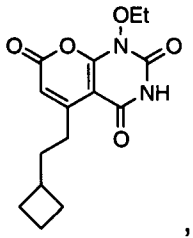
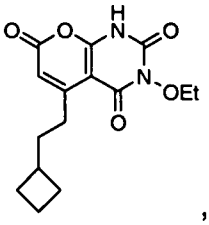
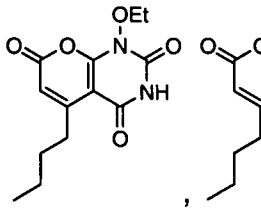
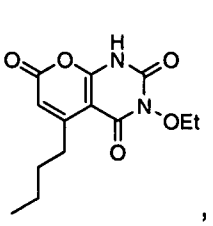
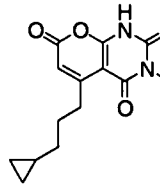
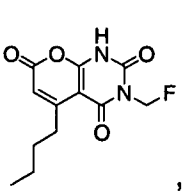
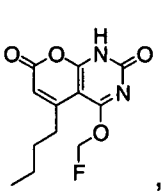
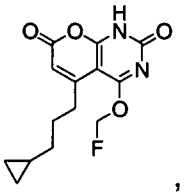
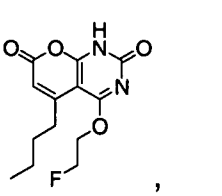
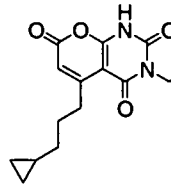
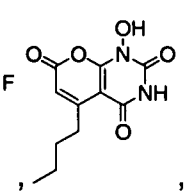
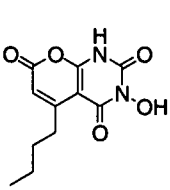
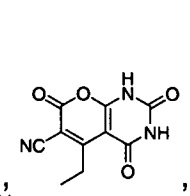
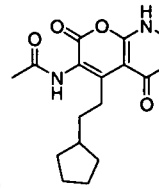
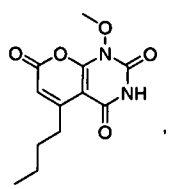
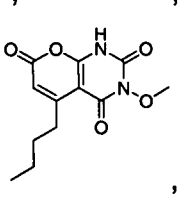
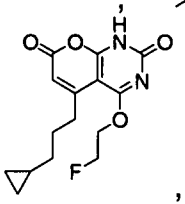
In another embodiment, R^6 is -O-haloalkyl, R^1 is –alkylene-cycloalkyl, R^2 is –H, and R^3 is alkyl.

In still another embodiment, R^6 is -O-haloalkyl, R^1 is –alkylene-cycloalkyl, R^2 is –H, and R^3 is –O-alkyl.

In yet another embodiment, R^6 is –O-haloalkyl, R^1 is –alkylene-cycloalkyl, R^2 is –H, and R^3 is –cycloalkyl.

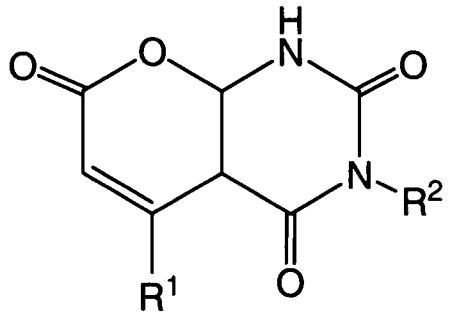
Non-limiting illustrative examples of the compounds of formula (III), include the following compounds:




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

In one embodiment, the compounds of formula (I) are compounds of formula (IV):



(IV)

and and pharmaceutically acceptable salts, solvates, esters, and tautomers thereof, wherein:

R^1 is haloalkyl; and

R^2 is H or cycloalkyl.

In one embodiment, R^1 is fluoroalkyl.

In another embodiment, R^1 is –alkylene-F.

In another embodiment, R^1 is –alkylene-CF_2.

In still another embodiment, R^1 is $-(CH_2)_2-CF_2$.

In another embodiment, R^1 is $-(CH_2)_3-CF_2$.

In another embodiment, R^1 is $-(CH_2)_4-CF_2$.

In yet another embodiment, R^1 is $-(CH_2)_5-CF_2$.

In still another embodiment, R^1 is $-(CH_2)_3-F$.

In another embodiment, R^1 is $-(CH_2)_4-F$.

In another embodiment, R^1 is $-(CH_2)_5-F$.

In yet another embodiment, R^1 is $-(CH_2)_6-F$.

In one embodiment, R^2 is H.

In another embodiment, R^2 is cyclopropyl.

In another embodiment, R^2 is cyclobutyl.

In still another embodiment, R^2 is cyclopentyl.

In another embodiment, R^2 is cyclohexyl.

In one embodiment, R^1 is fluoroalkyl and R^2 is H.

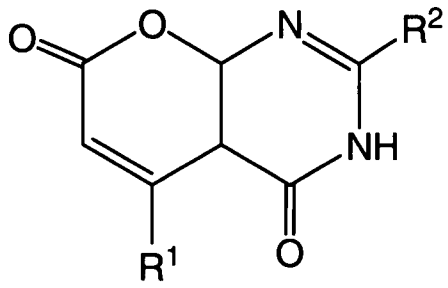
In another embodiment, R^1 is fluoroalkyl and R^2 is cycloalkyl.

In another embodiment, R^1 is –alkylene-CF_2 and R^2 is H.

In another embodiment, R^1 is –alkylene-CF_2 and R^2 is cycloalkyl.

Non-limiting examples of compounds of formula (IV) include compounds **834**, **835** and **837-841** as depicted in the Examples section below, and and pharmaceutically acceptable salts, solvates, esters, and tautomers thereof.

In another embodiment, the compounds of formula (I) are compounds of formula (V):



(V)

and and pharmaceutically acceptable salts, solvates, esters, and tautomers thereof, wherein:

R^1 and R^2 are each, independently, haloalkyl.

In one embodiment, R^1 is fluoroalkyl.

In another embodiment, R^1 is –alkylene-F.

In another embodiment, R^1 is –alkylene-CF_2.

In still another embodiment, R^1 is $-(CH_2)_2-CF_2$.

In another embodiment, R^1 is $-(CH_2)_3-CF_2$.

In another embodiment, R^1 is $-(CH_2)_4-CF_2$.

In yet another embodiment, R^1 is $-(CH_2)_5-CF_2$.

In still another embodiment, R^1 is $-(CH_2)_3-F$.

In another embodiment, R^1 is $-(CH_2)_4-F$.

In another embodiment, R^1 is $-(CH_2)_5-F$.

In yet another embodiment, R^1 is $-(CH_2)_6-F$.

In one embodiment, R^2 is fluoroalkyl.

In another embodiment, R^2 is $-CHF_2$.

In one embodiment, R^1 is fluoroalkyl and R^2 is fluroalkyl.

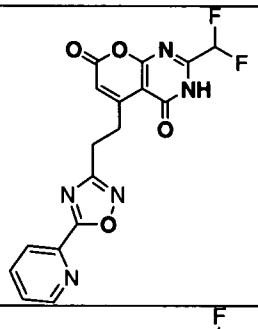
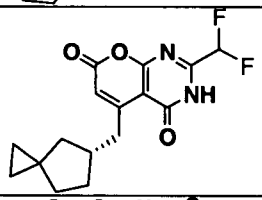
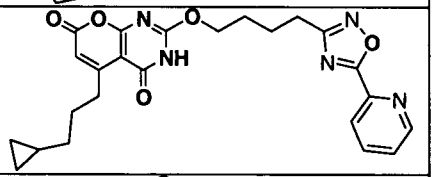
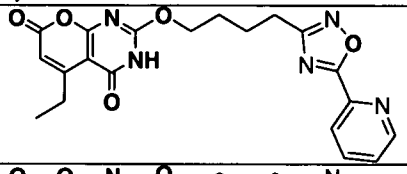
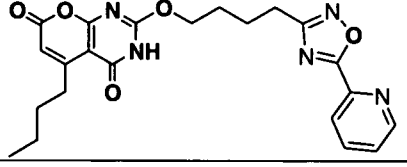
In another embodiment, R^1 is fluoroalkyl and R^2 is -CHF_2.

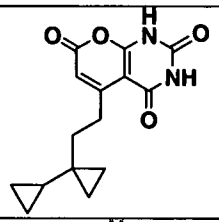
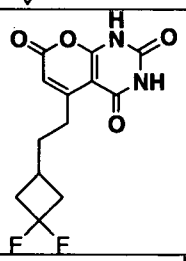
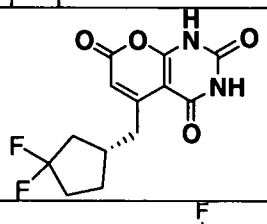
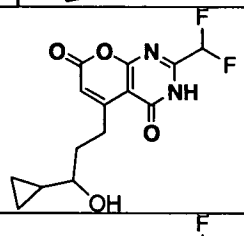
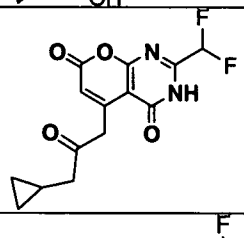
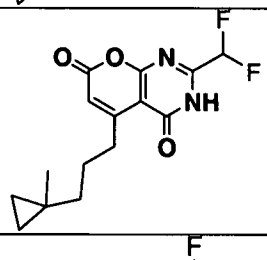
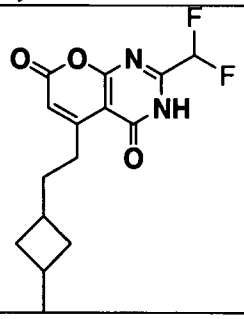
In another embodiment, R^1 is –alkylene-CF_2 and R^2 is fluoroalkyl.

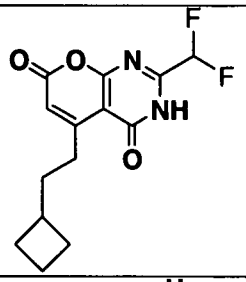
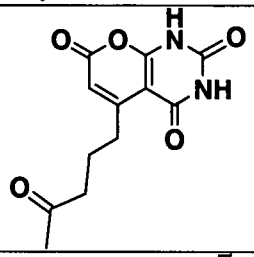
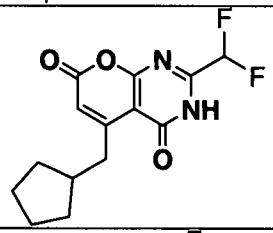
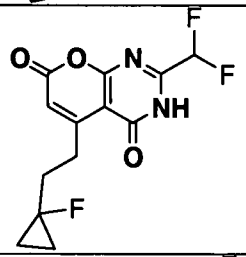
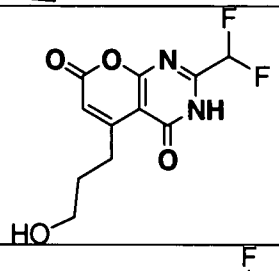
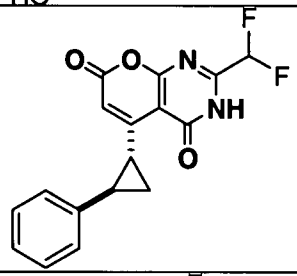
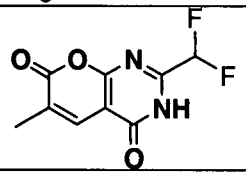
In still another embodiment, R^1 is –alkylene-CF_2 and R^2 is -CHF_2.

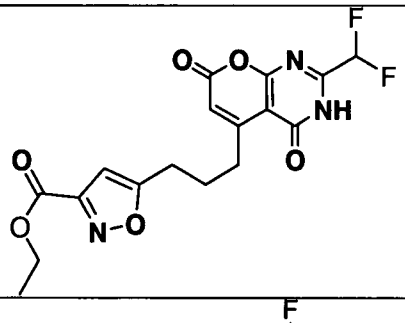
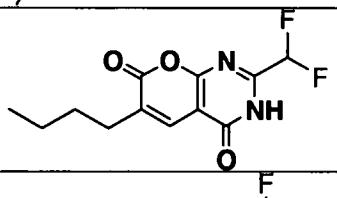
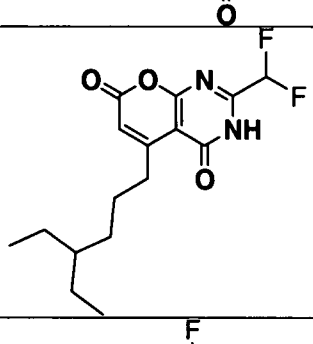
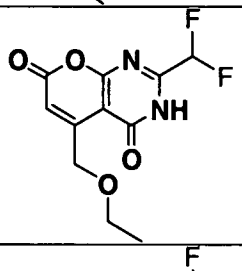
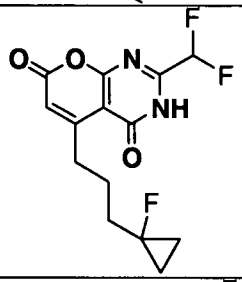
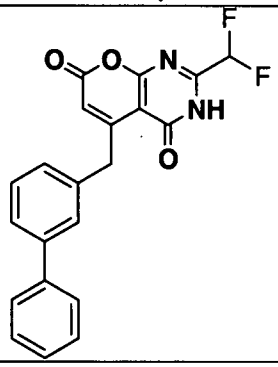
Non-limiting examples of compounds of formula (V) include compounds **836** and **842-844** as depicted in the Examples section below, and and pharmaceutically acceptable salts, solvates, esters, and tautomers thereof.

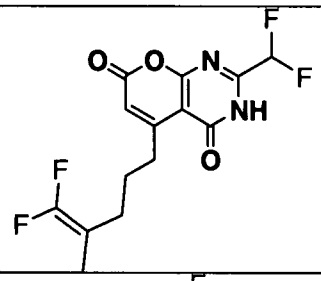
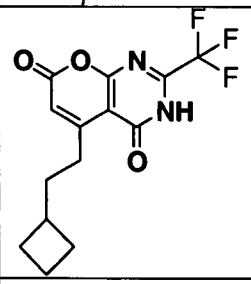
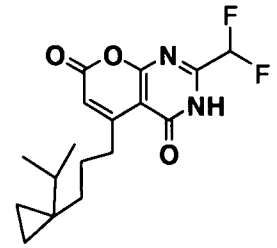
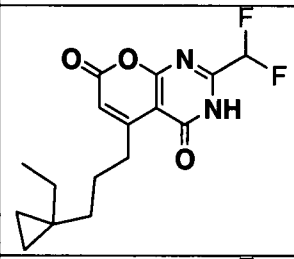
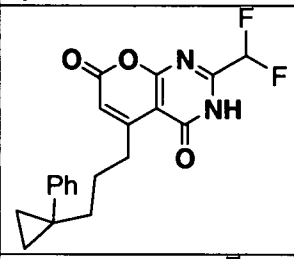
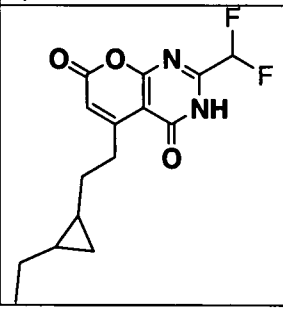
Additional non-limiting examples of compounds of formula (I) include compounds **845-911** as depicted in the following table:

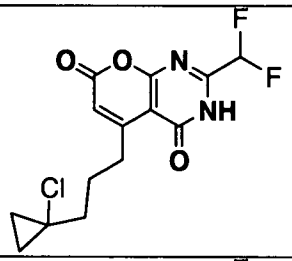
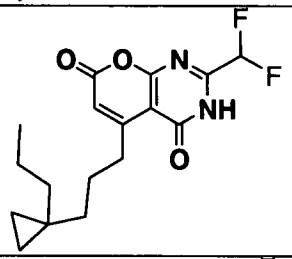
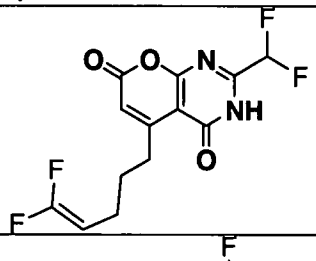
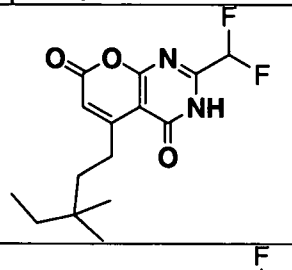
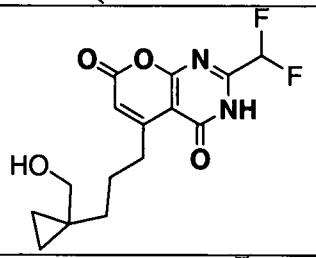
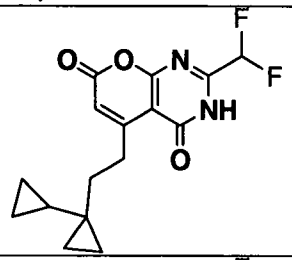
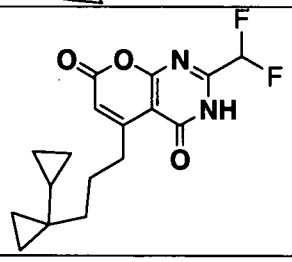
Compound No.	Structure
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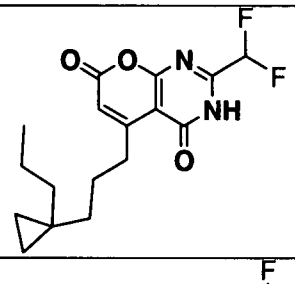
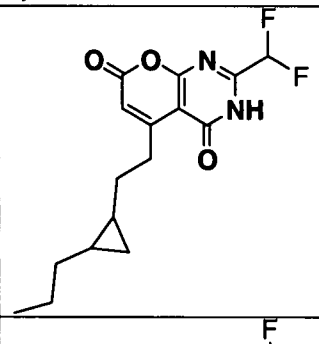
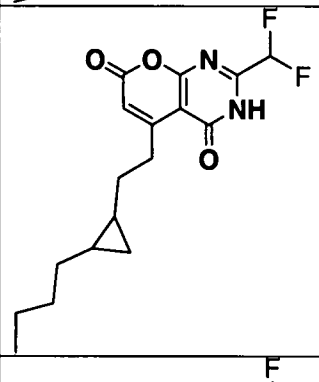
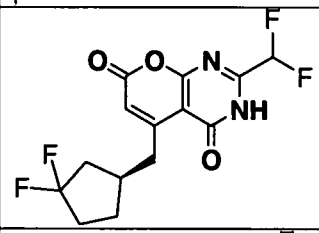
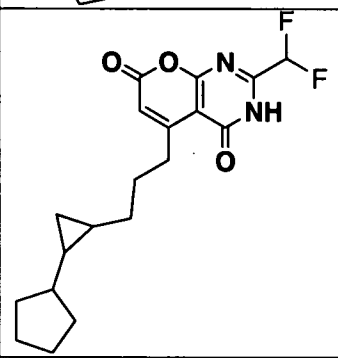
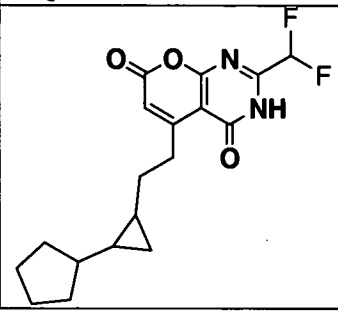
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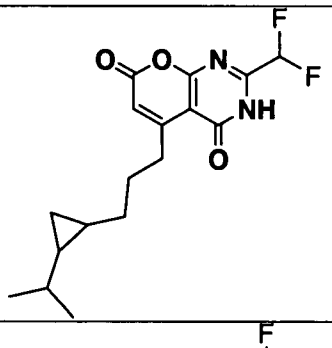
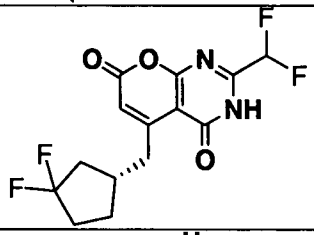
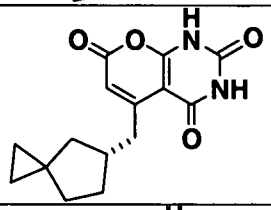
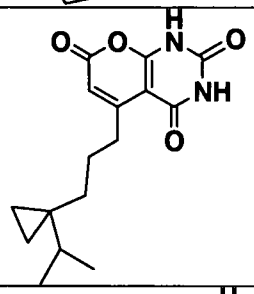
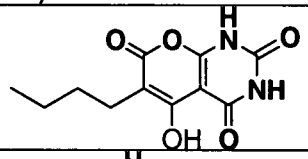
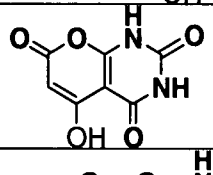
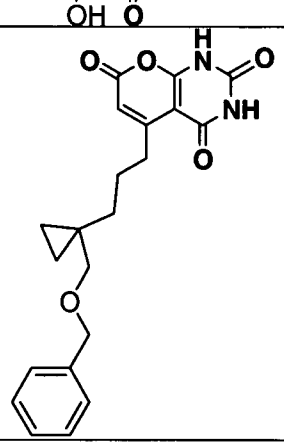
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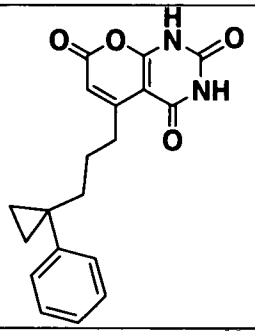
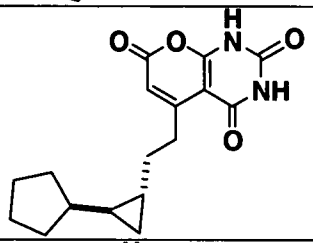
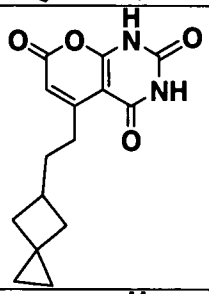
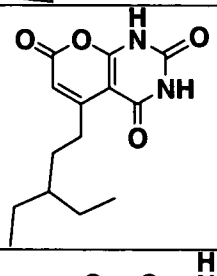
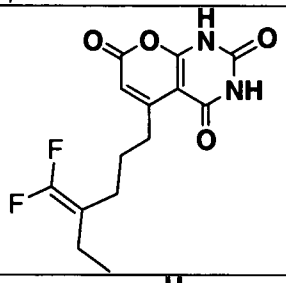
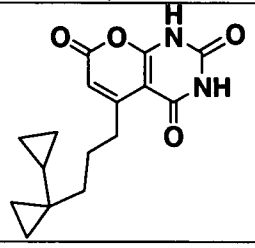
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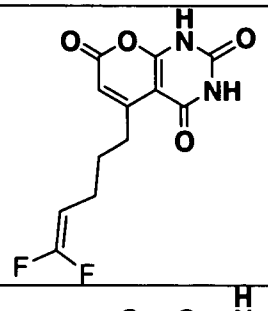
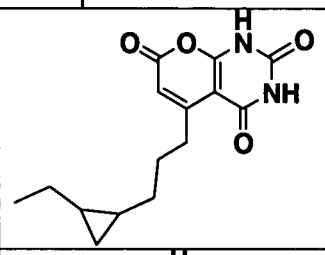
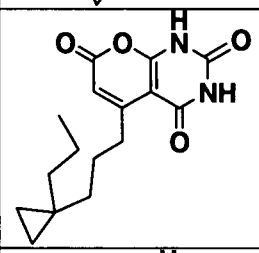
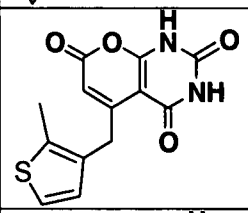
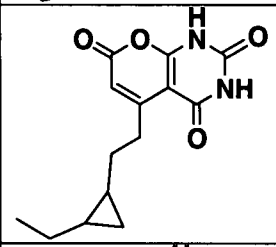
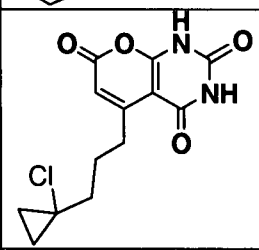
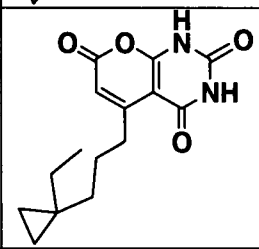
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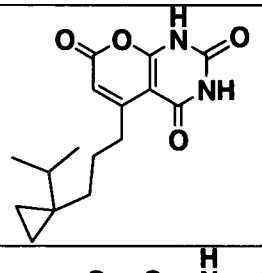
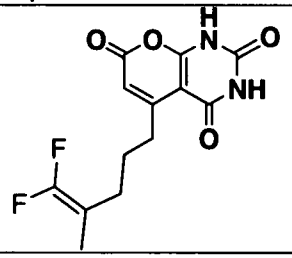
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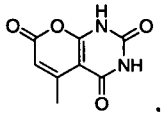
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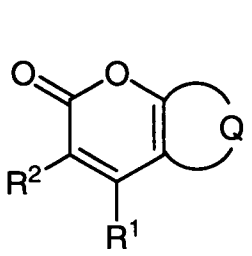
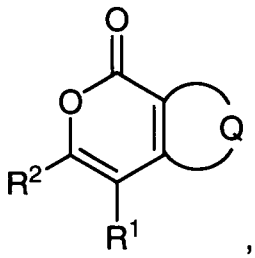
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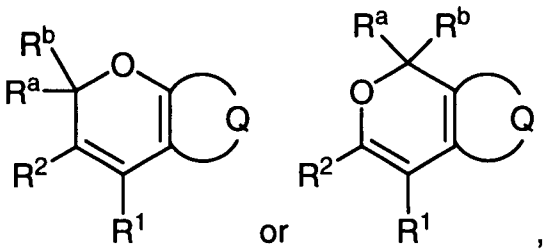
and and pharmaceutically acceptable salts, solvates, esters, and tautomers thereof.

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:

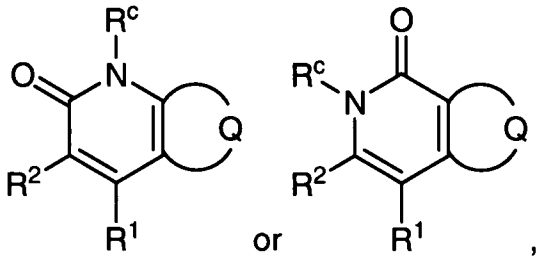


The moiety L of Formula (I) of the present invention can have any chemically stable orientation. That is, when L is (f), the compounds of Formula (I) of the present invention can include the following:

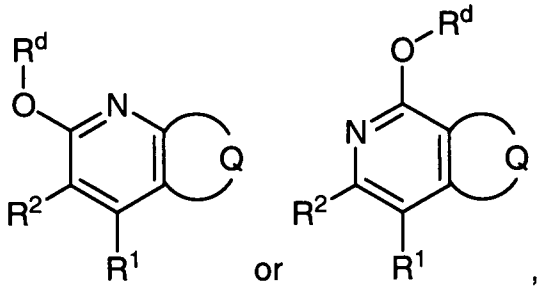
 or , or salts, solvates, esters, or tautomers thereof. When L is (g), the compounds of Formula (I) of the present invention can include the following:



, 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:



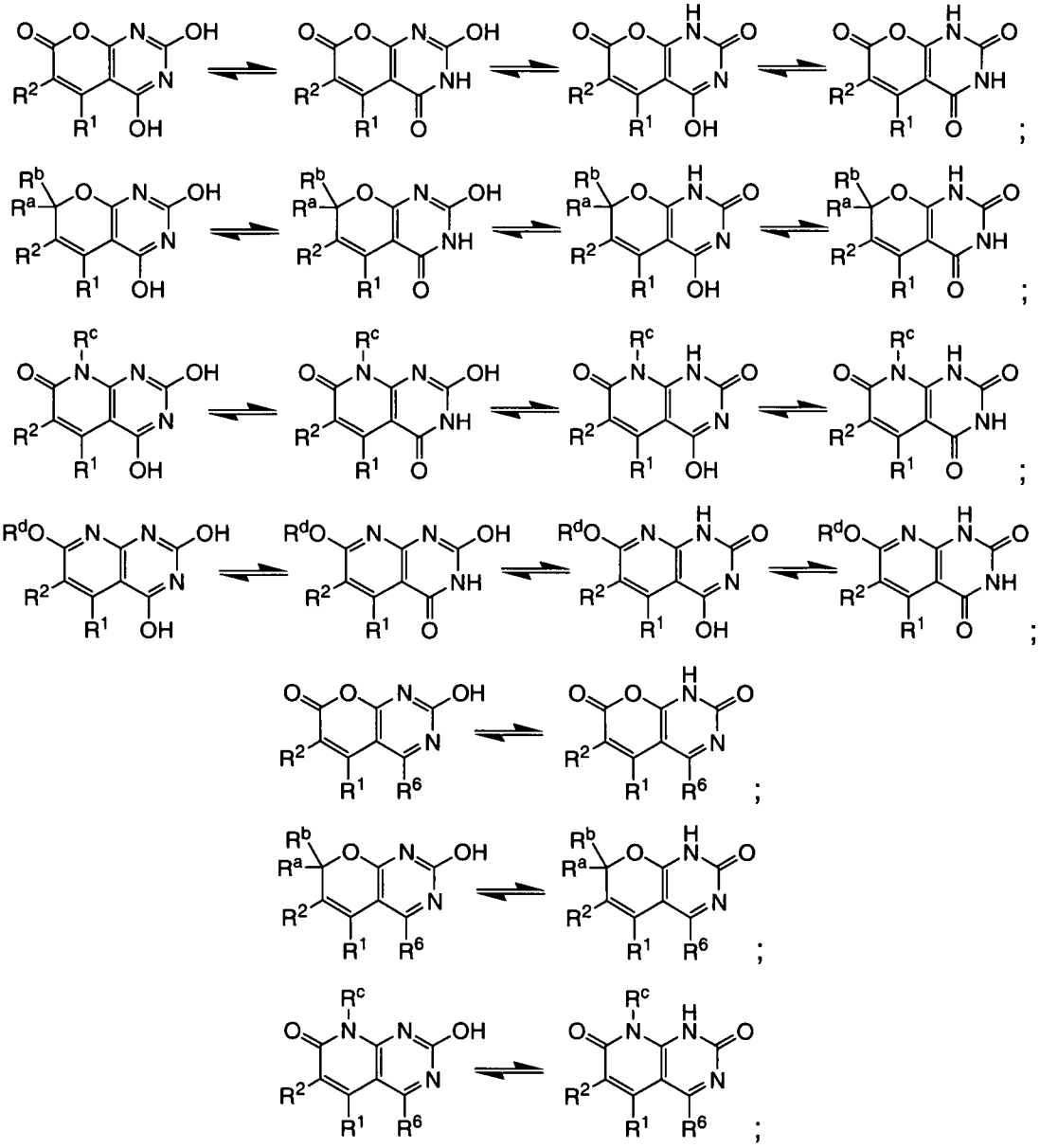
, or salts, solvates, esters, or tautomers thereof.

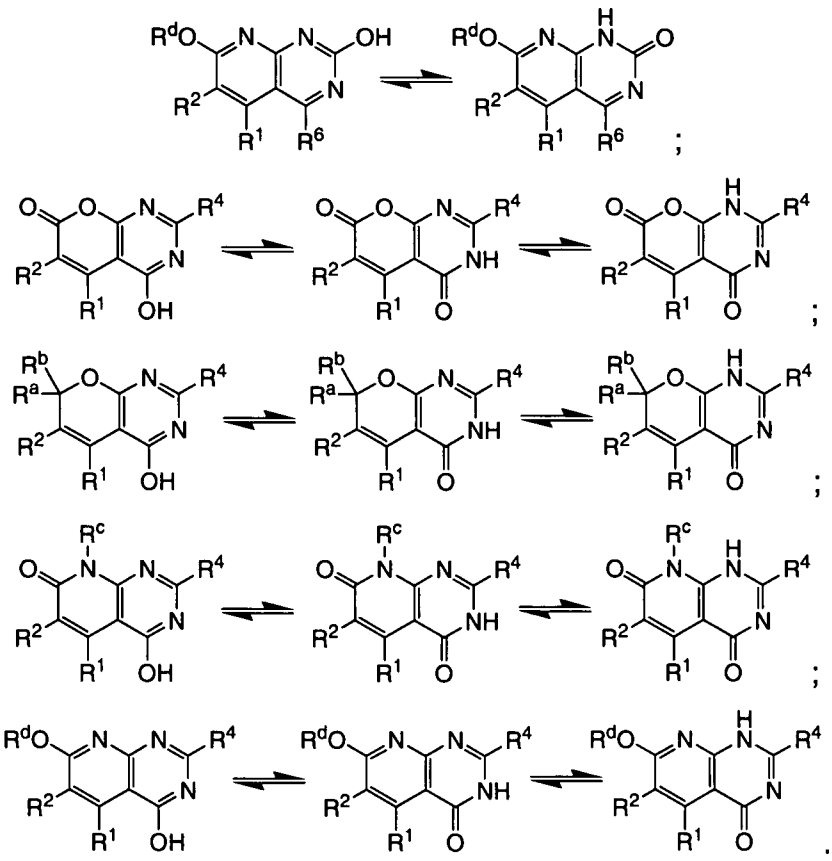
The compounds of Formula (I) can be purified to a degree suitable for use as a pharmaceutically active substance. That is, the compounds of Formula (I) can have a purity of 95 wt% or more (excluding adjuvants such as pharmaceutically acceptable carriers, solvents, etc., which are used in formulating 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:





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 meanings:

"AcOH" means acetic acid.

"Bn" means benzyl.

"BnBr" means benzyl bromide.

"BnOH" means benzyl alcohol.

"CDI" means carbodiimide.

"DCM" means dichloromethane (CH_2Cl_2).

"DIAD" means diisopropyl azodicarboxylate.

"DIEA" means N,N-diisopropylethylamine.

"DMF" means dimethylformamide.

"Et" means ethyl.

"EtO_2" means diethyl ether.

"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.

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

"Me" means methyl.

"MeCN" means acetonitrile.

"MeI" means iodomethane.

"Me_2S" means dimethyl sulfide.

"MeOH" means methanol.

"NaOEt" means sodium ethoxide.

"NaOMe" means sodium methoxide.

"NBS" means *N*-bromosuccinimide.

"NEt_3" means triethylamine.

"NIS" means *N*-iodosuccinimide.

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

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

"TFA" means trifluoroacetic acid.

"TfOH" means trifluromethanesulfonic acid.

"THF" means tetrahydrofuran.

"TLC" means thin layer chromatography.

"PMBOH" means 4-methoxybenzyl alcohol.

"PMBCl" means 4-methoxybenzyl chloride.

"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. 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 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 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 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 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 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-, $-C(CH_3)=CH-$, and $–CH=CHCH_2-$.

"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 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 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 of suitable alkynyl groups include ethynyl, propynyl, 2-butynyl 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.

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

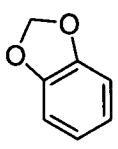
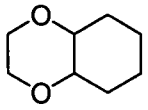
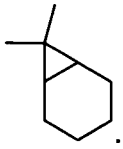
"Cycloalkenylalkyl" means a cycloalkenyl moiety as defined above linked via an alkyl moiety (defined above) to a parent core. Non-limiting examples of suitable cycloalkenylalkyls include cyclopentenylmethyl, cyclohexenylmethyl and the like.

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

The term "haloalkyl" as used herein refers to an alkyl group, as defined above, wherein one or more of the alkyl group's hydrogen atoms is independently replaced with a halogen. In one embodiment, a haloalkyl group is a "fluoroalkyl group."

The term "fluoroalkyl group" as used herein, refers to an alkyl group, wherein one or more of the alkyl group's hydrogen atoms are replaced with a –F atom. In various embodiments, a fluorooalkyl group contains one F atom, two F atoms or three F atoms. Illustrative example of fluoroalkyl groups include, but are not limted to, -CH_2F, -$CH(F)_2$, CH_2CH_2F, -CF_3, and -$(CH_2)_3CF_3$.

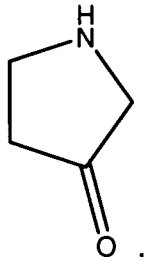
"Ring system substituent" means a substituent attached to an aromatic or non-aromatic ring system which, for example, replaces an available hydrogen on the ring system. Ring system substituents may be the same or different, each being independently selected from the group consisting of alkyl, alkenyl, 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, -$C(CH_3)_2$- and the like which form moieties such as, for example:



and

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"Heteroarylalkyl" means a heteroaryl moiety as defined above linked 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

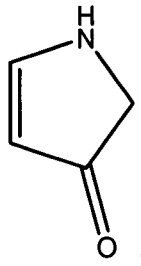
atoms, in which one or more of the atoms in the ring system is an element other than carbon, for example nitrogen, oxygen or sulfur, alone or in combination. There are no adjacent oxygen and/or sulfur atoms present in the ring system. Preferred heterocyclyls contain about 5 to about 6 ring atoms. The prefix aza, oxa or thia before the heterocyclyl root name means that at least a nitrogen, oxygen or sulfur atom respectively is present as a ring atom. Any –NH in a heterocyclyl ring may exist protected such as, for example, as an -N(Boc), -N(CBz), -N(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 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 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:



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

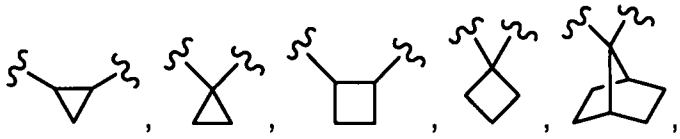
"Heterocyclenyl" means a non-aromatic monocyclic or multicyclic ring system comprising about 3 to about 10 ring atoms, preferably about 5 to about 10 ring atoms, in which one or more of the atoms in the ring system is an element other than carbon, for example nitrogen, oxygen or sulfur atom, alone or in combination, and which contains at least one carbon-carbon 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 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, 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 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:

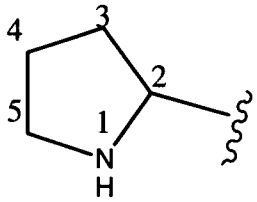


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"Heterocyclenylalkyl" means a heterocyclenyl moiety as defined above linked via an alkyl moiety (defined above) to a parent core.

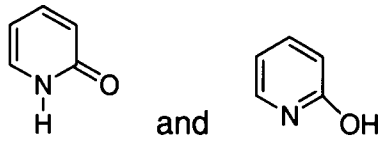
"Cycloalkylene" means a difunctional group obtained by removal of a hydrogen atom from a cycloalkyl group that is defined above. Non-limiting examples of cycloalkylene include , and .

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:



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.

"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 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 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.

"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 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 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.

"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 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 benzylthio. The bond to the parent moiety is through the sulfur.

"Alkoxycarbonyl" means an alkyl-O-CO- group. Non-limiting examples of suitable alkoxycarbonyl groups include methoxycarbonyl and ethoxycarbonyl. 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 example of a suitable aralkoxycarbonyl group is benzyloxycarbonyl. The bond to the parent moiety is through the carbonyl.

"Alkylsulfonyl" means an alkyl-S(O_2)- group. Preferred groups are those in which the alkyl group is lower alkyl. The bond to the parent moiety is through the sulfonyl.

"Arylsulfonyl" means an aryl-S(O_2)- 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 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 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 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, 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, (C_1–C_8)alkyl, (C_2-C_{12})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-(C_1-C_2)alkylamino(C_2-C_3)alkyl (such as β-dimethylaminoethyl), carbamoyl-(C_1-C_2)alkyl, N,N-di (C_1-C_2)alkylcarbamoyl-(C1-C2)alkyl and piperidino-, pyrrolidino- or morpholino(C_2-C_3)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, (C_1-C_6)alkanoyloxymethyl, 1-((C_1-C_6)alkanoyloxy)ethyl, 1-methyl-1-((C_1-C_6)alkanoyloxy)ethyl, (C_1-

C_6)alkoxycarbonyloxymethyl, N-(C_1-C_6)alkoxycarbonylaminomethyl, succinoyl, (C_1-C_6)alkanoyl, α-amino(C_1-C_4)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, $P(O)(OH)_2$, $-P(O)(O(C_1-C_6)alkyl)_2$ 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 (C_1-C_{10})alkyl, (C_3-C_7) cycloalkyl, benzyl, or R-carbonyl is a natural α-aminoacyl or natural α-aminoacyl, —C(OH)C(O)OY^1 wherein Y^1 is H, (C_1-C_6)alkyl or benzyl, —$C(OY^2)Y^3$ wherein Y^2 is (C_1-C_4) alkyl and Y^3 is (C_1-C_6)alkyl, carboxy (C_1-C_6)alkyl, amino(C_1-C_4)alkyl or mono-N—or di-N,N-(C_1-C_6)alkylaminoalkyl, —$C(Y^4)Y^5$ wherein Y^4 is H or methyl and Y^5 is mono-N— or di-N,N-(C_1-C_6)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 ethanolates, methanolates, and the like. "Hydrate" is a solvate wherein the solvent molecule is H_2O.

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 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 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, 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 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, 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 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.

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 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 example, halogen, C_{1-4}alkyl, or C_{1-4}alkoxy 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 C_{1-20} alcohol or reactive derivative thereof, or by a 2,3-di (C_{6-24})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.

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 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 ^{2}H, ^{3}H, ^{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 ^{3}H and ^{14}C) are useful in compound and/or substrate tissue distribution assays. Tritiated (i.e., ^{3}H) 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., ^{2}H) 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 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.

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, 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 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 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.

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. In one embodiment, the amount is from about 0.5 mg/kg/d to about 40 mg/kg/d. In another embodiment, the amount is from about 0.5 mg/kg/d to about 10 mg/kg/d. In another embodiment, the amount is from about 1 mg/kg/d to about 5 mg/kg/d. In still another embodiment, the amount is from about 1 mg/kg/d to about 3 mg/kg/d. In a specific embodiment, the amount is about 1 mg/kg/d. In another specific embodiment, the amount is about 3 mg/kg/d. In another specific embodiment, the amount is about 5 mg/kg/d. In another specific embodiment, the amount is about 7 mg/kg/d. In still another specific embodiment, the amount is about 10 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 anti-flushing agents, 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, CB_1 antagonists/inverse agonists, ghrelin antagonists, H_3 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, 5HT2c agonists, Mc4r agonists, monoamine reuptake inhibitors, serotonin reuptake inhibitors, GLP-1, GLP-1 agonists, GLP-1 mimetics, phentermine, topiramate, phytopharm compound 57, ghrelin antibodies, Mc3r agonists, ACC inhibitors, β3 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, 11β HSD-1 inhibitors, SCD-1 inhibitors, lipase inhibitors, fatty acid transporter inhibitors, dicarboxylate transporter inhibitors, glucose transporter inhibitors, phosphate transporter inhibitors, anti-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, 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 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 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 compound is ezetimibe (for example, ZETIA® which is available from Schering-Plough Corporation).

In one embodiment, the additional agent is an anti-flushing agent.

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 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).

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).

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).

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.

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).

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 from Pharmacia), colesevelam 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 Cholesteral 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.,* 188, 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.

Non-limiting examples of GLP-1 mimetics useful in combination with the nicotinic acid receptor agonists of the present invention include exendin-3, exendin-4, Byetta-Exanatide, Liraglutinide, CJC-1131 (ConjuChem), Exanatide-LAR (Amylin), BIM-51077 (Ipsen/LaRoche), ZP-10 (Zealand Pharmaceuticals), and compounds disclosed in International Publication No. WO 00/07617.

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.

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, benzafibrate, ciprofibrate, clofibrate, etofibrate, fenofibrate, and 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 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 invention include GW 320659, despiramine, talsupram, and nomifensine.

Non-limiting examples of CB_1 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 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 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 combination with the nicotinic acid receptor agonists of the present invention).

Non-limiting examples of H_3 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 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 H_3-receptor antagonists described in Lazewska, D. et al., Pharmazie, 56:927-32 (2001) (herein incorporated by reference), 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 (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 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.

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 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 0248152, WO 02/49648, WO 01/14376, WO 04/110375, WO 05/000217 and Norman et al., 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.

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. 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 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 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).

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 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 the nicotinic acid receptor agonists of the present invention include nalmefene (Revex^{TM}), 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 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 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 5HT2c agonists useful in combination with the nicotinic acid receptor agonists of the present invention include BVT933, 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 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 combination with the nicotinic acid receptor agonists of the present invention include sibutramine (Meridia™/Reductil™), 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 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).

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

Non-limiting examples of 11β 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, PPARα/γ agonists, biguanides, PTP-1B inhibitors, DP-IV inhibitors, DPP-IV inhibitors, insulin secretagogues, 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, mitiglinide 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 Al-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-BTZD, GW-0207, LG-100641, LY-300512, LY-519818, R483 (Roche), and T131 (Tularik).

Non-limiting examples of PPARα/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 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 DPP-IV inhibitors (dipeptidyl peptidase IVi inhibitors) useful in combination with the nicotinic acid receptor agonists of the present invention include sitagliptin, saxagliptin, denagliptin, vildagliptin, alogliptin, alogliptin benzoate, Galvus (Novartis), ABT-279 and ABT-341 (Abbott), ALS-2-0426 (Alantos), ARI-2243 (Arisaph), BI-A and BI-B (Boehringer Ingelheim), SYR-322 (Takeda), MP-513 (Mitsubishi), DP-893 (Pfizer) and RO-0730699 (Roche), 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 linogliride 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 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 suspension (lente and ultralente), Lys-Pro insulin, GLP-1 (73-7) (insulintropin), and GLP-1 (7-36)-NH_2).

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 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-adrendergic 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.

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 epirenone.

Non-limiting examples of β-adrendergic 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.

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.

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, lemildipine, lercanidipine, nicardipine, nifedipine, nilvadipine, nimodepine, nisoldipine, nitrendipine, manidipine, pranidipine, and verapamil.

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, peridropril, 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 include candesartan, eprosartan, irbesartan, losartan, pratosartan, 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 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 nicotinyl alcohol (roniacol).

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 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 the nicotinic acid receptor agonists of the present invention include aspirin, Niaspan, Norvsac® (amlodipine), NSAIDS agents (e.g., Celecoxib (Celebrex®), Diclofenac (Cataflam®, Voltaren®, Arthrotec®,) Diflunisal (Dolobid®), Etodolac (Lodine®), Fenoprofen (Nalfon®), Flurbirofen (Ansaid®), Ibuprofen (Motrin®, ADVIL®, NUPRIN®, Tab-Profen®, Vicoprofen®, Combunox®), Indornethacin (Indocin®, Indo-Lemmon®, Indornethagan®), 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, 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 homocysteinase, orphan GPCR modulator, HRE-based gene therapy, gene therapy, dual PPARα/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, heparin, GO-EPO, IDN-6734, ISIS-301012, HIF-alpha gene therapy, α2b 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 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 Exelixis/Bristol Myers Squibb), Heberkinasa (from Y. M. Biosciences), atorvastatin-amlodipine combination, AGN-195795 (Allergan), angiotensisn (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 Roche/Speedel), Coxagen (from geneRx+ Inc), MC-4262 (from Medicure), VNP-489 (from Novartis), felodipine (from Pierre Fabre SA), 2-methoxyestradiol (from PR Pharmaceuticals), α1 adrenoreceptor antagonsists (e.g., from Recordati SpA), lercanidipine-enalapril

combination (from Recordati SpA). NO donors 9e.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), 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, meclinertant, TAK-536, SR-121463, irbesatran + HCTZ 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 (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.

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 simvastatin and ezetimibe).

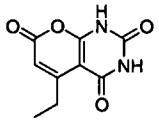
The invention disclosed herein is exemplified by the following preparations and examples which should not be construed to limit the scope of the disclosure. Alternative mechanistic pathways and analogous structures will be apparent to those skilled in the art.

EXAMPLES

In the examples and tables that follow, the exemplary compounds of the invention are referred to by number. In some instances, the compounds of the invention are referred to as "Example X," wherein "X" would be the representative

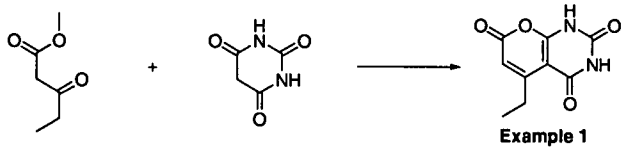
number of that particular compound. In other instances, the compounds of the invention are referred to as "compound X," wherein "X" would be the representative number of that particular compound. In other instances, a compound of the invention may simply be referred to by it's number. It is to be understood that these terms are used interchangeably. For example, the compound labeled "Example 1" can also be referred to as "compound 1" and vice versa.

PREPARATIVE EXAMPLE 1



Example 1

Step A:



Example 1

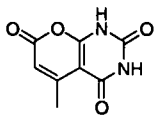
Methyl propionylacetate (12.5 g, 96.1 mmol, 1.23 eq.) and barbituric acid (10 g, 78.1 mmol, 1 eq.) were mixed together and without solvent, the mixture was heated to 195°C in air for 2 hr., at which time all of the liquids had evaporated. The solid was washed with boiling distilled water twice. The remaining solid was recrystallized with 2-methoxyethanol/water to give 4 g of **Example 1** as a yellow solid (20% yield).

^{1}H 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

Mass for $C_9H_9N_2O_4$ $(MH)^+$: 209. Found: 209.

PREPARATIVE EXAMPLE 2



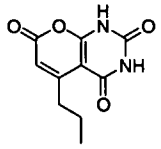
Example 2

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

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

Mass for $C_8H_7N_2O_4$ $(MH)^+$: 195. Found: 195.

PREPARATIVE EXAMPLE 3



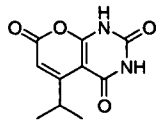
Example 3

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.

^{1}H NMR (CD_3OD): δ 0.96 (t, 3 H, J = 7.6 Hz), 1.57 (m, 2 H), 2.86 (m, 2 H), 5.75 (s, 1 H)

Mass for $C_{10}H_{11}N_2O_4$ $(MH)^+$: 223. Found: 223.

PREPARATIVE EXAMPLE 4



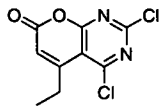
Example 4

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).

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

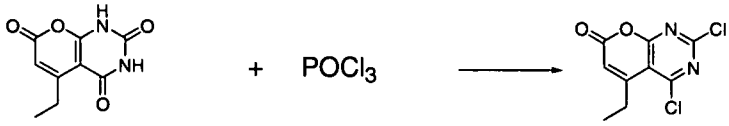
Mass for $C_{10}H_{11}N_2O_4$ $(MH)^+$: 223. Found: 223.

PREPARATIVE EXAMPLE 5



Example 5

Step A:



Example 1 + $POCl_3$ → Example 5

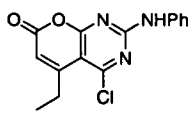
Example 1 (5 g, 24.04 mmol, 1 eq), $POCl_3$ (36.86g, 240 mmol, 10 eq.) and pyridine (0.95g, 12 mmol, 0.5 eq) were mixed and heated to 115°C for 8 hours. After cooling to room temperature, the solvent was removed and the brownish residue was

purified using flash chromatography with 20% EtOAc/hexane as the eluting solvent. The desired product (4 g) was obtained in 68% yield.

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

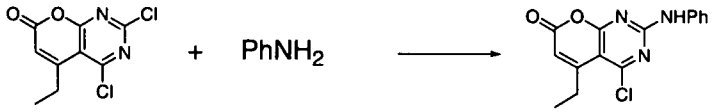
Mass for $C_9H_7Cl_2N_2O_2$ $(MH)^+$: 245. Found: 245.

PREPARATIVE EXAMPLE 6



Example 6

Step A:



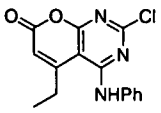
Example 5 + $PhNH_2$ → Example 6

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. 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).

^{1}H NMR (CD_3OD): 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)

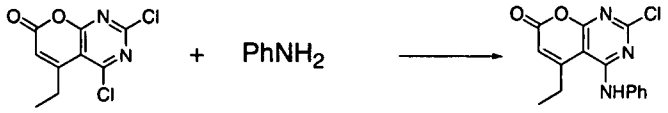
Mass for $C_{15}H_{13}ClN_3O_2$ $(MH)^+$: 302. Found: 302.

PREPARATIVE EXAMPLE 7



Example 7

Step A:



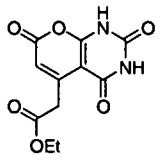
Example 5 Example 7

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).

^{1}H NMR (CD_3OD): 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)

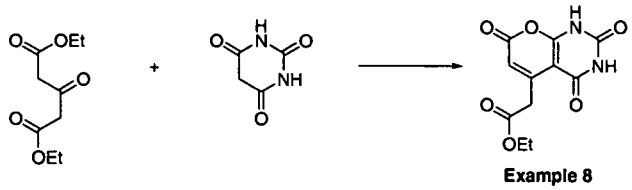
Mass for $C_{15}H_{13}ClN_3O_2$ $(MH)^+$: 302. Found: 302.

PREPARATIVE EXAMPLE 8



Example 8

Step A:



Example 8

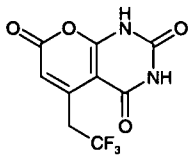
Example 8 was prepared using a method analogous to the method used to prepare **Example 1**, except that diethyl 1,3-acetonedicarboxylate was used instead of methyl propionylacetate.

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

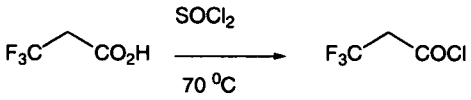
Mass for HRMS for $C_{11}H_{11}N_2O_6$ $(MH)^+$: calcd 267.0617, found 267.0623.

PREPARATIVE EXAMPLE 9



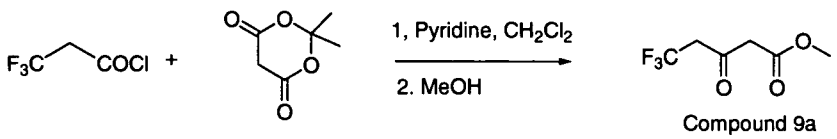
Example 9

Step A:



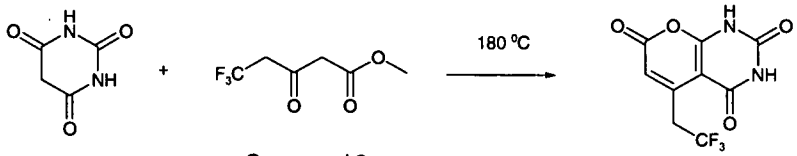
A mixture of 3,3,3,-trifluoropropionic acid (16 g, 125 mmol), thionyl chloride (29.75 g, 250 mmol), and DMF (0.5 mL) was heated to 70°C for 4 hours. The reaction mixture was distilled under reduced pressure to give 3,3,3,-trifluoropropionyl chloride (11.5 g, 72%).

Step B:



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%).



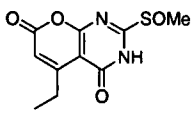
Compound 9a

Example 9

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

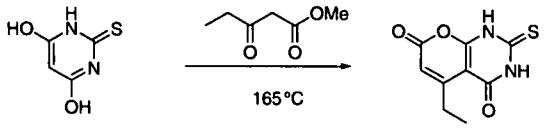
eluting with formic acid (0.1%)/acetonitrile to give **Example 9** (0.17 g, 5 %). Electrospray MS $[M+1]^+$ 263.

PREPARATIVE EXAMPLE 10



Example 10

Step A:



Compound 10a

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%).

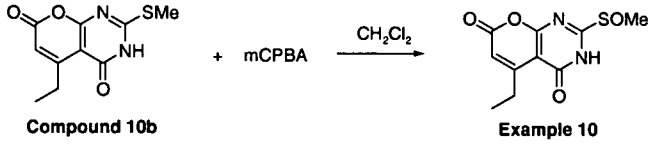
Step B:



Compound 10a Compound 10b

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%).

Step C:

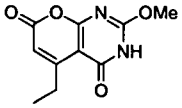


Compound 10b Example 10

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

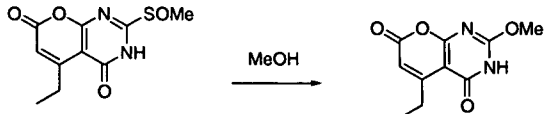
silica gel flash column chromatography, eluting first with hexane/EtOAc (v/v = 1/1) then CH_2Cl_2/MeOH (v/v = 2/1) to give **Example 10** (2.0 g, 94%). Electrospray MS $[M+1]^+$ 255.1.

PREPARATIVE EXAMPLE 11



Example 11

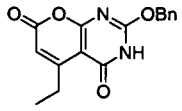
Step A:



Example 10 Example 11

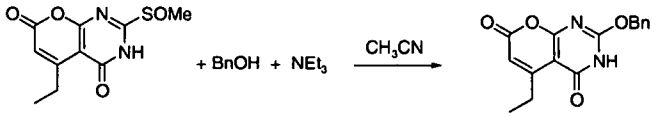
Example 10 (0.35 g, 1.37 mmol) in MeOH (40 mL) was heated at reflux overnight. After cooling to room temperature, the solvent was removed under reduced pressure and the crude product was purified using silica gel flash column chromatography eluting with CH_2Cl_2/MeOH (v/v = 50/1) to give **Example 11** (0.23 g, 76%). Electrospray MS $[M+1]^+$ 223.1.

PREPARATIVE EXAMPLE 12



Example 12

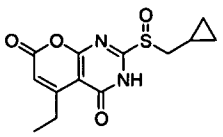
Step A:



Example 10 Example 12

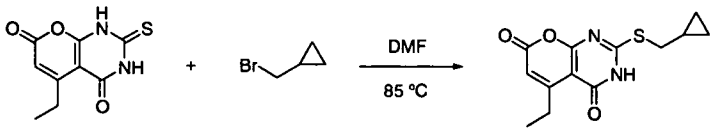
BnOH (2.46 mL, 23.76 mmol) was added to a solution of **Example 10** (0.404 g, 1.58 mmol) and NEt_3 (0.22 mL, 1.58 mmol) in CH_3CN (12.0 mL) at room temperature. The reaction mixture was heated at 85°C overnight. After cooling to room temperature, HOAc (0.09 mL, 1.58 mmol) was added and the solvent was removed under reduced pressure. The crude product was purified using silica gel flash column chromatography eluting with CH_2Cl_2/MeOH (v/v = 50/1) to give **Example 12** (0.20 g, 42%). Electrospray MS $[M+1]^+$ 299.1.

PREPARATIVE EXAMPLE 13



Example 13

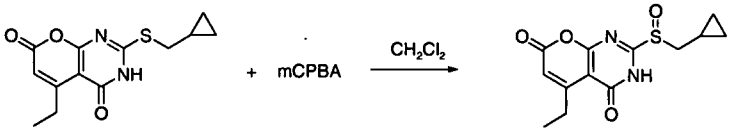
Step A:



Compound 10a Compound 13a

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 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%).

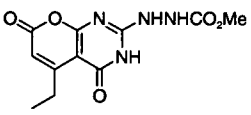
Step B:



Compound 13a Example 13

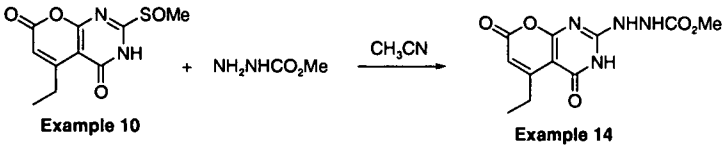
m-CPBA (0.33 g, 70%, 1.35 mmol) was added to a suspension of **Compound 13a** (0.25 g, 0.9 mmol) in CH_2Cl_2 (30 mL) at room temperature. Solvent was removed after 3 hours, and the crude product was purified using silica gel flash column chromatography eluting with EtOAc/CH_2Cl_2/MeOH (v/v = 4/1/2) to give **Example 13** (0.15 g, 57%). Electrospray MS $[M+1]^+$ 295.1.

PREPARATIVE EXAMPLE 14



Example 14

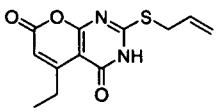
Step A:



Example 10 Example 14

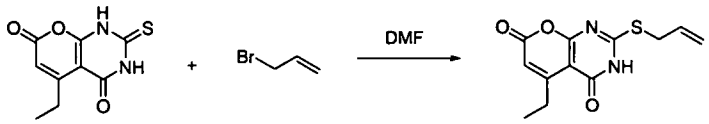
A mixture of **Example 10** (0.205 g, 0.804 mmol) and NH_2NHCO_2Me (0.145 g, 1.608 mmol) in MeCN (4.0 mL) was heated at reflux for 3 hours. After cooling to room temperature, the solvent was removed under reduced pressure and the crude product was washed with water (3 x 25 mL) with filtration. The solid was dried under vacuum to give **Example 14** (0.2 g, 89%). Electrospray MS $[M+1]^+$ 281.1.

PREPARATIVE EXAMPLE 15



Example 15

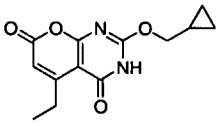
Step A:



Compound 10a Example 15

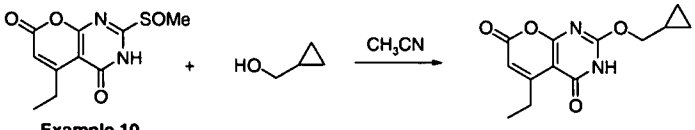
Allyl bromide (1.74 mL, 20.1 mmol) was added to a suspension of **Compound 10a** (1.5 g, 6.7 mmol) in DMF (15.0 mL) at room temperature. The reaction mixture was stirred at 45°C overnight. The reaction mixture was cooled down and poured into water (200 mL) and then filtered through a sintered funnel. 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 $[M+1]^+$ 265.1.

PREPARATIVE EXAMPLE 16



Example 16

Step A:

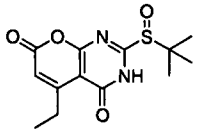


Example 10 Example 16

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. 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

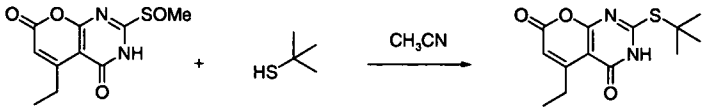
flash column chromatography eluting with hexane/EtOAc (v/v = 1/1) to give **Example 16** (0.027 g, 52%). Electrospray MS $[M+1]^+$ 263.1.

PREPARATIVE EXAMPLE 17



Example 17

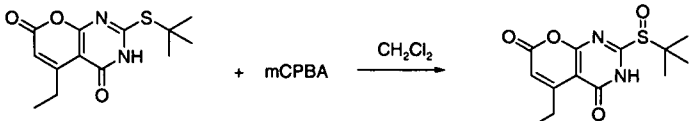
Step A:



Example 10 Compound 17a

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%).

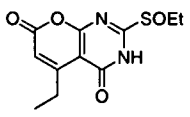
Step B:



Compound 17a Example 17

m-CPBA (0.049 g, 70%, 0.20 mmol) was added to a suspension of **Compound 17a** (0.040 g, 0.143 mmol) in CH_2Cl_2 (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 CH_2Cl_2/MeOH (v/v = 5/1) to give **Example 17** (0.030 g, 71%). Electrospray MS $[M+1]^+$ 297.1.

PREPARATIVE EXAMPLE 18



Example 18

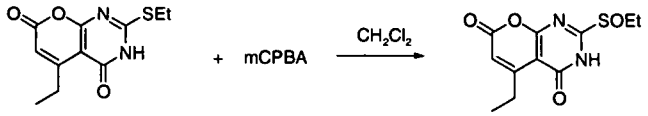
Step A:



Compound 10a Compound 18a

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%).

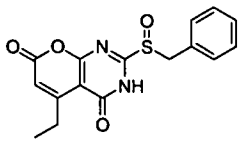
Step B



Compound 18a Example 18

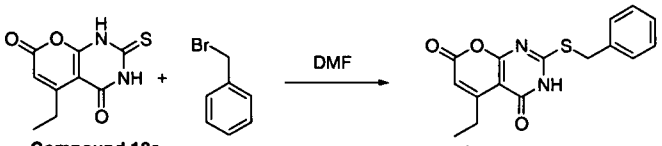
m-CPBA (74 mg, 70%, 3 mmol) was added to a suspension of **Compound 18a** (0.5g, 2 mmol) in CH_2Cl_2 (50 mL) at room temperature. After stirring at room temperature 3 hours, the solvent was removed, and the crude product was purified using silica gel flash column chromatography eluting with AcOH/MeOH/CH_2Cl_2 (v/v/v = 0.1/4.9/95) to give **Example 18** (0.4 g, 74%). Electrospray MS $[M+1]^+$ 269.

PREPARATIVE EXAMPLE 19



Example 19

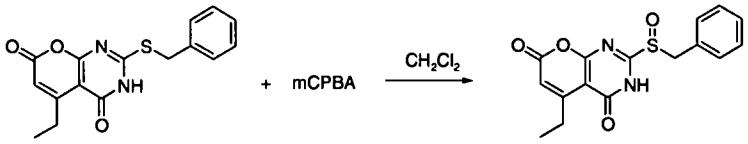
Step A:



Compound 10a Compound 19a

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%).

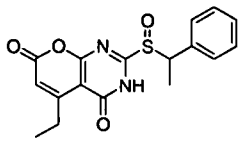
Step B:



Compound 19a Example 19

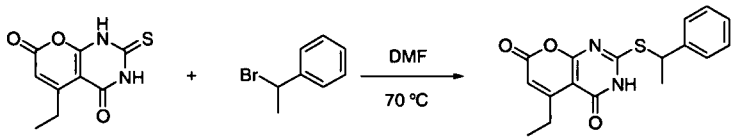
m-CPBA (72 mg, 70%, 3 mmol) was added to a suspension of **Compound 19a** (0.5g, 2 mmol) in CH_2Cl_2 (50 mL) at room temperature. After stirring at room temperature 3 hours, the solvent was removed, and the crude product was purified using silica gel flash column chromatography eluting with AcOH/MeOH/CH_2Cl_2 (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

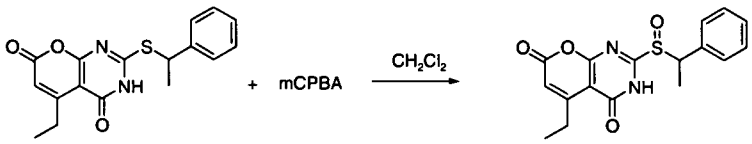
Step A:



Compound 10a Compound 20a

(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 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:

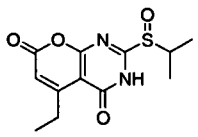


Compound 20a Example 20

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

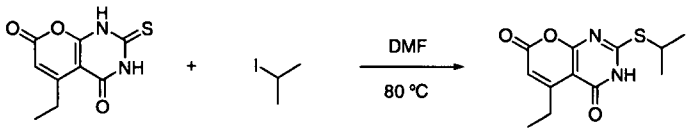
after 3 hours and the crude product was purified using silica gel flash column chromatography eluting with 5 % EtOH in EtOAc/hexanes (v/v = 1:1) to give **Example 20** (0.1 g, 50%). Electrospray MS $[M+1]^+$ 345.

PREPARATIVE EXAMPLE 21



Example 21

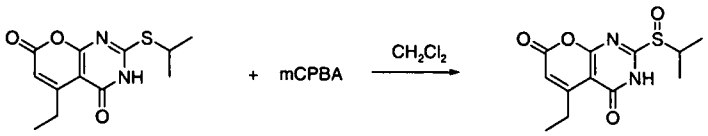
Step A:



Compound 10a Compound 21a

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 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%).

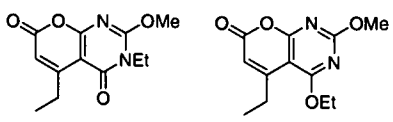
Step B



Compound 21a Example 21

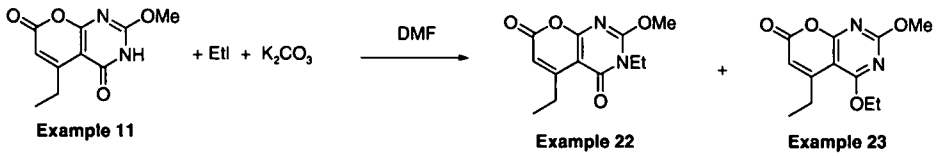
m-CPBA (0.74 g, 70%, 3 mmol) was added to a suspension of **Compound 21a** (0.53 g, 2 mmol) in CH_2Cl_2 (30 mL) at room temperature. Solvent was removed after 3 hours, the crude product was purified using a silica gel flash column chromatography eluting with 0.1% AcOH in MeOH/CH_2Cl_2 (v/v = 2:98) to give **Example 21** (0.45 g, 80%). Electrospray MS $[M+1]^+$ 283.

PREPARATIVE EXAMPLES 22 and 23



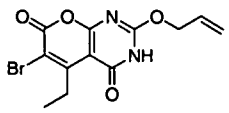
Example 22 Example 23

Step A:



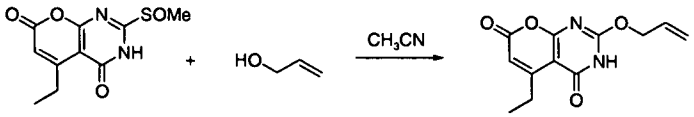
K_2CO_3 (36.7 mg, 0.266 mmol) was added to a mixture of **Example 11** (29.6 mg, 0.133 mmol) and EtI (0.064 mL, 0.8 mmol) in DMF (1.0 mL) at room temperature. The reaction was stirred over night before it was diluted with by the addition of EtOAc (50 mL) and water (10 mL). The organic phase was washed with water (3x15 mL), brine (15 mL), and dried over $MgSO_4$. 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 **Example 22** (7.0 mg, 21%) and **Example 23** (20 mg, 60%). Electrospray MS $[M+1]^+$ 251.1.

PREPARATIVE EXAMPLE 24



Example 24

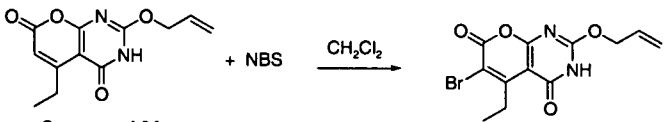
Step A:



Example 10 Compound 24a

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%).

Step B:

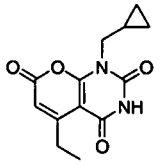


Compound 24a Example 24

NBS (36 mg, 0.202 mmol) was added to a solution of **Compound 24a** (0.040 g, 0.161 mmol) in CH_2Cl_2 (2.0 mL) at room temperature. Solvent was removed over 1 hour and the crude product was purified using silica gel flash column chromatography

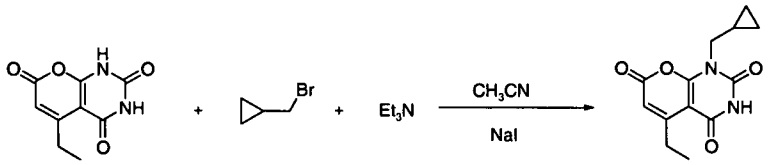
eluting with hexane/EA (v/v = 1/1) to give **Example 24** (0.025 g, 48%). Electrospray MS $[M+1]^+$ 327.1.

PREPARATIVE EXAMPLE 25



Example 25

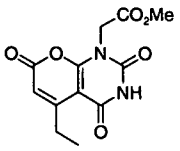
Step A:



Example 1 Example 25

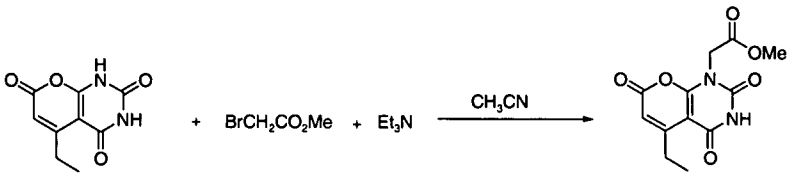
Example 1 (0.5 g, 2.4 mmol) was taken up in CH_3CN (10 mL). Triethylamine (0.33 mL, 2.4 mmol) was added to the suspension followed by cyclopropyl methyl bromide (0.26 mL, 2.64 mmol) and NaI (0.36 g, 2.4 mmol). The reaction mixture was heated to reflux overnight. After cooling to room temperature, the solvent was evaporated in vacuo. The crude product was purified by crystallization from EtOAc/hexanes to give **Example 25** (0.25 g, 40%).

PREPARATIVE EXAMPLE 26



Example 26

Step A:

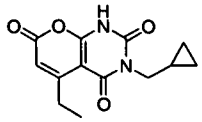


Example 1 Example 26

Example 1 (0.1 g, 0.48 mmol) was taken up in CH_3CN (3.0 mL). Triethylamine (0.067 mL, 0.48 mmol) was added to the suspension followed by methyl bromoacetate

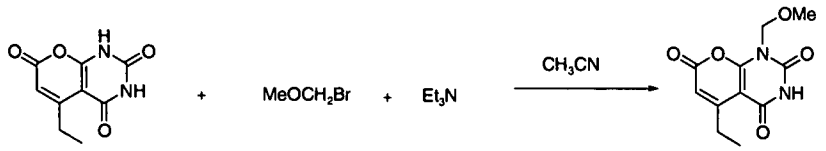
(0.046 mL, 0.48 mmol). The reaction mixture was allowed to stir overnight at room temperature. The solvent was removed under reduced pressure and the crude mixture was purified by column chromatography eluting with EtOAc/hexanes (2/3: v/v) to yield **Example 26** (0.06 g, 45%).

PREPARATIVE EXAMPLE 27



Example 27

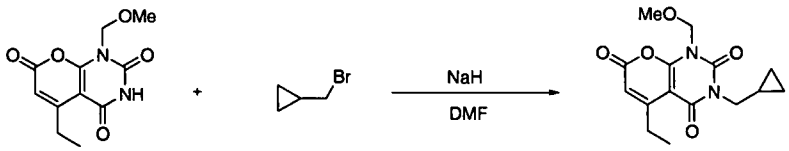
Step A:



Example 1 Compound 27a

Example 1 (1.0 g, 4.8 mmol) was taken up in CH_3CN (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. 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:

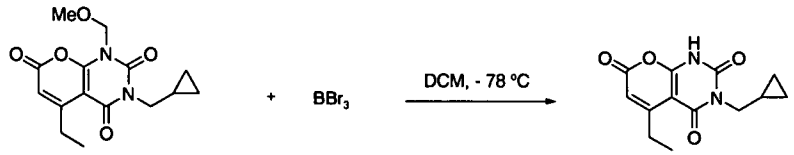


Compound 27a Compound 27b

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 $MgSO_4$, 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 27b** (0.175 g, 43%).

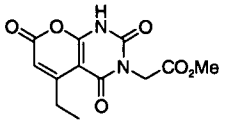
Step C:



Compound 27b Example 27

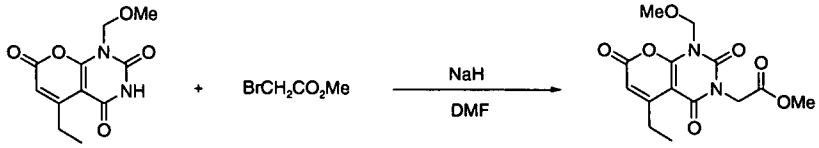
Boron tribromide (2.85 mL, 2.85 mmol, 1.0 M solution in DCM) was added to a solution of **Compound 27b** (0.175 g, 0.57 mmol) in CH_2Cl_2 (8.0 mL) at -78°C. The reaction was allowed to stir for 2 h before being quenched with water (5.0 mL). The reaction mixture was extracted with EtOAc (2 x 5 mL). The 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

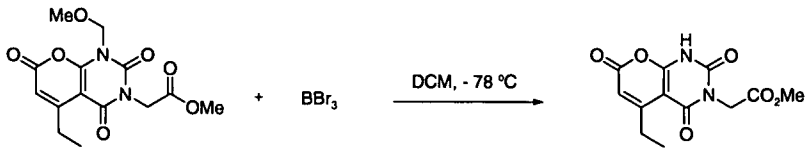
Step A:



Compound 27a Compound 28a

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%).

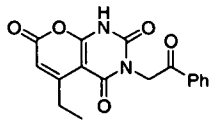
Step B:



Compound 28a Example 28

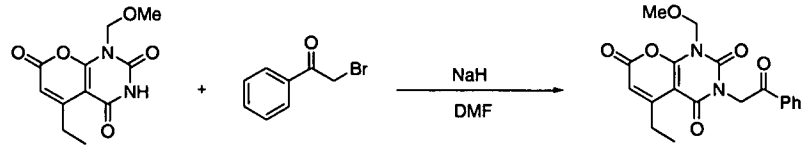
Boron tribromide (1.1 mL, 1.1 mmol, 1.0 M solution in DCM) was added to a solution of **Compound 28a** (0.07 g, 0.22 mmol) in CH_2Cl_2 (3.0 mL) at -78°C. The reaction was allowed to stir for 2 h before being quenched with water (5.0 mL). The reaction mixture was extracted with EtOAc (2 x 5 mL). The organic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

PREPARATIVE EXAMPLE 29



Example 29

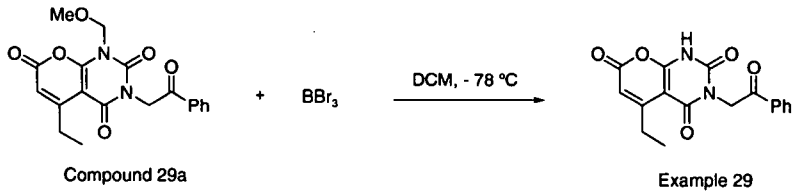
Step A:



Compound 27a Compound 29a

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%).

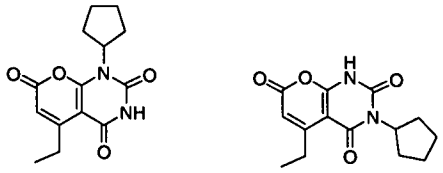
Step B:



Compound 29a Example 29

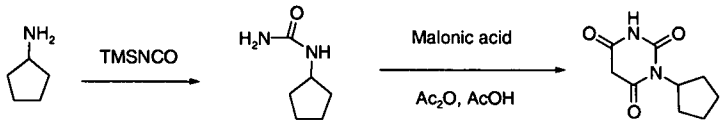
Boron tribromide (4.7 mL, 4.7 mmol, 1.0 M solution in DCM) was added to a solution of **Compound 29a** (0.350 g, 0.95 mmol) in CH_2Cl_2 (10.0 mL) at -78°C. The reaction was allowed to stir for 2 h before being quenched with water (5.0 mL). The reaction mixture was extracted with EtOAc (2 x 15 mL). The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



Example 30 Example 31

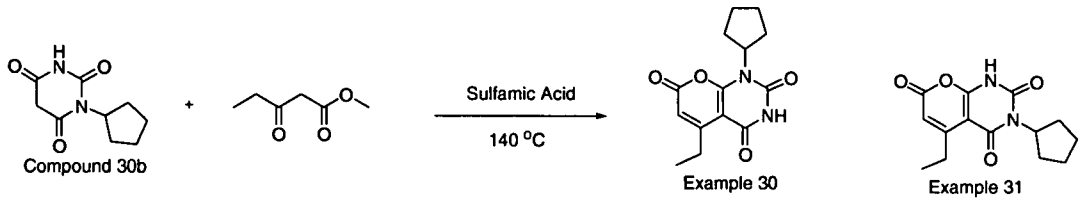
Step A:



Compound 30a Compound 30b

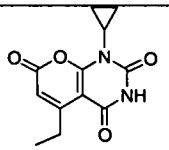
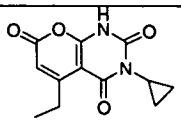
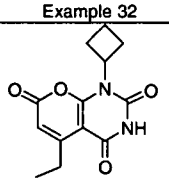
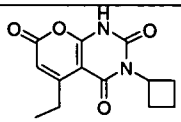
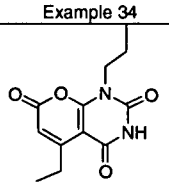
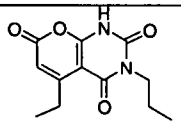
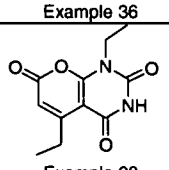
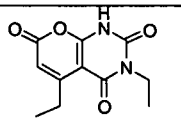
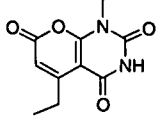
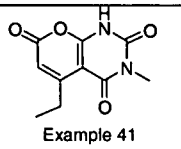
To a CH_2Cl_2 solution of cyclopentylamine was added trimethylsilyl isocyanate. The reaction mixture was stirred overnight. To this was added 200 ml of CH_3OH, and the mixture was stirred for another 2 hrs. The reaction mixture was concentrated and was titrated using diethyl ether to give an off-white precipitate. The precipitate was filtered through a Buchner funnel to 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 EtO_2/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%).

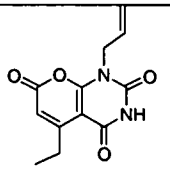
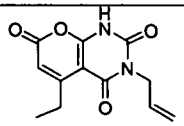
Step B:



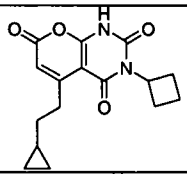
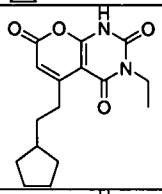
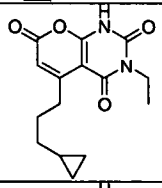
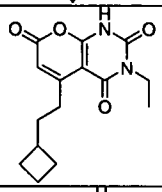
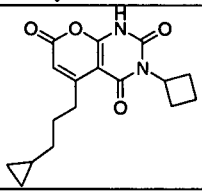
Compound 30b (0.75 g, 1.0 equiv., 3.82 mmol) was condensed with methyl propional acetate (0.48mL, 3.82 mmol) in the presence of sulfamic acid and heated to 140°C for 6 hrs, forming a dark brown solid. The reaction mixture was diluted with EtOAc, washed with H_2O, dried using Na_2SO_4 and concentrated to give a crude mixture. Prep TLC purification of the crude mixture in 95/5 CH_2Cl_2/CH_3OH yielded both the N_1 and N_3 isomers, **Example 30** LCMS: (M+1) 277.1 and **Example 31** LCMS: (M+1). 277.1

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

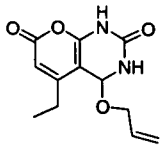
substituents	N-1 products	LCMS: (M+1) of N-1 products	N-3 products	LCMS: (M+1) of N-3 products
cyclopropyl	 Example 32	249.1	 Example 33	249.1
cyclobutyl	 Example 34	263.1	 Example 35	263.1
Pr	 Example 36	251.1	 Example 37	251.1
Et	 Example 38	237.1	 Example 39	237.1
Me	 Example 40		 Example 41	223.0

substituents	N-1 products	LCMS: (M+1) of N-1 products	N-3 products	LCMS: (M+1) of N-3 products
allyl	 Example 42	249.1	 Example 43	249.1

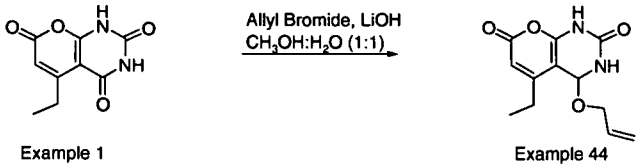
Using the procedure set forth above for making the compound of Example 30, and substituting the appropriate reagents and intermediates, compounds **780-785** were prepared:

Compound No.	Structure	Electrospray LCMS [M+1]+
780		303.1
781		305.2
782		291.2
783		291.2
784		317.2

PREPARATIVE EXAMPLE 44



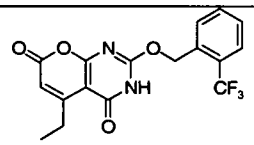
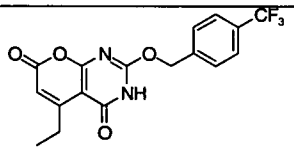
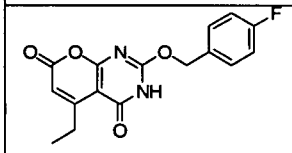
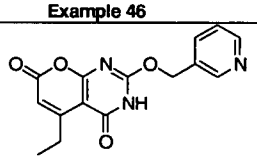
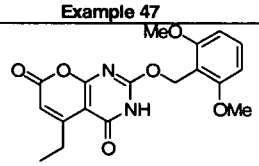
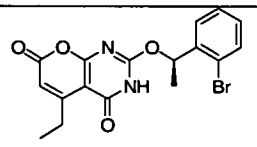
Example 44

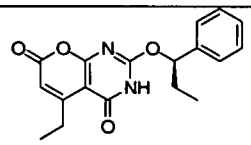
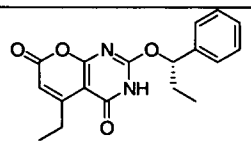
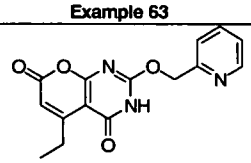
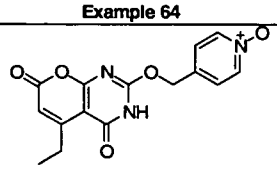
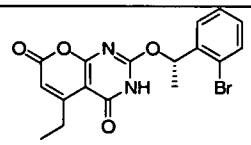
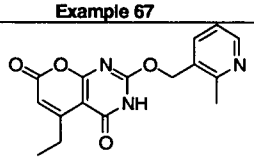
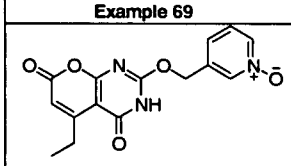
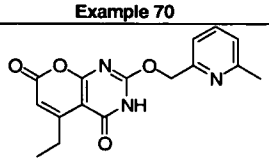
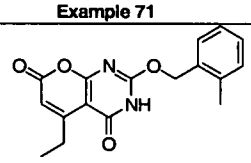
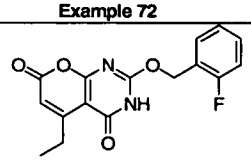
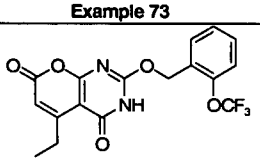
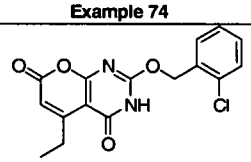
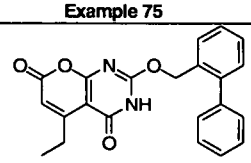
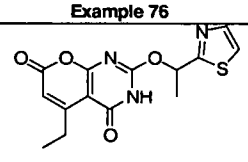
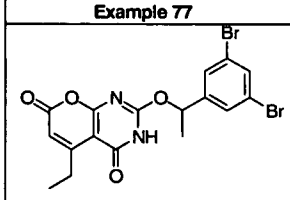


Example 1 Example 44

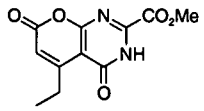
To **Example 1** (0.456 g, 2.2 mmol) in MeOH:H_2O (1:1) was added allyl bromide followed by LiOH, and the reaction mixture was heated to 82°C for 8 hours. The progress of the reaction was monitored by TLC which indicated presence of some starting material. The reaction mixture was then heated for another 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 CH_2Cl_2/CH_3OH 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 $[M+1]^+$
 Example 45	367.1	 Example 46	367.1
 Example 47	317.1	 Example 51	300.1
 Example 61	359.1	 Example 62	391.1

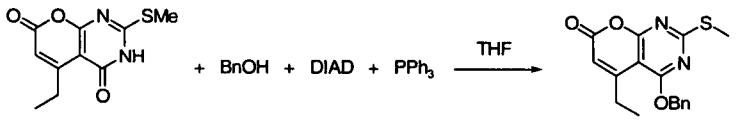
PREPARATIVE EXAMPLE	Electrospray LCMS $[M+1]^+$	PREPARATIVE EXAMPLE	Electrospray LCMS $[M+1]^+$
 Example 63	327.1	 Example 64	327.1
 Example 66	300.1	 Example 67	316.1
 Example 69	391.2	 Example 70	314.1
 Example 71	316.1	 Example 72	314.1
 Example 73	313.1	 Example 74	317.1
 Example 75	383.1	 Example 76	333.1
 Example 77	375.1	 Example 78	320.1
 Example 79	469.1		

PREPARATIVE EXAMPLE 48



Example 48

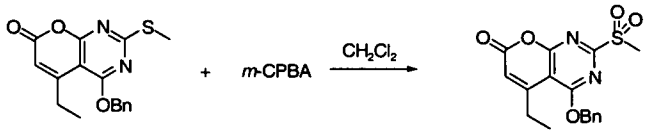
Step A:



Compound 10b Compound 48a

DIAD (0.488 mL, 2.52 mmol) was added dropwise to a solution of **Compound 10b** (0.5 g, 2.10 mmol), BnOH (0.261 mL, 2.52 mmol) and PPh_3 (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%).

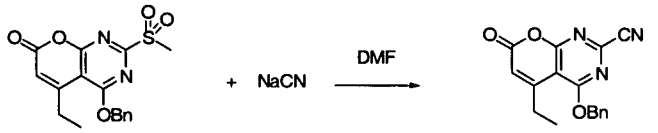
Step B:



Compound 48a Compound 48b

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 uL, 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%).

Step C:

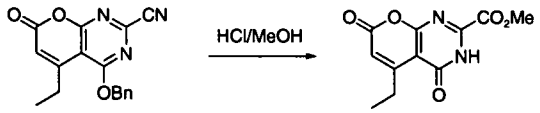


Compound 48b Compound 48c

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%).

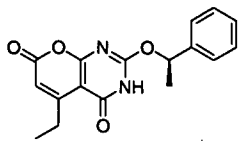
Step D:



Compound 48c Example 48

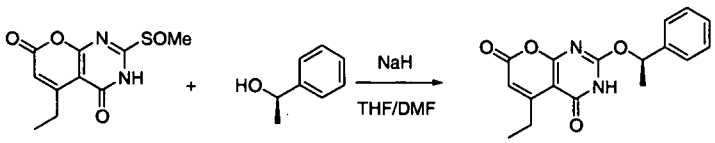
A solution of **Compound 48c** (10 mg, 0.0326 mmol) in 4.0 M HCl in dioxane (0.7 mL) and MeOH (0.7 mL) in a sealed tube was heated at 70°C for 7 hours. The mixture was cooled to room temperature and solvent was removed under reduced pressure to give crude product. The crude product was purified with preparative thin layer silica gel chromatography eluting with hexane/CH_2Cl_2/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

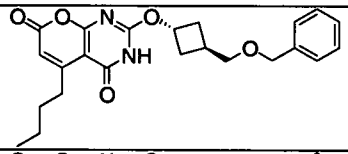
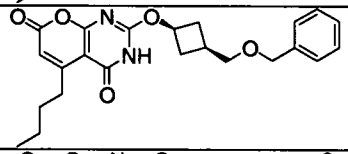
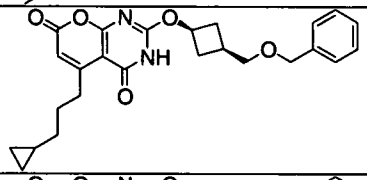
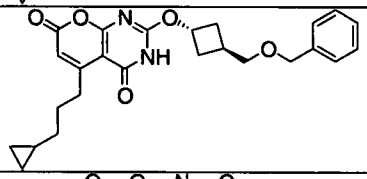
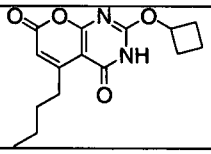
Step A:



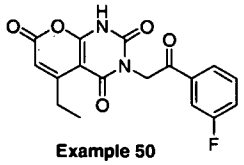
Example 10 Example 49

(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/CH_2Cl_2 (8/2), washed with diluted HCl (0.1 M), water and brine, then dried ($MgSO_4$). The solvent was removed under reduced pressure. The crude product was purified using silica gel flash column chromatography eluting with hexane/CH_2Cl_2/EtOAc (v/v/v = 7/3/2) to give **Compound 49** (0.25 g, 80%). Electrospray MS $[M+1]^+$ 313.1.

Using the method set forth above and substituting the appropriate reagents and intermediates, compounds **791-795** were prepared:

Compound No.	Structure	Electrospray LCMS [M+1]+
791		411.2
792		411.2
793		437.2
794		437.2
795		291.2

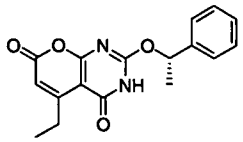
PREPARATIVE EXAMPLE 50



Example 50

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.

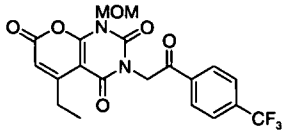
PREPARATIVE EXAMPLE 52



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.

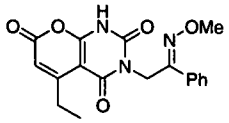
PREPARATIVE EXAMPLE 53



Example 53

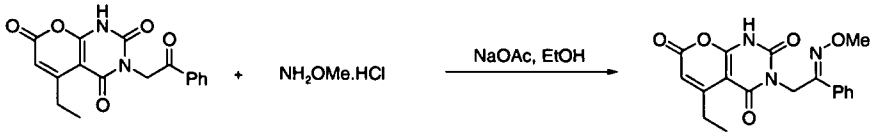
Example 53 prepared by a procedure similar to that used in Step A of the preparation of **Example 29**, using **Compound 27a** and the appropriate corresponding bromide. Electrospray MS $[M+1]^+$ 439.1.

PREPARATIVE EXAMPLE 54



Example 54

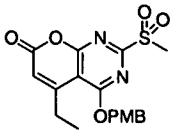
Step A:



Example 29 + $NH_2OMe.HCl$ —NaOAc, EtOH→ Example 54

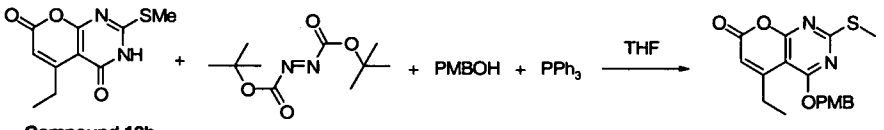
Example 29 (0.05 g, 0.153 mmol) was taken up in ethanol (3.0 mL). Methoxylamine hydrochloride (0.051 g, 0.61 mmol) was added to the mixture followed by sodium acetate (0.038 g, 0.46 mmol). The reaction mixture was stirred at 60°C overnight. After being cooled to room temperature, the solvent was removed under reduced pressure, diluted with CH_2Cl_2 (5 mL) and water (5 mL). The product was extracted from CH_2Cl_2 (2 x 5 mL), dried over $MgSO_4$, concentrated. The crude product was dissolved in minimum CH_2Cl_2, diluted with hexanes and filtered to give **Example 54**. Electrospray MS $[M+1]^+$ 356.1.

PREPARATIVE EXAMPLE 55



Example 55

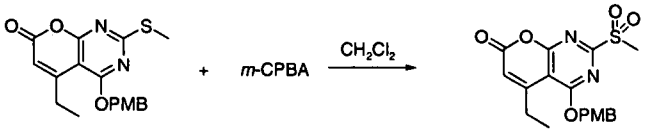
Step A:



Compound 10b Compound 55a

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 PPh_3 (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/CH_2Cl_2/EtOAc (v/v/v = 9/1/1) to give **Compound 55a** (1.6 g, 53%).

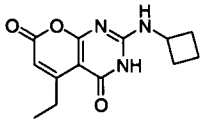
Step B:



Compound 55a Example 55

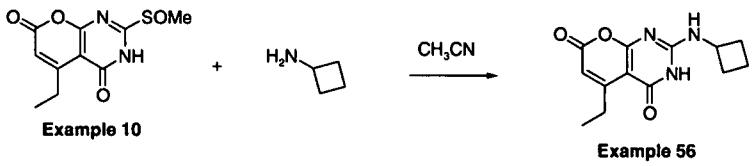
m-CPBA (0.47 g, 1.92 mmol, 60-70%)was added at room temperature to a solution of **Compound 55a** (0.287 g, 0.80 mmol) in CH_2Cl_2 (8 mL). The reaction mixture was stirred for 5 hours before it was quenched by the addition of Me_2S (124 µL, 1.92 mmol). The mixture was then diluted with EtOAc and washed with $NaHCO_3$ solution. The organic phase was washed with water, brine, and dried (Na_2SO_4). Solvent was removed under reduced pressure, crude product was purified with silica gel flash column chromatography eluting with hexane/CH_2Cl_2/EtOAc (v/v/v = 7/3/2) to give **Example 55** (0.15 g, 80%). Electrospray MS $[M+1]^+$ 391.1.

PREPARATIVE EXAMPLE 56



Example 56

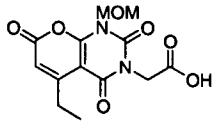
Step A:



Example 10 Example 56

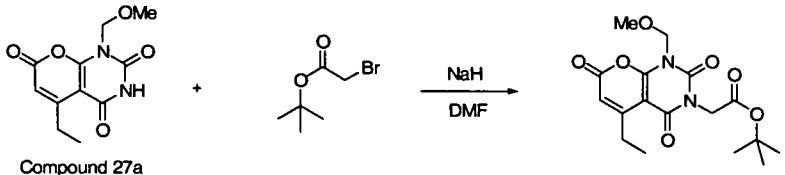
Cyclobutylamine (0.14 g, 2 mmol) was added to a suspension of **Example 10** (0.25 g, 1 mmol) in CH_3CN (15 mL). The reaction mixture was stirred at room temperature for 16 hours. Solvent was removed and the crude product was purified using silica gel flash column chromatography eluting with 10% NH_4OH in $MeOH/CH_2Cl_2$ (v/v = 3:97) to give **Example 56** (0.045 g, 17%). Electrospray MS $[M+1]^+$ 262.1

PREPARATIVE EXAMPLE 57



Example 57

Step A:



Compound 27a Compound 57a

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 $MeOH/CH_2Cl_2$ (v/v = 2:98) to give **Compound 57a** (1.8 g, 62%). Electrospray MS $[M+1]^+$ 367.2.

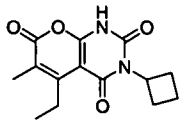
Step B:



Compound 57a Example 57

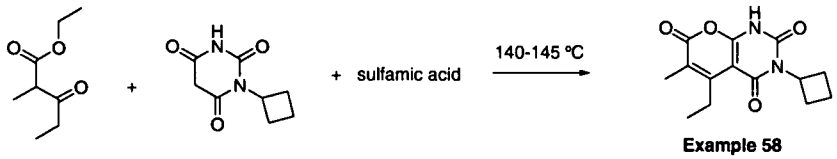
A mixture of **Compound 57a** (0.95g, 2.6 mmol) in CH_2Cl_2 (5 mL) and trifluoroacetic acid (1.5g, 13 mmol) was stirred at room temperature for 4 hours. Removal of solvent and excess trifluoroacetic acid gave **Example 57** (0.8g, 100%). Electrospray MS $[M+1]^+$ 311.2

PREPARATIVE EXAMPLE 58



Example 58

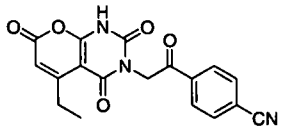
Step A:



Example 58

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: M+1: 277.1

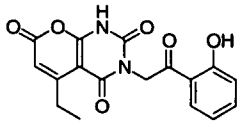
PREPARATIVE EXAMPLE 59



Example 59

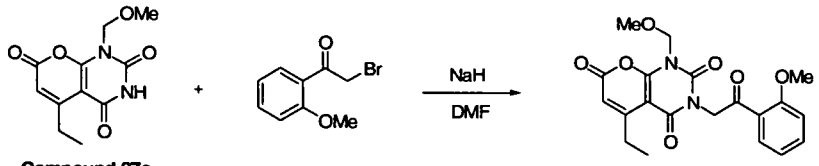
EXAMPLE 59 was prepared using a two step procedure similar to that used for the preparation of **Example 29**, using **Compound 27a** and the appropriate corresponding bromide. Electrospray MS $[M+1]^+$ 252.1.

PREPARATIVE EXAMPLE 60



Compound 60

Step A:

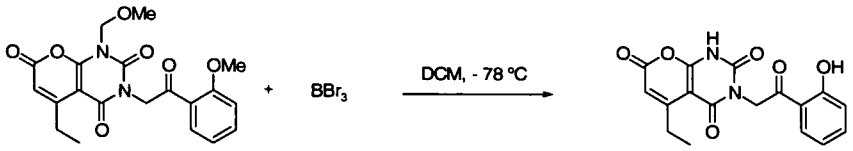


Compound 27a

Compound 60a

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 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 60a**.

Step B:

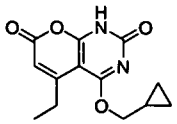


Compound 60a

Compound 60

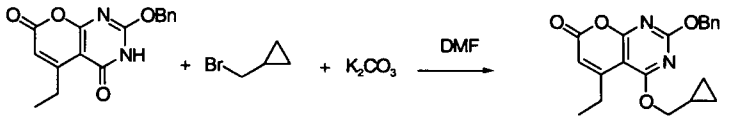
Boron tribromide (1.3 mL, 1.31 mmol, 1.0 M solution in DCM) was added to a solution of **Compound 60a** (0.105 g, 0.262 mmol) in CH_2Cl_2 (5.0 mL) at -78°C. The reaction mixture was allowed to stir for 2 h before being quenched with water (5.0 mL). The reaction mixture was extracted with EtOAc (2 x 5 mL). The organic layers were combined, dried over $MgSO_4$, 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 60**. Electrospray MS $[M+1]^+$ 343.1.

PREPARATIVE EXAMPLE 65



Example 65

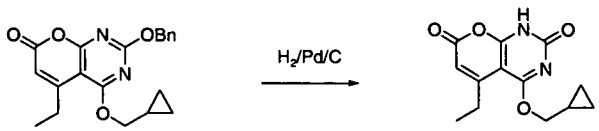
Step A:



Compound 12 Compound 65a

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%).

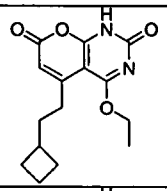
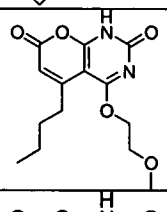
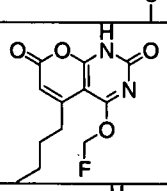
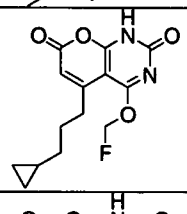
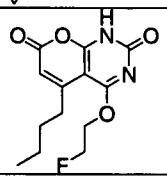
Step B:



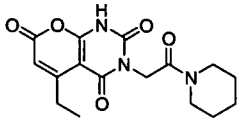
Compound 65a Example 65

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 $[M+1]^+$ 263.1.

Using the method set forth above and substituting the appropriate reagents and intermediates, compounds **786-790** were prepared:

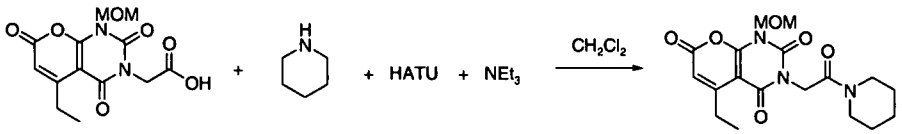
Compound No.	Structure	Electrospray LCMS [M+1]+
786		291.2
787		295.2
788		269.1
789		295.2
790		283.2

PREPARATIVE EXAMPLE 68



Example 68

Step A:



Example 57 Compound 68a

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 $[M+1]^+$ 378.2.

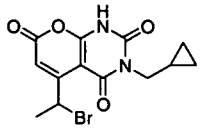
Step B:



Compound 68a Example 68

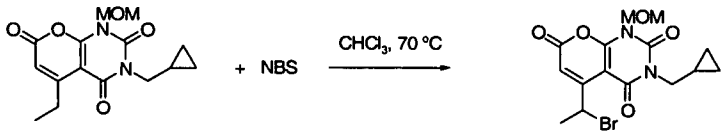
1M BBr_3 solution in CH_2Cl_2 (0.75 mL, 0.75 mmol) was added to a solution of **Compound 68a** (0.056 g, 0.15 mmol) at -78°C. After the reaction mixture was stirred at -78°C for 2 hours, water (5 mL) was added. The organic solution was dried (Na_2SO_4) and concentrated. The crude product was purified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

PREPARATIVE EXAMPLE 80



Example 80

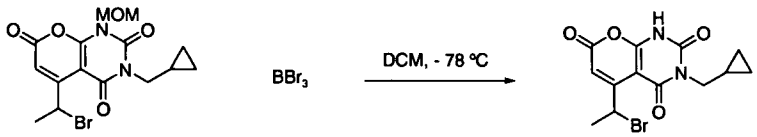
Step A:



Compound 27b Compound 80a

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

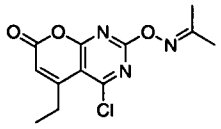
Step B:



Compound 80a Example 80

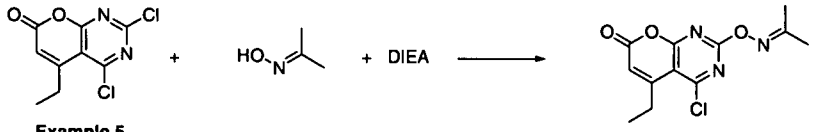
Compound 80a (0.070g, 0.18 mmol) was taken up in CH_2Cl_2 and the mixture was cooled to -78°C. 1M BBr_3 (0.909 mL, 0.9 mmol) was added. The reaction mixture was stirred for 4 hours. Upon completion of the reaction, the mixture was diluted with CH_2Cl_2, washed with H_2O, dried with Na_2SO_4, and then 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 $[M+1]^+$ 341.2.

PREPARATIVE EXAMPLE 81



Example 81

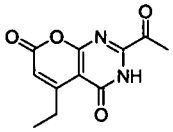
Step A:



Example 5 Example 81

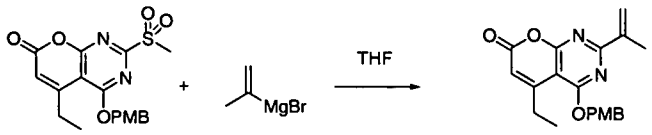
To a mixture of **Example 5** (84 mg, 0.34 mmol) and acetone oxime (27.5 mg, 0.37 mmol) was added DIEA (0.09 ml, 0.52 mmol) and the mixture was stirred for 3 days. The mixture was concentrated and was subjected to silica gel column chromatography to give **Example 81** (30 mg, 31%). LCMS: M+1: 282.1

PREPARATIVE EXAMPLE 92



Example 92

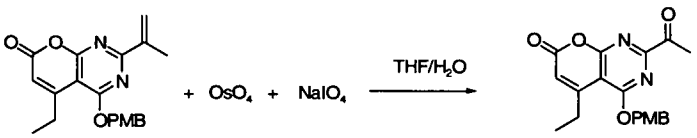
Step A:



Example 55 Compound 92a

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%).

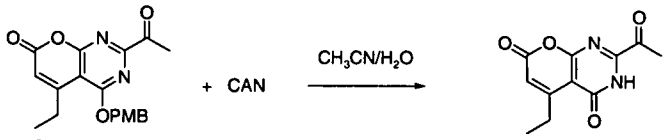
Step B:



Compound 92a Compound 92b

$NaIO_4$ (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%).

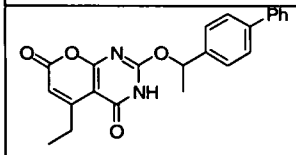
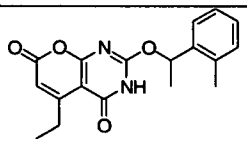
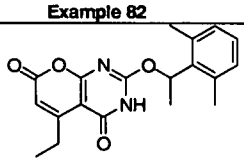
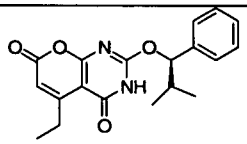
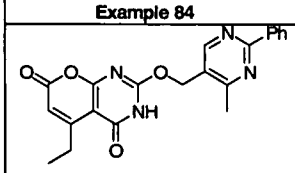
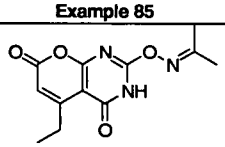
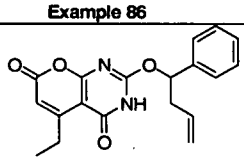
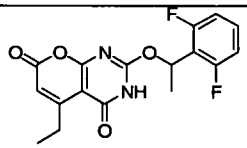
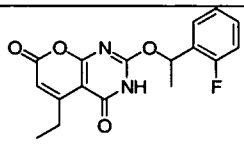
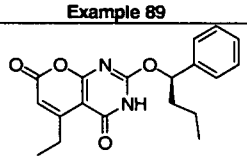
Step C:



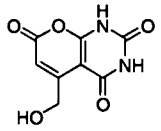
Compound 92b Example 92

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 $[M+1]^+$ 235.1.

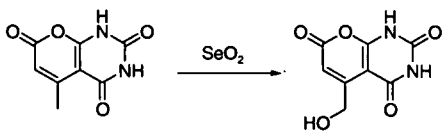
Examples 82-91 were prepared by procedures similar to those used for the preparation of **Example 49**, using **Example 10** and the appropriate corresponding alcohols.

PREPARATIVE EXAMPLE	Electrospray LCMS $[M+1]^+$	PREPARATIVE EXAMPLE	Electrospray LCMS $[M+1]^+$
 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

PREPARATIVE EXAMPLE 92



Example 92



Example 2 Example 92

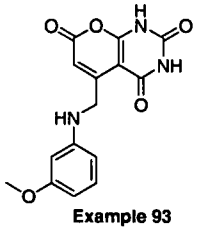
Example 2 (0.71 g, 3.66 mmol, 1 eq) and SeO_2 (0.46 g, 1.1 eq) were mixed together in 1,4-dioxane (10.5 mL) and THF (1.5 mL) and the mixture was heated to 90°C in air for 24 hr. 5% of the resulting crude product was purified by directly loading

it onto a reverse-phase HPLC column to afford the desired product **Example 92** (7.4 mg) as a white solid.

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

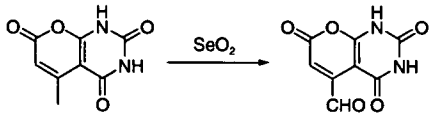
Mass of $C_8H_7N_2O_5$ $(MH)^+$: 211. Found: 211.

PREPARATIVE EXAMPLE 93



Example 93

Step A:

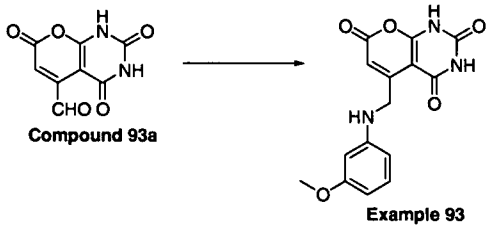


Example 2 Compound 93a

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 reverse-phase HPLC, **Compound 93a** (90 mg) was obtained.

Mass of $C_8H_5N_2O_5$ $(MH)^+$: 209. Found: 209.

Step B:



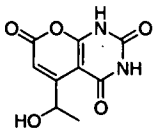
Compound 93a Example 93

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.**

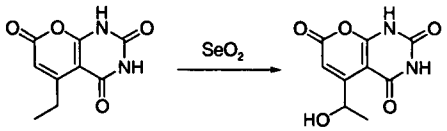
^{1}H NMR (CD_3OD): δ 3.60 (s, 3 H) 4.60 (s, 2 H) 5.75 (s, 1 H) 6.20 (m, 3 H) 6.95 (m, 1 H)

Mass of $C_{15}H_{14}N_3O_5$ $(MH)^+$: 316. Found: 316.

PREPARATIVE EXAMPLE 94



Example 94



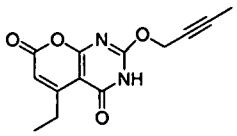
Example 1 Example 94

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**.

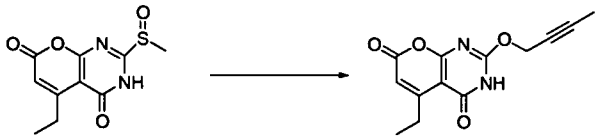
^{1}H NMR (CD_3OD): δ 1.38 (d, 2 H, J = 6.8 Hz) 5.50 (q, 1 H, J = 6.8 Hz) 6.20 (s, 1 H)

Mass of $C_9H_9N_2O_5$ $(MH)^+$: 225. Found: 225.

PREPARATIVE EXAMPLE 95



Example 95



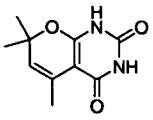
Example 10 Example 95

2-butyn-1-ol (140 mg, 2 mmol, 2 equiv.) in 4 mL of THF was treated with 1.6 M n-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.

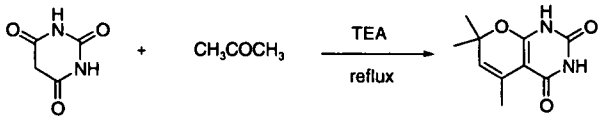
^{1}H NMR ($CDCl_3$): δ 1.20 (t, 2 H, J = 6.8 Hz) 1.83 (s, 3 H) 3.00 (q, 2 H, J = 6.98 Hz) 5.00 (s, 2 H) 6.00 (s, 1 H)

Mass of $C_{13}H_{13}N_2O_4$ $(MH)^+$: 261. Found: 261.

PREPARATIVE EXAMPLE 96



Example 96

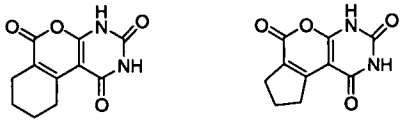


Example 96

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 $[M+1]^+$ for **Example 96** is 209.0

PREPARATIVE EXAMPLES 97 and 98

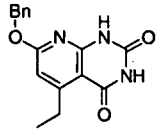


Example 97 Example 98

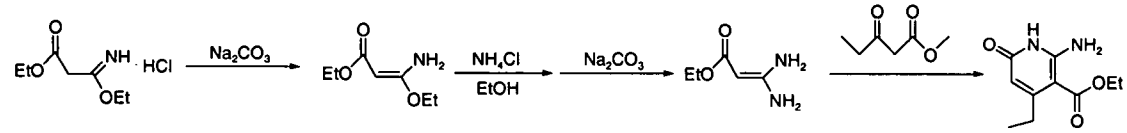
Examples 97 and **98** were prepared by methods analogous to the method used to prepare **Example 1**, except that 2-oxo-cyclohexanecarboxylic acid methyl ester and 2-oxo-cyclopentanecarboxylic acid methyl ester, respectively, were used instead of methylpropionylacetate.

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

PREPARATIVE EXAMPLE 99



Example 99



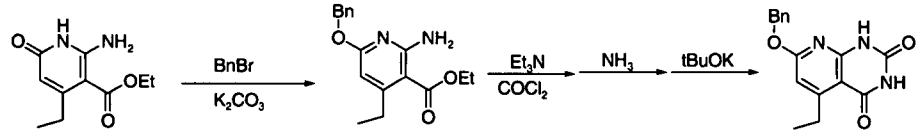
Compound 99a Compound 99b Compound 99c Compound 99d

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 $C_{10}H_{15}N_2O_3$ $(MH)^+$: 211. Found: 211.



Compound 99d Compound 99e Example 99

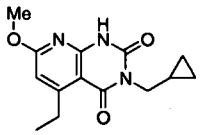
Compound 99d (3.0 g, 14.28 mmol) was treated with BnBr (2.44 g, 1 eq) and K_2CO_3 (3.94 g, 2 eq) in 100 mL acetone at 70°C for 17 h. The solvent was removed and chromatographic purification (5% EtOAc in hexane) provided 2.53 g pure **Compound 99e** in 58% yield.

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 $C_{16}H_{16}N_3O_3$ $(MH)^+$: 298. Found: 298.

PREPARATIVE EXAMPLE 100



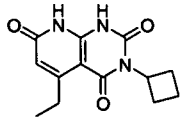
Example 100

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.

^{1}H 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 $C_{14}H_{18}N_3O_3$ $(MH)^+$: 276. Found: 276.

PREPARATIVE EXAMPLE 101



Example 101



Compound 101a Example 101

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

^{1}H 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)

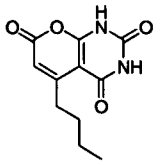
Mass of $C_{20}H_{22}N_3O_3$ $(MH)^+$: 352. Found: 352.

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**.

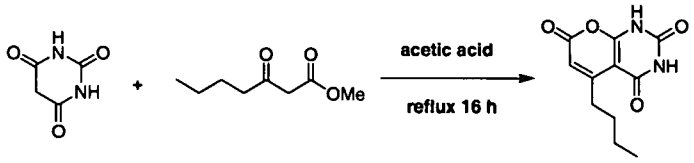
^{1}H NMR ($CDCl_3$): δ 1.20 (t, 2 H, J = 7.3 Hz) 1.60-1.80 (m, 2 H) 2.10 (m, 2 H) 2.95 (m, 2 H) 3.20 (q, 2 H, J = 7.3 Hz) 5.30 (m, 1 H) 6.40 (s, 1 H) 8.00 (br s, 1 H).

Mass of $C_{14}H_{17}N_3O_3$ $(MH)^+$: 276. Found: 276.

PREPARATIVE EXAMPLE 102



Example 102



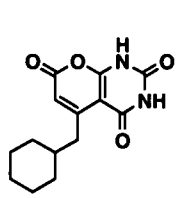
Example 102

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**.

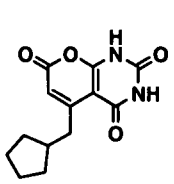
^{1}H NMR (DMSO): δ 0.9 (t, 3 H, J = 7.5 Hz) 1.32-1.40 (m, 2 H) 1.45-1.51 (m, 2 H) 2.84-2.87 (t, 2 H, J = 7.5 Hz) 5.82 (s, 1 H) 11.34 (s, 1 H) 12.72 (br s, 1 H)

Mass of $C_{11}H_{12}N_2O_4$ $(MH)^+$: 236.22. Found: 237.1.

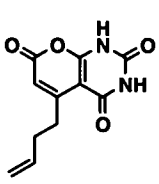
EXAMPLES 103-135



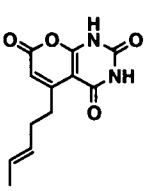
Example 103



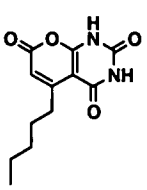
Example 104



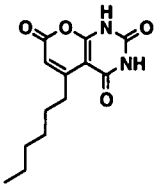
Example 105



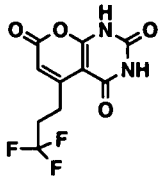
Example 106



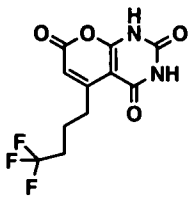
Example 107



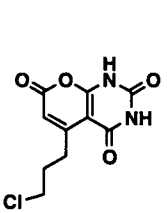
Example 108



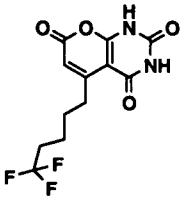
Example 109



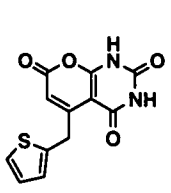
Example 110



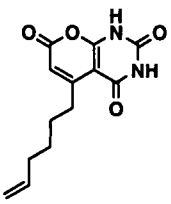
Example 111



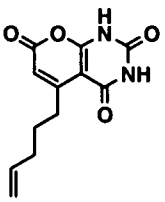
Example 112



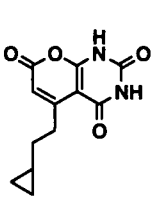
Example 113



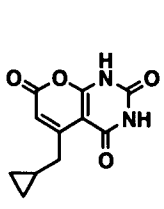
Example 114

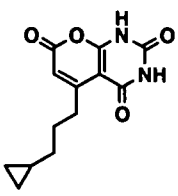


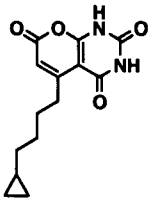
Example 115

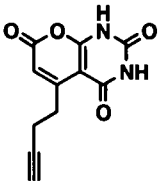


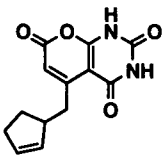
Example 116

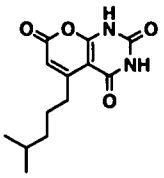

Example 117

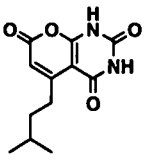

Example 118

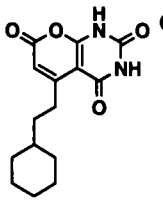

Example 119

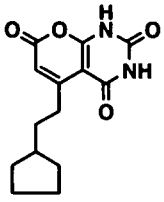

Example 120

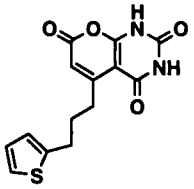

Example 121

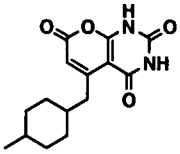

Example 122

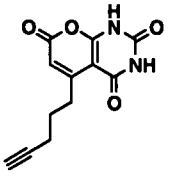

Example 123

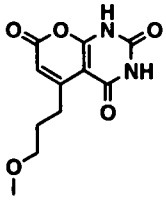

Example 124

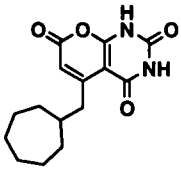

Example 125

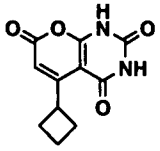

Example 126

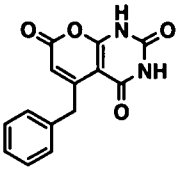

Example 127


Example 128

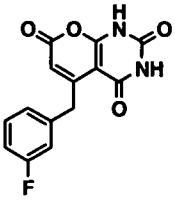

Example 129

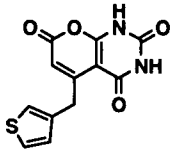

Example 130


Example 131


Example 132


Example 133


Example 134


Example 135

Examples 103-135 where 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.

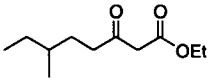
The examples **200, 210, 241, 242, 245, 246, 252-260, 274-278, 280, 281, 282, 284, 285, 291** were prepared by a procedure similar to that used for the preparation of Example **30 and 31**.

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.

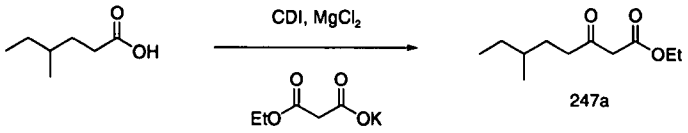
The preparation of ketoesters starting material where appropriate is shown below.

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

Preparative example 247a



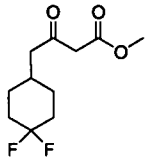
247a



247a

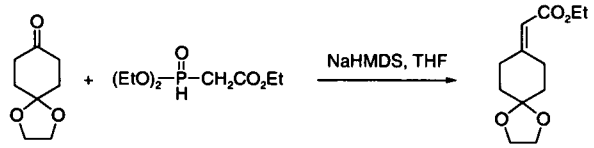
4-Methylhexanoic acid (3.0 g, 23.08 mmol) was taken in 40 mL THF. 1,1'-Carbonyldiimidazole (4.49 g, 27.69 mmol) was added and the reaction was stirred at room temperature for 1 h after which $MgCl_2$ (2.2 g, 23.08 mmol) and ethyl potassium malonate (5.89 g, 34.62 mmol) was added. The reaction was allowed 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



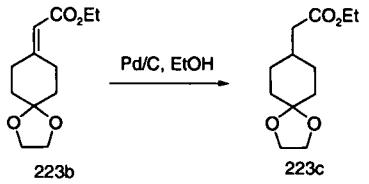
223a

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

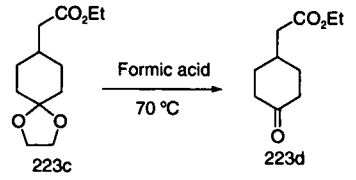


223b

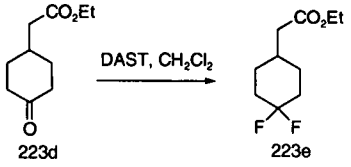
Step A: A solution of triethyl phosphonate (44.8g, 200 mmol) in THF (30 ml) at 0 °C was treated with a 1M solution (200 ml) of sodium bis(trimethylsilylamide) in THF. The resulting mixture was stirred at room temperature for 0.5 hour, and then cooled to 0 °C. A solution of 1,4-cyclohexanedione mono ethylene 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 was extracted with EtOAc. The extract was washed with satd. aqueous $NaHCO_3$, brine, dried over Na_2SO_4, filtered, and the filtrate was concentrated. The residue was chromatographed on silica gel, eluting with a gradient of CH_2Cl_2/EtOAc to afford **223b** (21g, 91%).



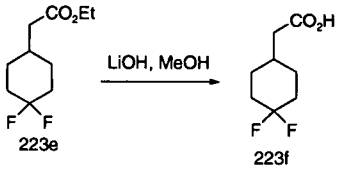
Step B: The compound **223b** (20g) was dissolved in EtOH (150 ml) and treated with 10% Pd/C under 1 atm of hydrogen for 3 days. The mixture was filtered and the filtrate was evaporated to **223c** (20.3g, 100%).



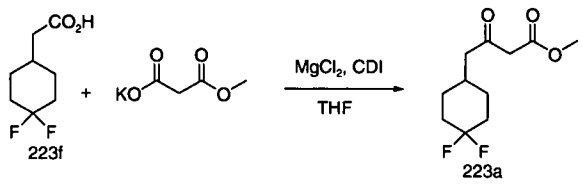
Step C: The compound **223c** (7g) was dissolved in formic acid (50 ml) and heated at 70 °C for 1 h. The solution was concentrated and the residue was taken up in EtOAc and washed with satd. aqueous $NaHCO_3$, brine, dried over Na_2SO_4 and concentrated. The residue was chromatographed on silica gel to afford **223d** (5g).



Step D: The compound **223d** (4.6 g) was dissolved in CH_2Cl_2 (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 CH_2Cl_2. The extract was washed with satd. aqueous $NaHCO_3$, brine, dried over Na_2SO_4 and concentrated to afford **223e** as brown oil (3.2 g, 62%).



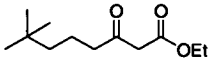
Step E: The compound **223e** (3.2 g, 15.5 mmol) was dissolved in MeOH (5 ml) and treated with LiOH (559 mg, 23.3 mmol) overnight. The reaction mixture was acidified by 3 N HCl to pH 4 and extracted with CH_2Cl_2. The extract was dried over Na_2SO_4 and concentrated to afford **223f** as brown oil (3 g, 100%).



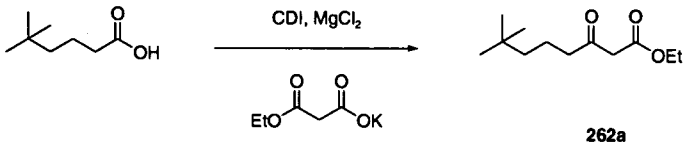
Step F: The compound **223f** (900 mg, 5.0 mmol) was dissolved in THF (15 ml), added with CDI (972 mg, 6.0 mmol) and stirred for 45 min. Then methyl malonate potassium salt (1.02 g, 6.0 mmol) and $MgCl_2$ (570 mg, 6.0 mmol) were added into the above solution. The resulting mixture was stirred overnight 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%).

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

Preparative example 262a



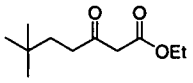
262a



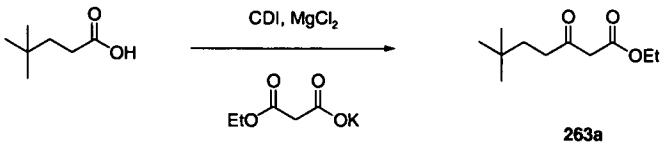
262a

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

Preparative example 263a



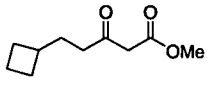
263a



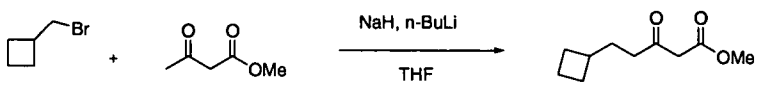
263a

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

Preparative example 266a



266a

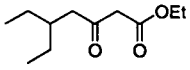


266a

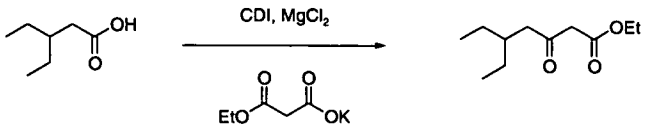
Sodium hydride (1.42 g, 35.56 mmol) was taken in THF (20 mL) in a round bottomed flask equipped with a stirring bar and nitrogen balloon. It was cooled to 0 °C

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 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 the addition of sat. NH_4Cl, extracted with EtOAc (2 x 30 mL), dried over $MgSO_4$, concentrated in vacuo. The crude product was purified by biotage (5% EtOAc/hexanes) to yield compound **266a**.

Preparative example 267a



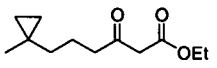
267a



267a

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

Preparative example 268a

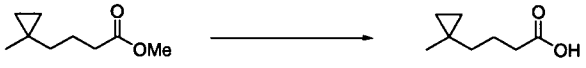


268a



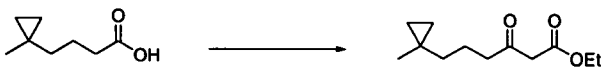
268b

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. NH_4Cl, extracted with DCM (2 x 30 mL), dried over $MgSO_4$, concentrated in vacuo to yield compound **268b** which was carried over to the next step without further purification.



268b **268c**

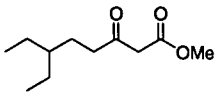
Ester **268b** (5.0 g, 32 mmol) was taken in MeOH (50 mL) and NaOH (3.2 g, 80 mmol) was added to it. The reaction was allowed to stir at room temperature overnight. The reaction was diluted with water (50 mL) and acidified with conc HCl. It was extracted with Et_2O (2 x 30 mL), washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The crude product **268c** was used as such without any further purification.



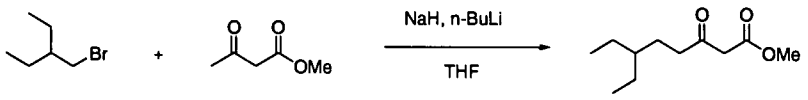
268c **268a**

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

Preparative example 269a



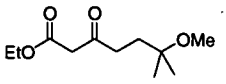
269a



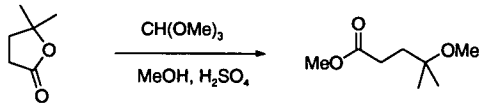
269a

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

Preparative example 279a

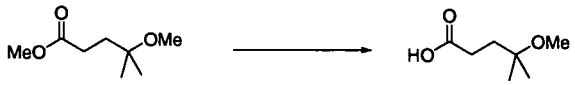


279a



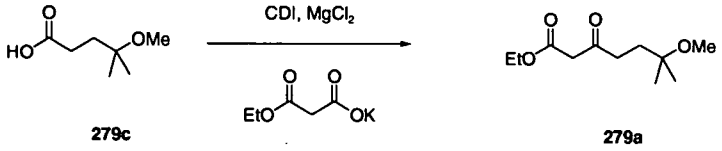
279b

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. $NaHCO_3$ and extracted with EtOAc (2 x 30 mL). The organic layer was washed with brine, dried over $MgSO_4$ and concentrated in *vacuo* to yield compound **279b** which was used without any further purification.



279b 279c

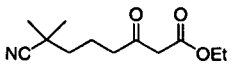
Prepared in the same manner as in example **268c**.



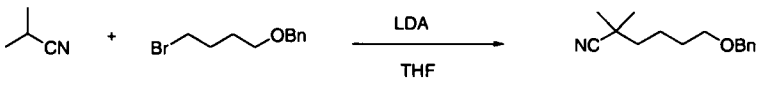
279c 279a

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

Preparative example 288a

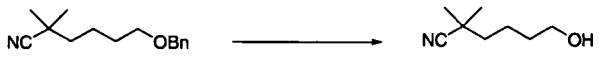


288a



288b

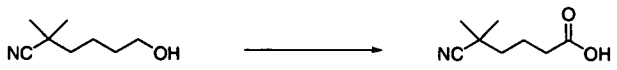
Lithium diisopropylamide (2.0 M solution in THF/heptane/ethyl benzene, 43.4 mL, 86.82 mmol) was taken in THF (30 mL) and cooled to – 78 °C. Isobutyronitrile (6 g, 86.82 mmol) in THF (10 mL) was added dropwise and the reaction was stirred at – 78 °C for 1 h and 0 °C for 2 h. Benzyl 4-bromobutyl ether (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 NH_4Cl and extracted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated in *vacuo*. The crude compound obtained was purified by biotage (5% EtOAc/hexanes) to yield compound **288b**.



288b 288c

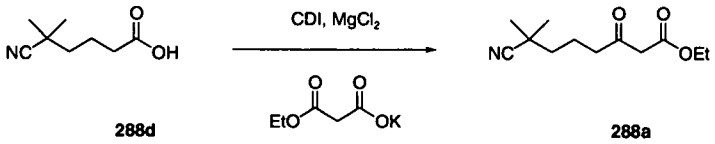
Compound **288b** was taken up in CH_2Cl_2 (25 mL) in a 100 mL round bottomed flask equipped with a stirring bar and nitrogen balloon and cooled to – 78 °C. Boron trichloride (1.0 M solution in hexanes, 43.2 mL, 43.2 mmol) was added dropwise and the reaction was allowed to gradually warm to 0 °C. After 1 h the reaction was quenched by the addition of sat. $NaHCO_3$, extracted with CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$, 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**.



288c **288d**

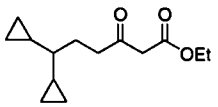
Compound **288c** (3.0 g, 21.2 mmol) was taken in acetone (20 mL) and cooled to 0 °C. Jones reagent was added dropwise until there was no change in color to green upon addition of the reagent. The excess reagent was quenched by the addition of *i*-PrOH, and water (20 mL) extracted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in *vacuo* to yield compound **288d** which was used without further purification.



288d **288a**

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

Preparative example 293a



293a



293b

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. Dicyclopropyl 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.

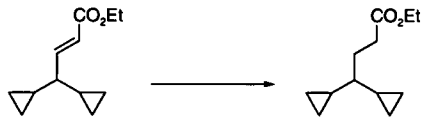
The crude enol ether was taken up in THF (100 mL) and 10 % HCl (100 mL) was added. The reaction was refluxed overnight. Upon cooling, diluted with water and

extracted with Et_2O (2 x 50 mL), washed with brine, dried over $MgSO_4$, concentrated in *vacuo*. The crude mixture **293b** was used as such without further purification.



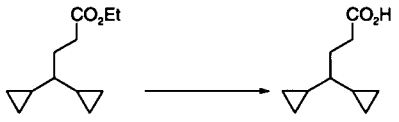
293b **293c**

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 Et_2O. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in *vacuo*. The crude was purified by biotage (2% EtOAc/haxanes) to yield compound **293c**.



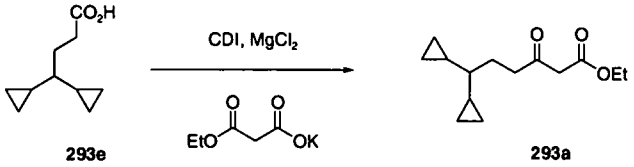
293c **293d**

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**.



293d **293e**

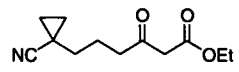
Prepared in the same manner as in example **268c**.



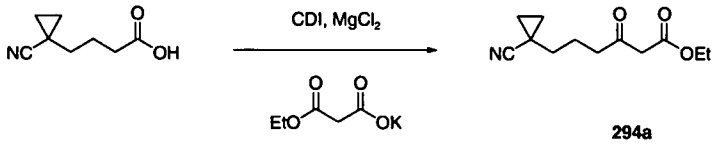
293e **293a**

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

Preparative example 294a



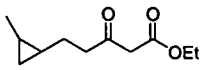
294a



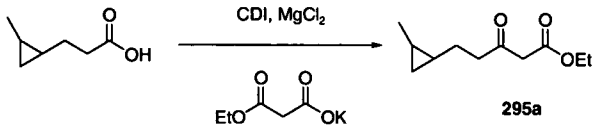
294a

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

Preparative example 295a



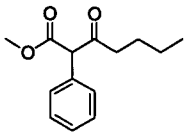
295a



295a

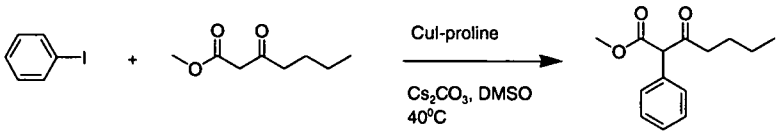
Prepared in the same manner as in example **262a**.

Preparative example 292a



292a

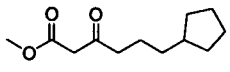
The starting material for the preparation of example **292** is as follows.



292a

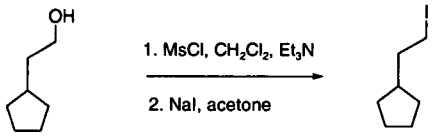
Into the solution of iodobenzene (10.2 g, 50 mmol) in anhydrous DMSO (150 mL) and 3-oxoenanthic acid methyl ester (15.8 g, 100 mmol) was added copper(I) iodide (1.9 g, 10 mmol), L-proline (2.3g, 20 mmol), and cesium carbonate (65.2g, 200 mmol). After stirred under N_2 at 40 ^{0}C for 18 hours, the reaction mixture was dissolved into ethyl acetate (250 mL), washed with 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



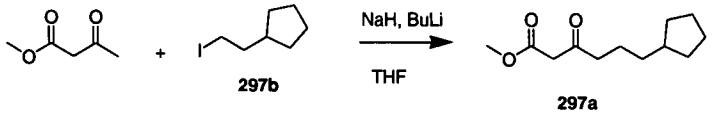
297a

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



297b

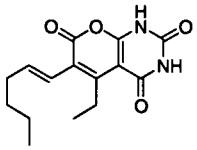
To a solution of 2-cyclopentyl ethanol (11.4 g, 100 mmol), anhydrous CH_2Cl_2 (80 mL), and triethyl amine(12 g, 120 mmol), which cooled to 0 ^{0}C, was added via syringe MsCl (13.7 g, 120 mmol). After stirring under N_2 at 0 ^{0}C for 1 hour then at room temperature for 18 hours, the reaction mixture 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 CH_2Cl_2 (250 mL) and mixed with NaI (20g, 200 mmol). After 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%).



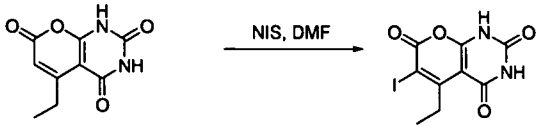
297b 297a

To a solution of methyl acetoacetate (5.8 g, 50 mmol) and anhydrous THF (100 mL), which cooled to 0 ^{0}C, was added NaH (60%, 2.4g, 60 mmol). After stirring under N_2 at 0 ^{0}C for 0.5 hour, n-BuLi (2.5 M in hexanes, 20 mL) was added *via* syringe. After stirring at 0 ^{0}C for 0.5 hour, the reaction mixtures was cooled to -25 ^{0}C, the compound **297b** was added *via* syringe. The reaction mixture was stirred at 0 ^{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** (3.2 g, 32%).

Preparative example 214

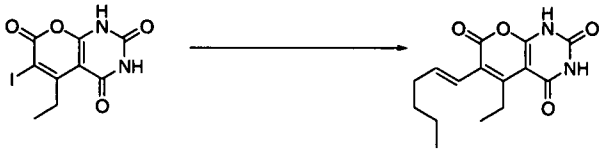


214



214a 214b

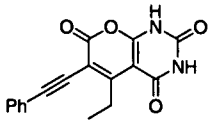
Compound **214a** (10 g, 48.04 mmol) was taken in DMF (50 mL) in a round bottomed flask equipped with a magnetic stirring bar. *N*-Iodosuccinimide (22 g, 97.79 mmol) was added portionwise and the reaction mixture was heated to 50°C overnight. After cooling to ambient temperature, H_2O (100 mL) was added. 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.



214b 214

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



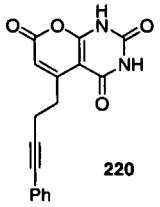
219



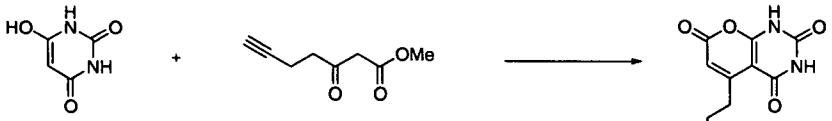
214b 219

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

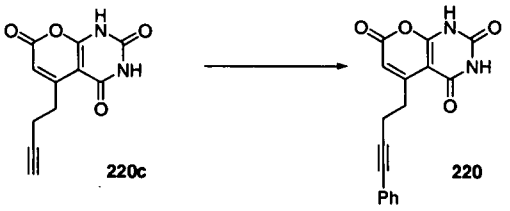


220



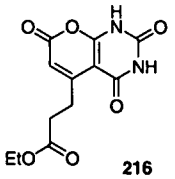
220a 220b 220c

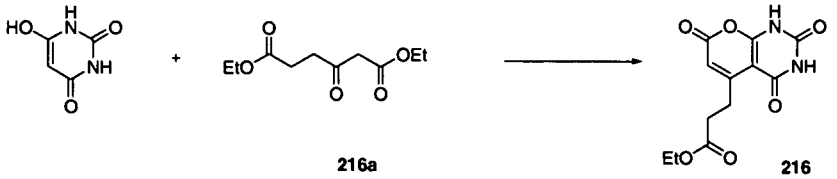
Barbituric acid **220a** (1.0 g, 7.81 mmol) and keto ester **220b** (1.45 g, 9.4 mmol) was taken in glacial acetic acid (8 mL) and the reaction mixture was heated to reflux overnight. After cooling to room temperature, the acetic acid was removed in *vacuo* and hot water was added to remove excess barbituric 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), $PdCl_2(PPh_3)_2$ (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

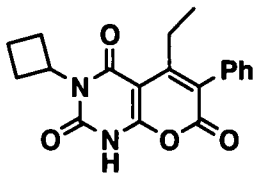




Barbituric acid (1.0 g, 7.81 mmol) and Diethyl β-ketoadipate **216a** (2.03 g, 9.4 mmol) was taken in glacial acetic acid (8 mL) and the reaction mixture was heated to reflux overnight. After cooling to room temperature, the acetic acid was removed in *vacuo* and hot water was added to remove excess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

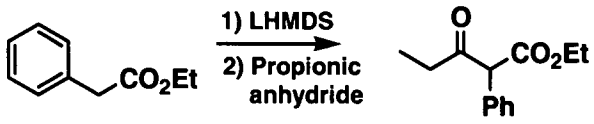
The starting material for the preparation of example **203** is as follows.

Preparative example 203



203

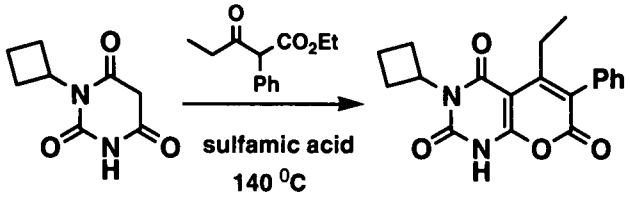
Step A:



203a

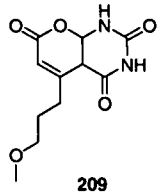
To a solution of ethylphenylacetate (8.2g, 0.05 mol) in THF at -78 ^{0}C was added LHMDS (1M in THF, 100 ml, 0.10 mol) and stirred for 20 min. Propionic anhydride (6.5 ml, 0.05 mol) was added rapidly. The mixture was allowed to warm up to 0 ^{0}C and stirred for 30 min. It was quenched with NH_4Cl (aq.) and extracted with EtOAc. Usual work up afforded the crude material which was chromatographed on silica gel to obtain product.

Step B:



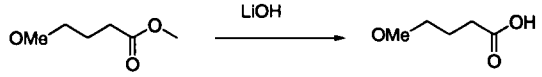
Compound **203** was obtained by normal condensation procedure with cyclobutylbarbituric acid.

Preparative example 209



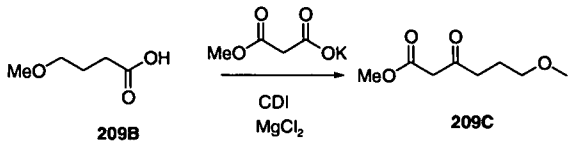
209

Step A:



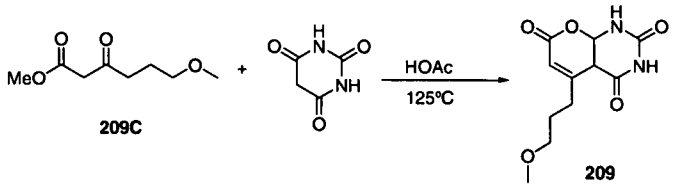
Starting material **209a** (9.9 g, 75 mmol) was dissolved in THF (100 mL) and water (25 mL). LiOH (3.4 g, 80.9 mmol), the resulting mixture was stirred at room temperature overnight. 1 N HCl (100 mL) was added and extracted with EtOAc. The organic extracts were combined, washed with brine, dried ($MgSO_4$) to give compound **209b** (8.8 g, 93%).

Step B:



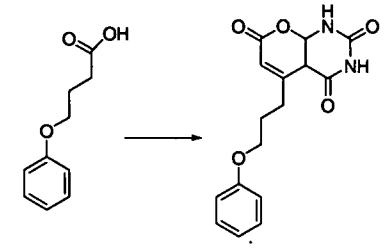
Compound 209c (1.9 g, 16.1 mmol) was dissolved in THF (50 mL), CDI (12.3 mmol) was added. The resulting mixture was stirred at room temperature for 1 h. $MgCl_2$ (1.5 g, 16.1 mmol) and $KOCOCH_2CO_2Me$ (3.8 g, 24.2 mmol) were added, the resulting mixture was stirred at room temperature overnight. EtOAc (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 ($MgSO_4$), filtered and concentrated. The residue was separated by silica gel chromatography, with Biotage 40S+ column, eluted with EtOAc: hexanes, 1:10, to give 2.1 g (74%) yellow liquid as **Compound 209d**.

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.

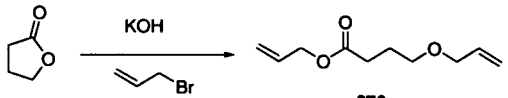
Compound 208 was prepared in a similar fashion as in **Compound 209**, from the commercially available **Compound 208a**.



compound 208A compound 208

Preparative example 270

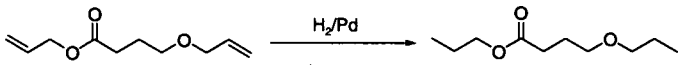
Step A:



270a

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 ($MgSO_4$), filtered and concentrated to give a yellow liquid as the desired **Compound 270a** (11.8 g, 55.2%).

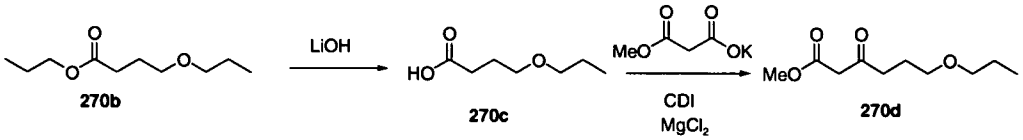
Step B:



270a 270b

Compound 270a (3.0 g, 16.3 mmol) was dissolve in EtOH (20 mL), 10 % Pd/C (300 mg) was added. The slurry was stirred under H_2 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%).

Step C:

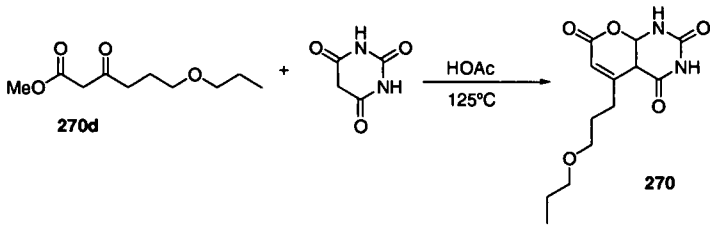


270b 270c 270d

Compound 270b (3.0 g, 16.3 mmol) was dissolve in THF (20 mL)-H_2O (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 extracted with Et_2O. The organic extracts were combined, dried ($MgSO_4$) 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. MgCl2 (1.3 g, 13.6 mmol) and $KOCOCH_2CO_2Me$ (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 ^0C 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

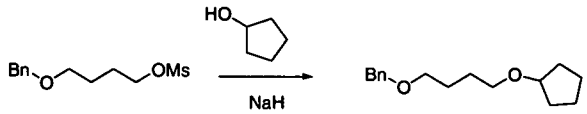
Step A:



271a

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. 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%).

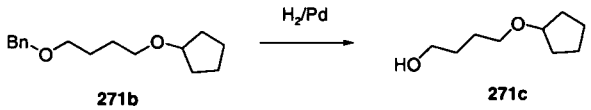
Step B:



271a 271b

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 ^{0}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 ($MgSO_4$), 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:

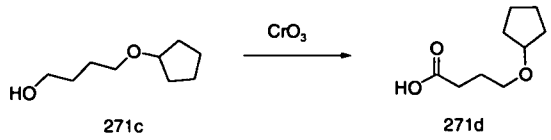


271b 271c

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.

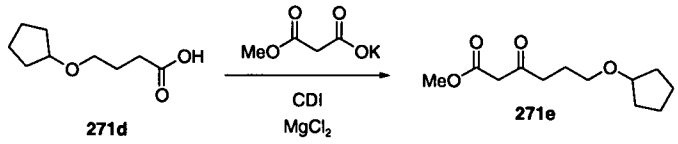
Step C:



271c 271d

CrO_3 was mixed with 4.7 mL of conc. H_2SO_4. 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 ($MgSO_4$), filtered and concentrated to give 1.99 g (71%).

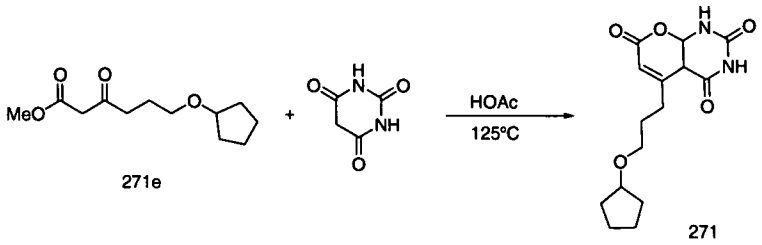
Step D:



271d 271e

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. $MgCl_2$ (1.5 g, 15.3 mmol) and $KOCOCH_2CO_2Me$ (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 ($MgSO_4$), 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:



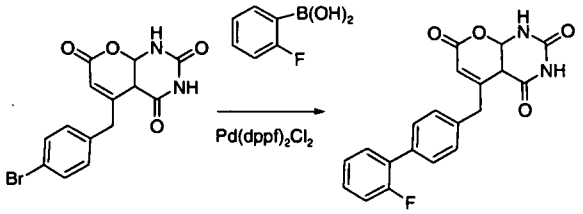
271e 271

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.

Preparative example 205

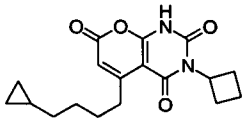


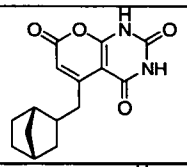
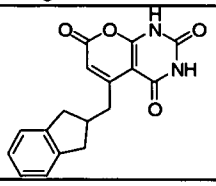
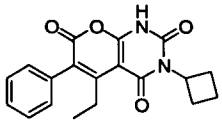
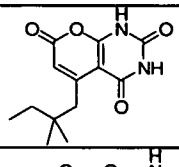
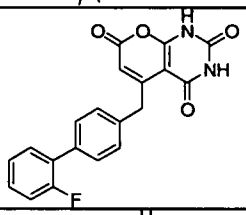
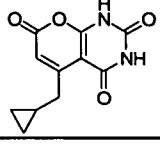
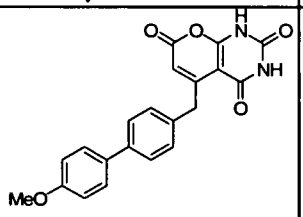
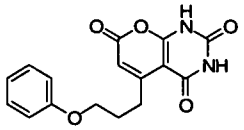
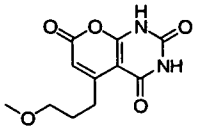
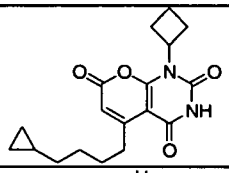
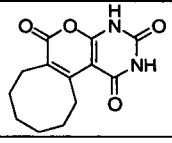
205a 205

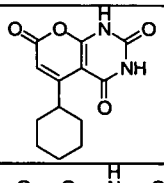
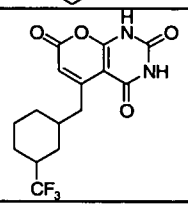
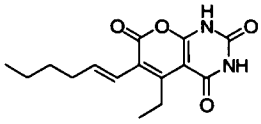
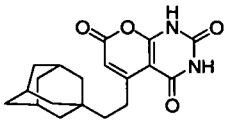
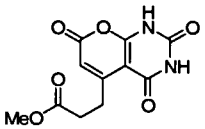
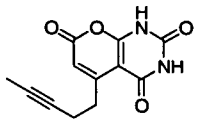
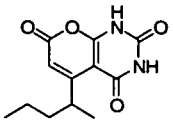
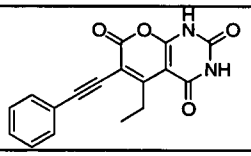
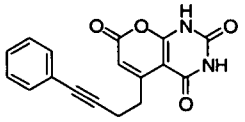
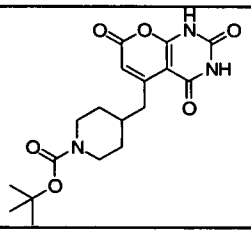
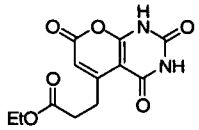
Compound 205a (50 mg, 0.14 mmol) was dissolved in DMF (2 mL) and H_2O (2 mL), $Pd(dppf)_2Cl_2$ and K_2CO_3 were added. The resulting mixture was heated at 85 ^{0}C under nitrogen for 5 h. The mixture was cooled to room temperature and filtered through Celite. The filtrated was concentrated. The residue 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.

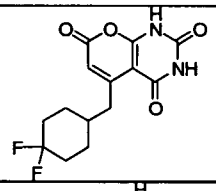
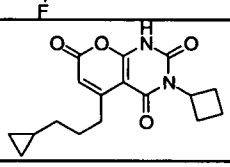
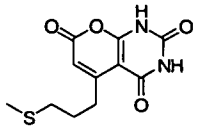
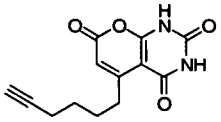
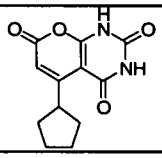
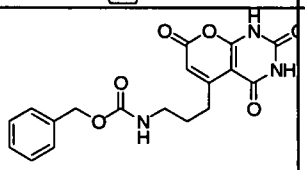
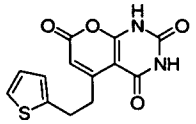
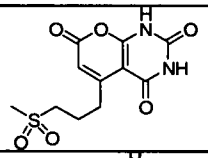
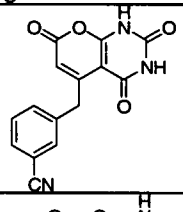
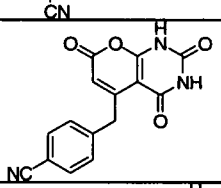
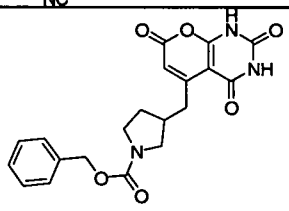
Compound 207 was prepared in a similar fashion as **Compound 205**, using the corresponding boronic acid.

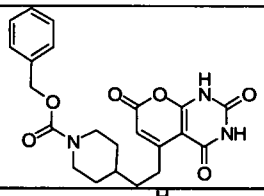
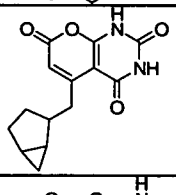
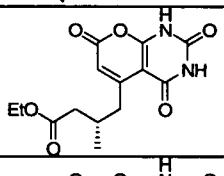
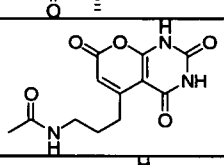
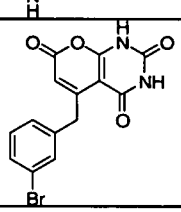
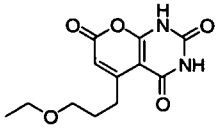
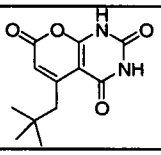
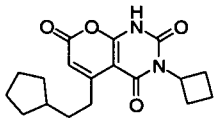
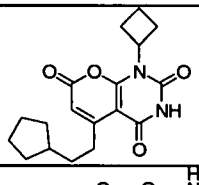
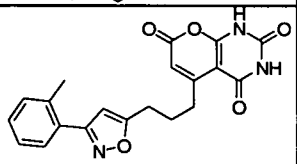
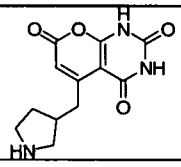
Several compounds of the invention are shown in the Table below as well as in the Tables presented later in this specification. The compounds shown in the table below were made using methods described in the preparative examples presented above herein. The LCMS data is also shown wherever available. The activity (EC_{50}) 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.

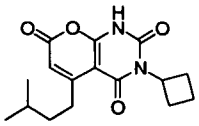
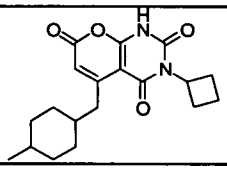
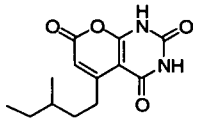
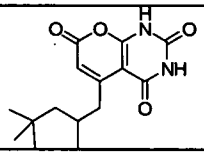
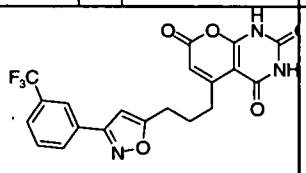
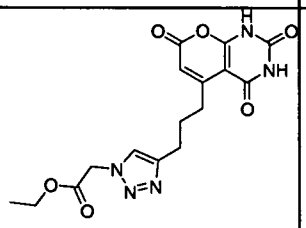
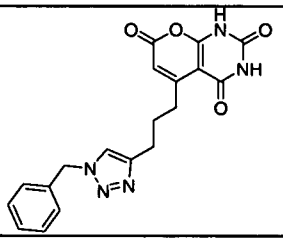
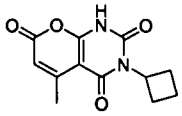
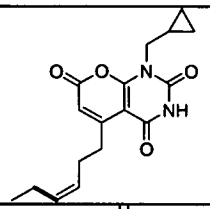
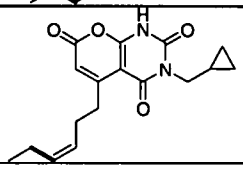
Compound No.	STRUCTURE	NA EC50 camp (nM)	Electrospray LCMS [M+1]+
200		B	331.2

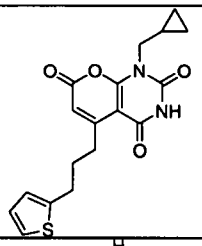
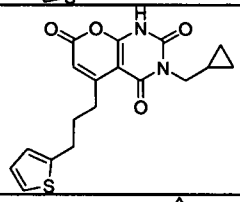
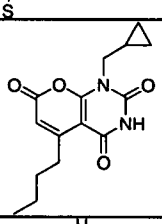
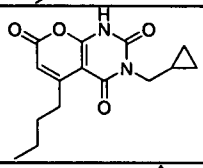
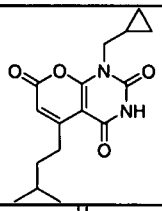
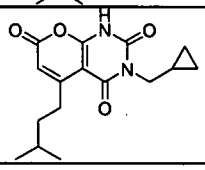
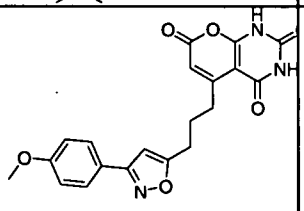
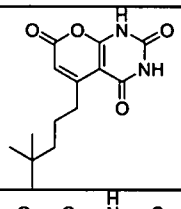
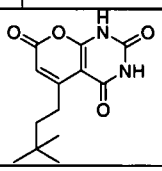
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202		B	311.2
203		C	339.1
204		C	265.1
205		B	365.2
206		B	235.1
207		C	377.2
208		C	316.2
209		B	253.1
210		B	331.2
211		C	263.1

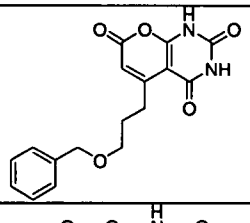
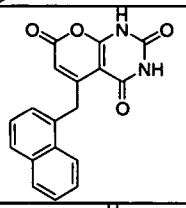
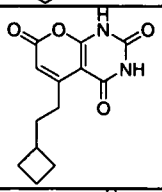
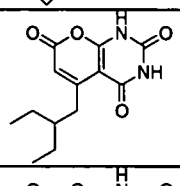
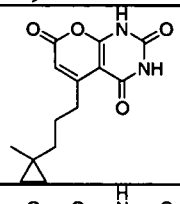
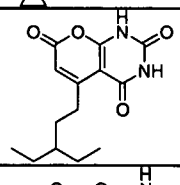
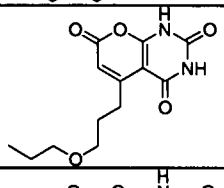
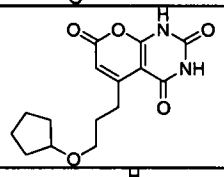
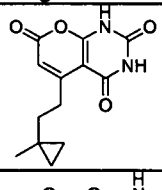
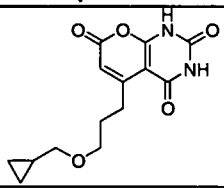
212		B	263.1
213		B	345.2
214		C	291.2
215		C	343.2
216		B	267.1
217		C	247.1
218		B	251.1
219		C	309.2
220		C	309.2
221		C	378.2
222		C	281.2

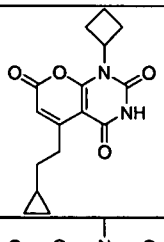
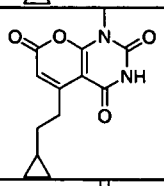
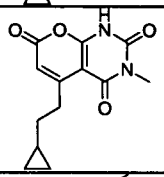
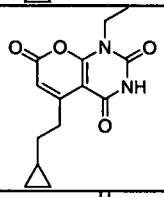
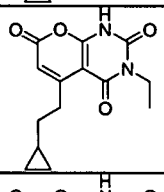
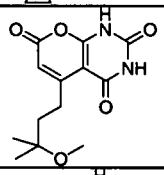
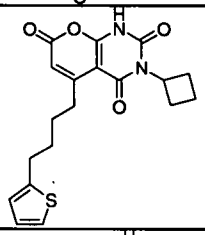
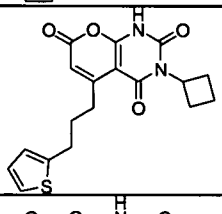
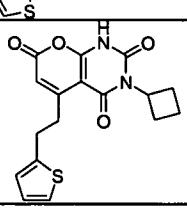
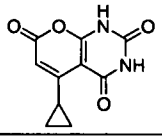
223		A	313
224		A	317.2
225		A	269.1
226		A	261.1
227		C	249.1
228		C	372.2
229		A	391.2
230		B	301.2
231		C	318.2 (M+Na)
232		C	368.2 (M+Na)
233		C	398

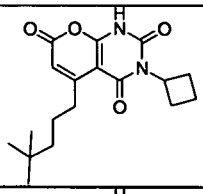
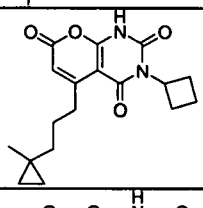
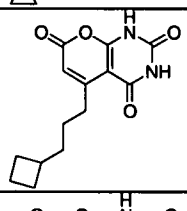
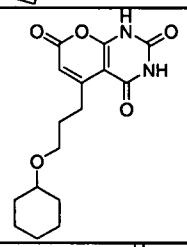
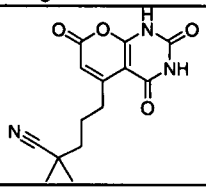
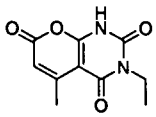
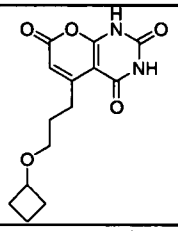
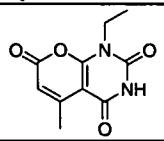
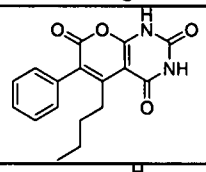
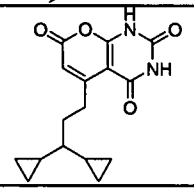
234		C	426
235		A	275.2
236		C	309.2
237		C	280.2
238		B	349.2
239		A	267.1
240		C	251
241		A	331.2
242		C	331.2
243		B	380
244		C	264

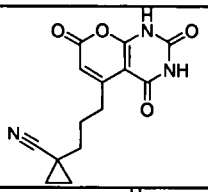
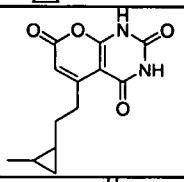
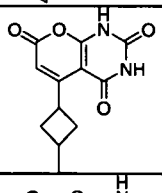
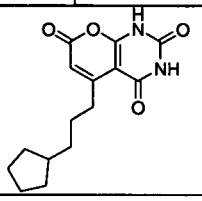
245		A	305.2
246		C	345.2
247		A	265.1
248		C	293.2
249		B	434
250		C	376
251		B	380
252		A	249.1
253		C	317.2
254		C	317.2

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

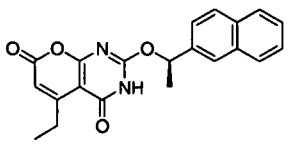
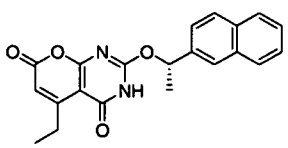
274		B	303.2
275		B	263.1
276		B	263.1
277		C	277.2
278		B	277.2
279		C	281.2
280		C	373.2
281		B	359.2
282		B	345.2
283		B	221.1

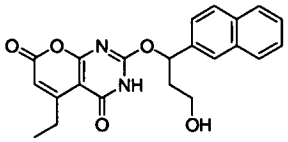
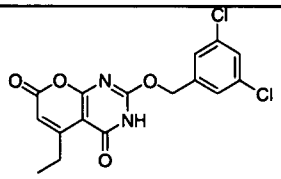
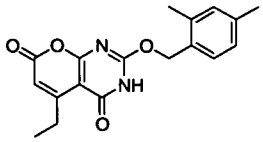
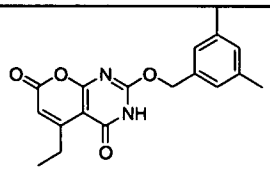
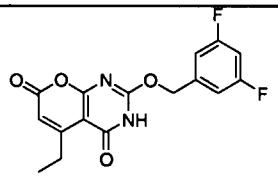
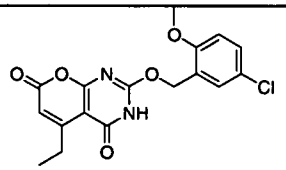
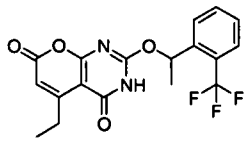
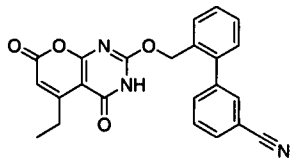
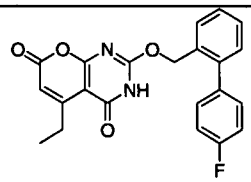
284		B	333.1
285		B	331.2
286		A	277.2
287		C	321.2
288		C	290.2
289		C	223.1
290		B	315.2 (M+Na)
291		C	223.1
292		B	313.2
293		B	303.2

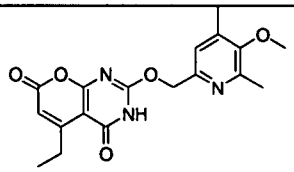
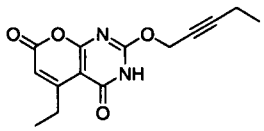
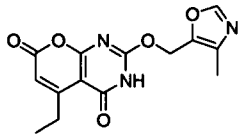
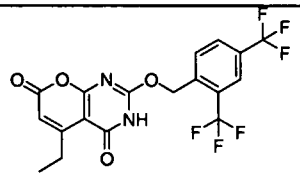
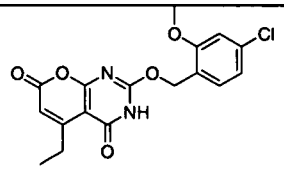
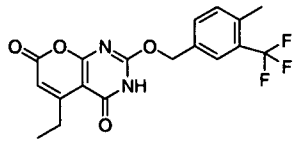
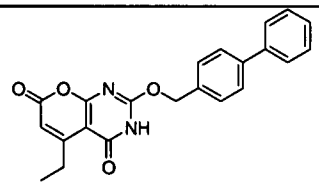
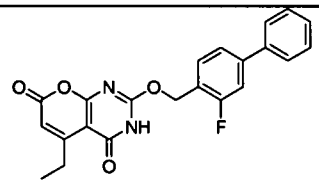
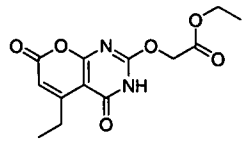
294		B	288.2
295		B	263.1
296		B	249.1
297		A	291.2

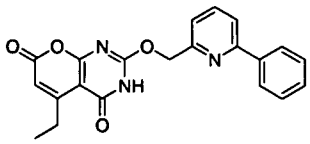
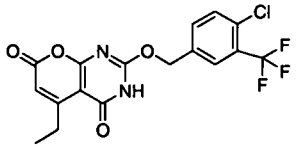
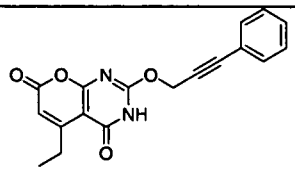
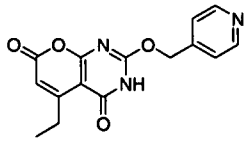
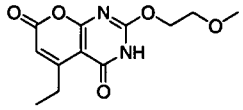
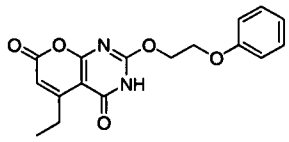
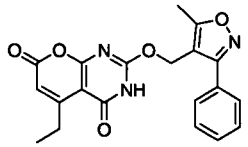
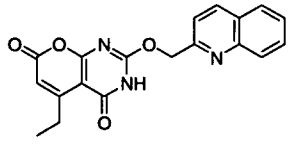
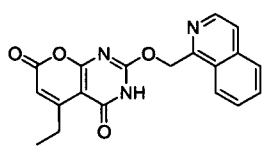
The compounds **500** to **690** were prepared by a procedure similar to that used for the preparation of **Example 49,** using **Example 10,** and the appropriate corresponding alcohol.

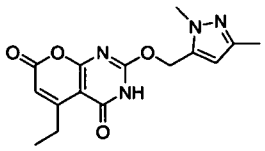
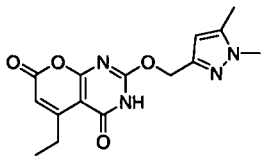
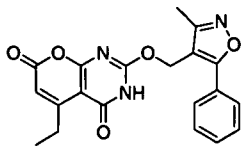
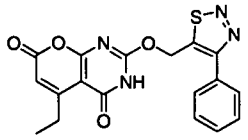
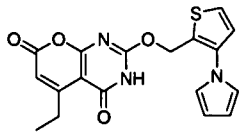
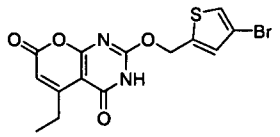
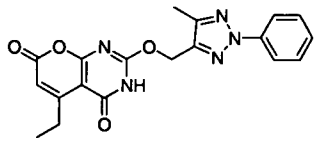
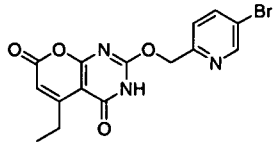
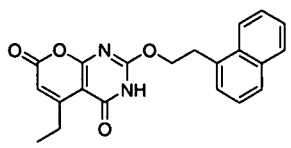
Compounds **691** and **698** were prepared by a procedure similar to Example 49, using appropriate oxyaminocarbamate and sulfoxide which was prepared using Example 10.

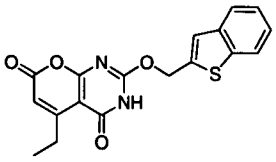
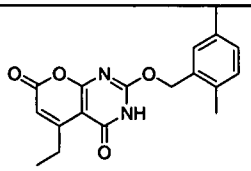
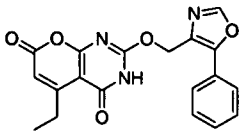
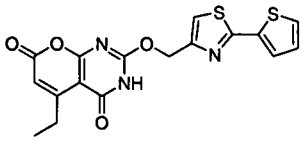
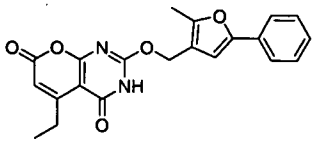
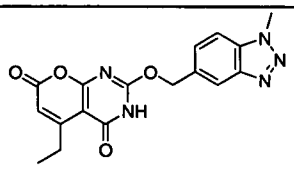
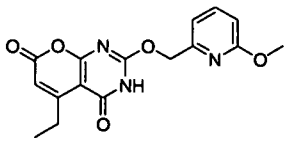
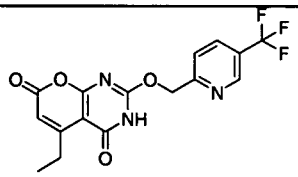
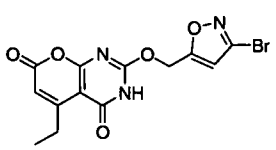
Compound No.	Structure	NA EC50 camp (nM)	Electrospray LCMS [M+1]+
500		B	363.1
501		A	363.1

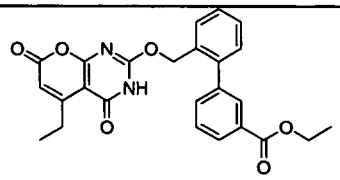
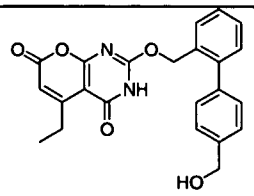
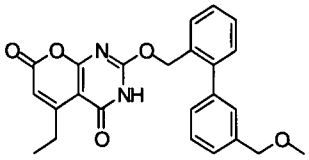
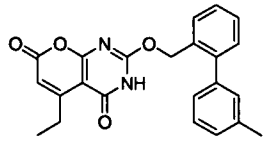
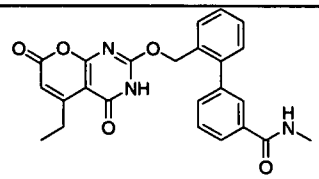
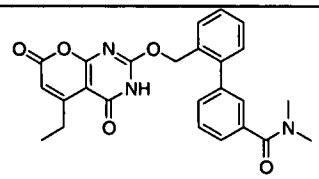
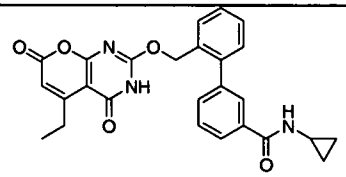
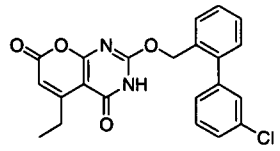
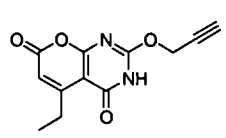
502		B	343
503		B	368
504		B	327
505		B	327
506		C	335
507		A	363
508		C	381.1
509		B	400
510		C	393

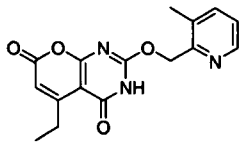
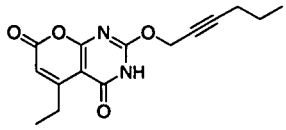
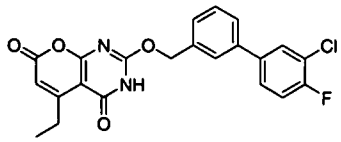
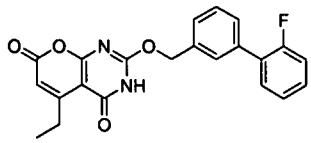
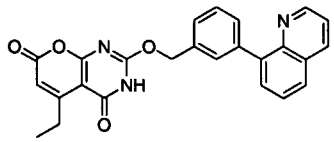
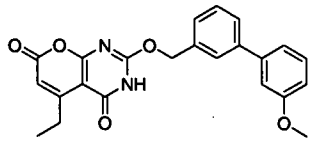
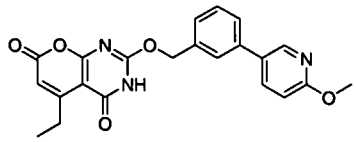
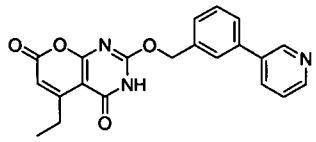
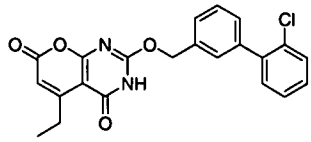
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515		B	363
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519		C	295.1

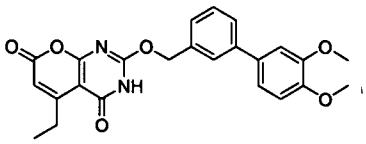
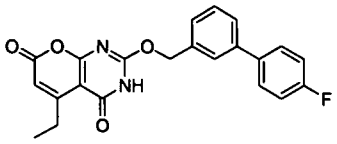
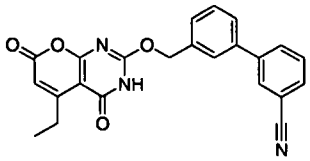
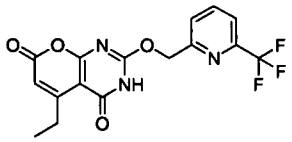
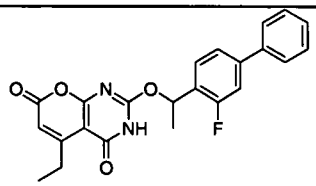
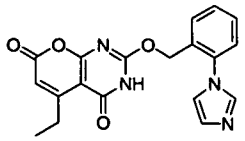
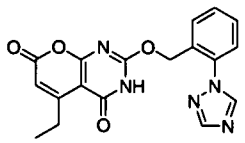
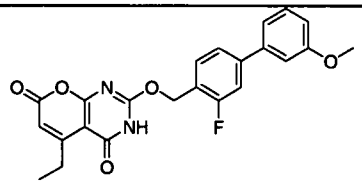
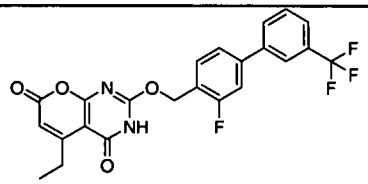
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522		B	323
523		A	300.2
524		B	267.1
525		B	329.2
526		B	380
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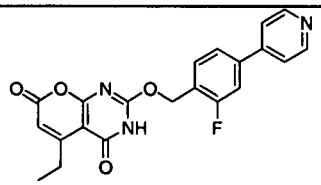
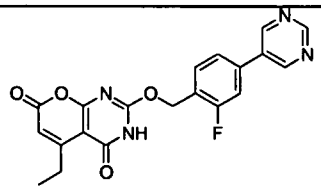
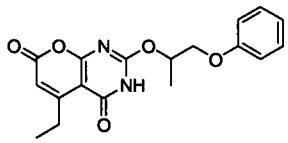
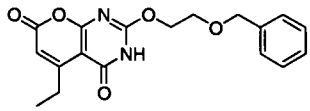
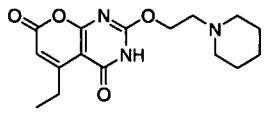
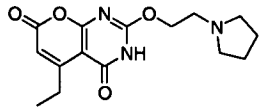
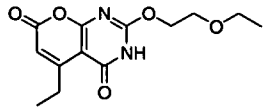
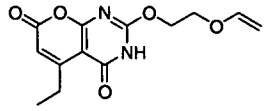
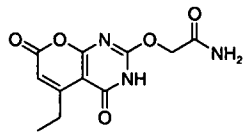
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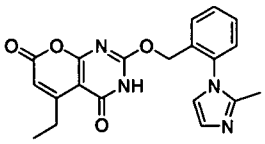
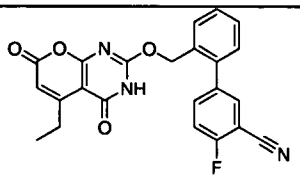
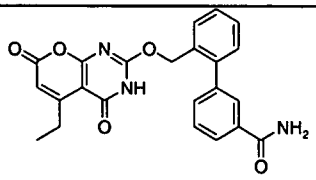
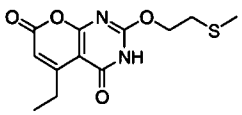
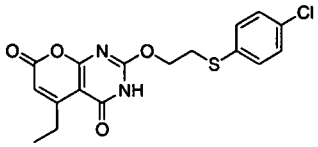
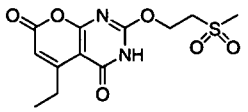
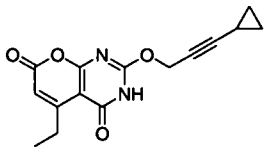
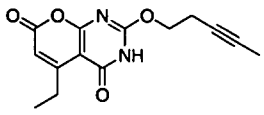
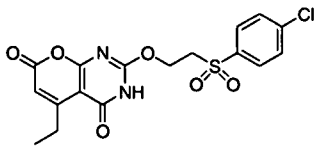
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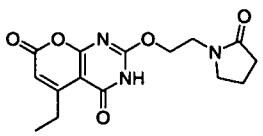
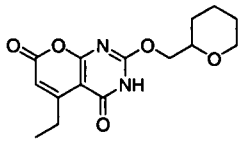
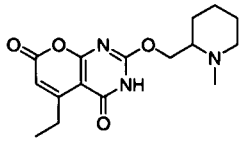
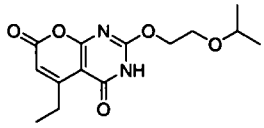
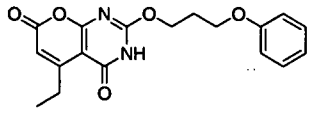
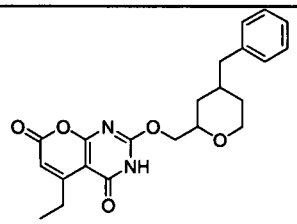
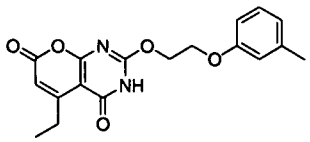
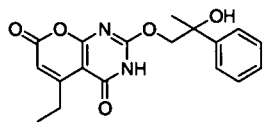
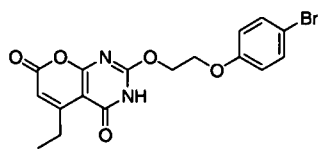
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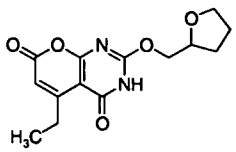
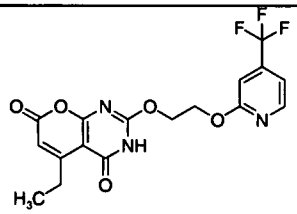
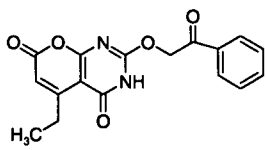
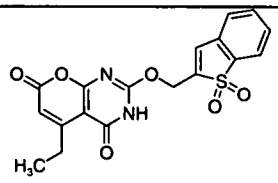
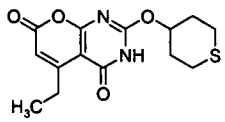
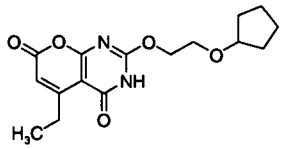
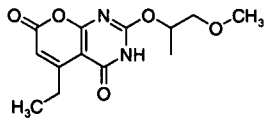
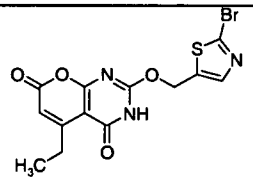
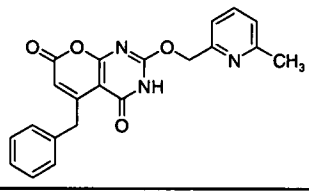
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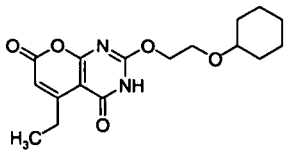
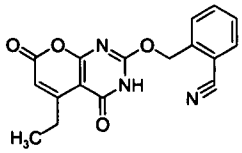
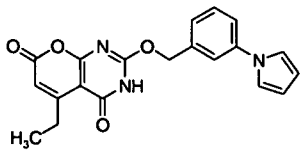
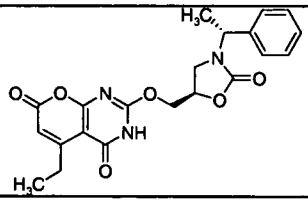
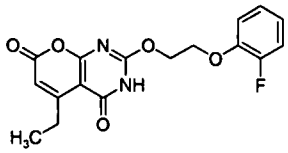
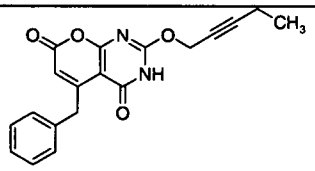
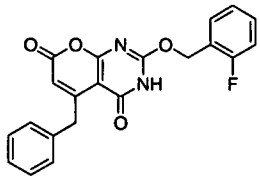
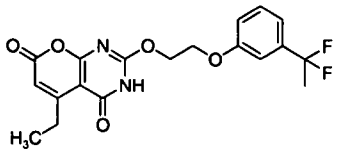
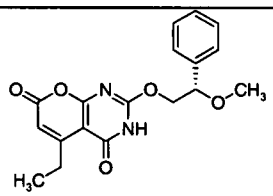
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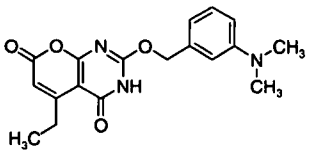
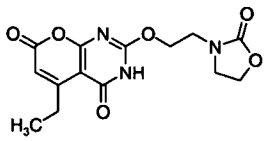
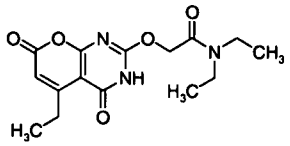
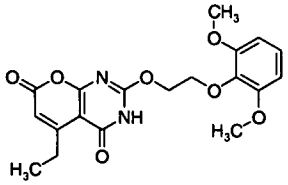
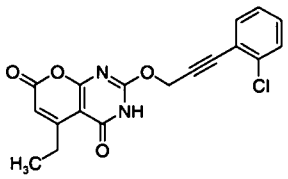
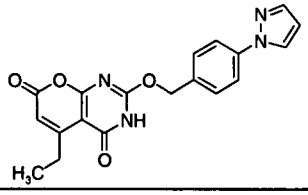
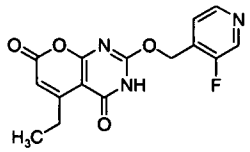
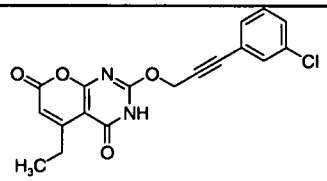
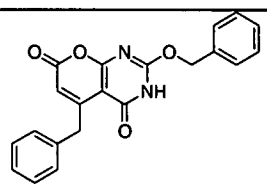
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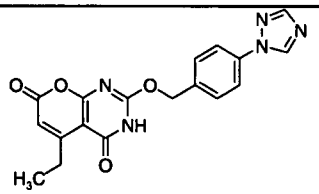
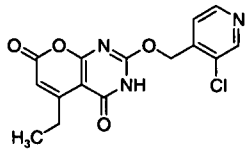
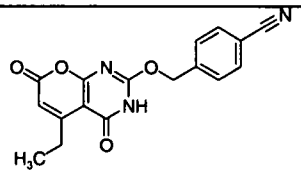
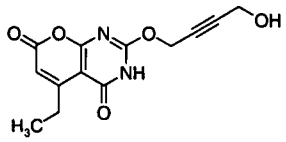
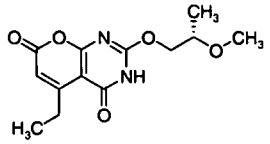
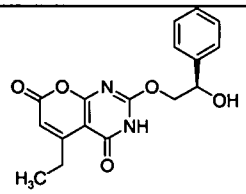
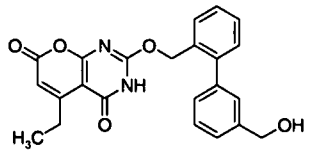
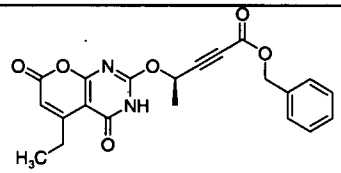
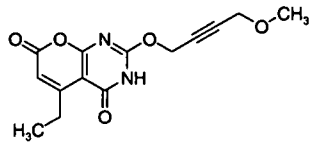
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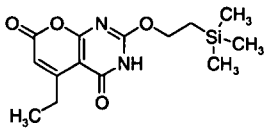
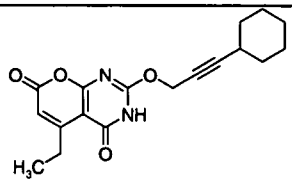
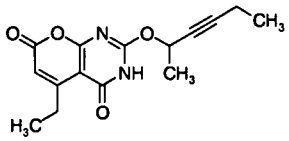
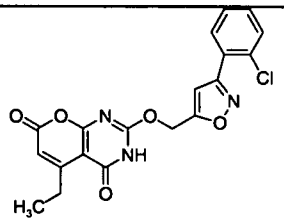
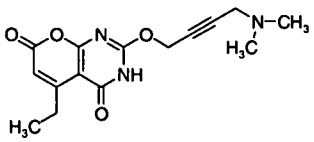
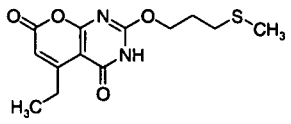
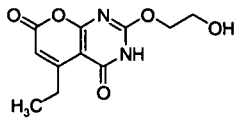
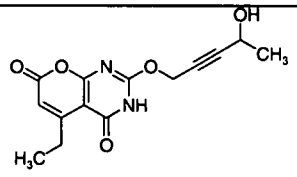
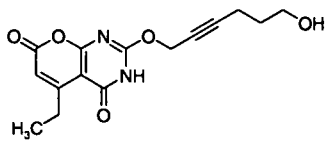
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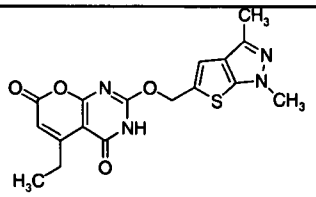
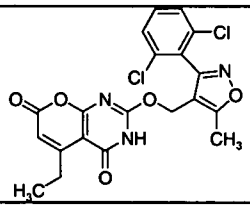
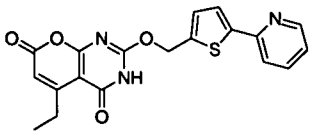
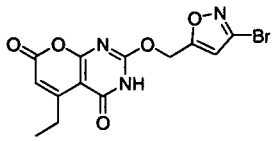
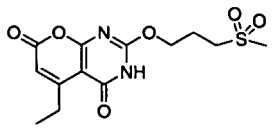
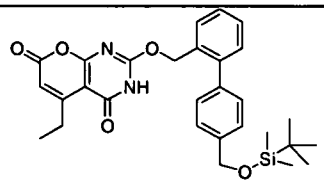
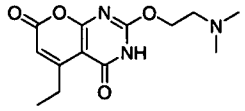
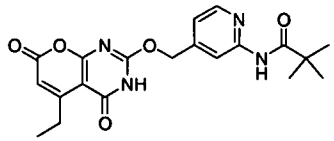
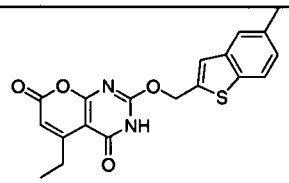
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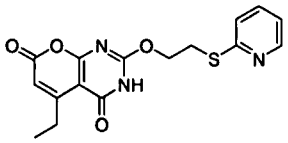
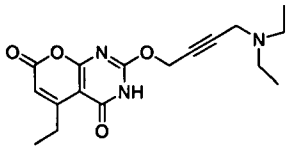
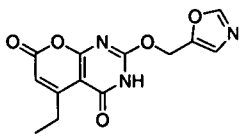
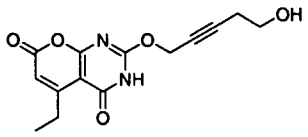
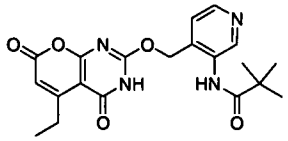
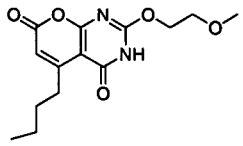
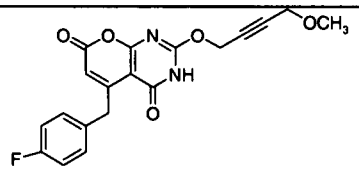
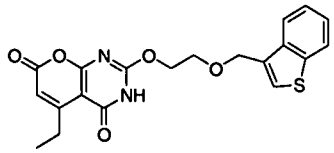
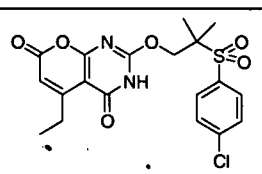
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612		C	364.2
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614		B	347.1
615		B	337.1
616		B	379.2
617		B	397.2
618		B	343.2

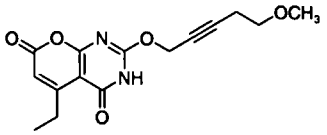
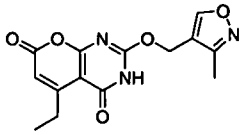
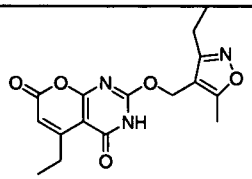
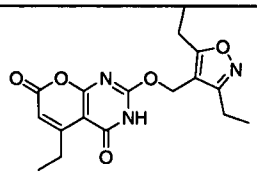
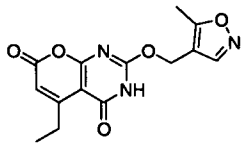
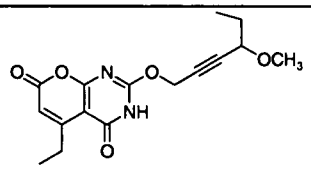
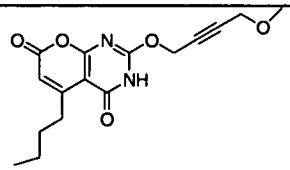
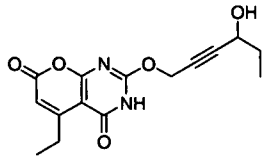
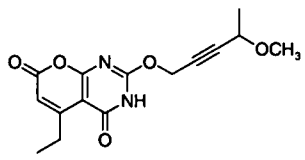
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620		C	322.2
621		B	322.2
622		B	389.2
623		A	357.2
624		B	365.2
625		B	318.2
626		A	358
627		C	361.2

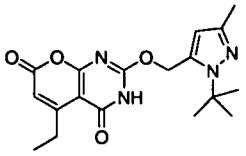
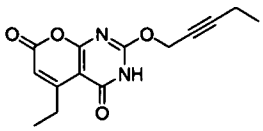
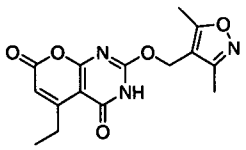
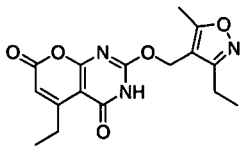
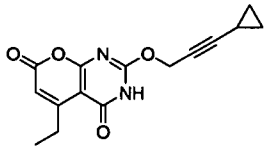
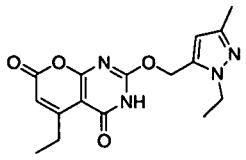
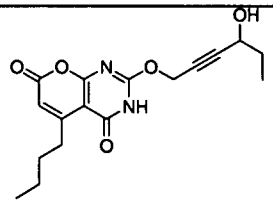
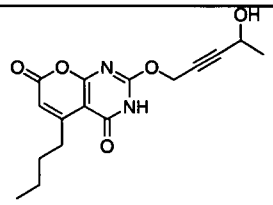
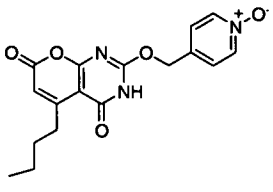
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632		B	281.2
633		B	329.2
634		B	405
635		C	395
636		B	291

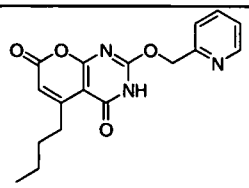
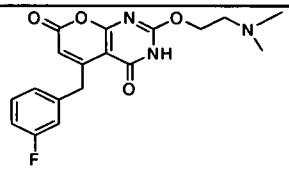
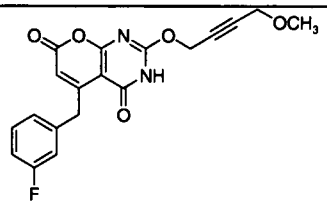
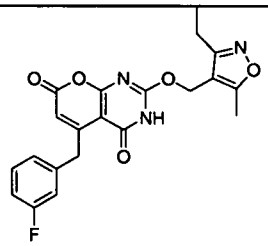
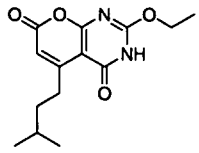
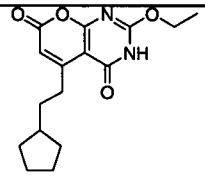
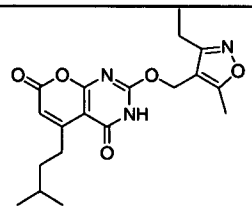
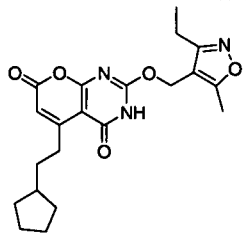
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638		B	329
639		B	283
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641		A	304
642		B	297.2
643		B	253.1
644		A	291
645		A	305

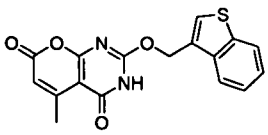
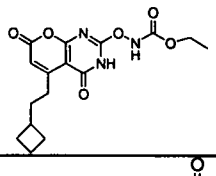
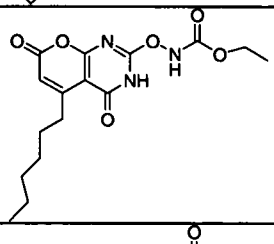
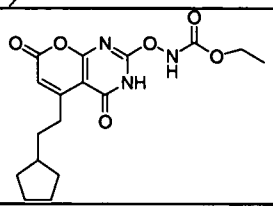
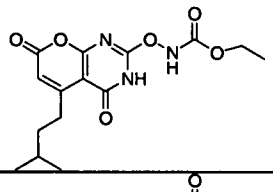
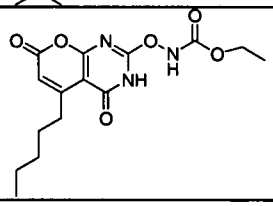
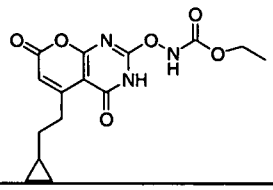
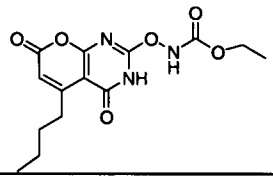
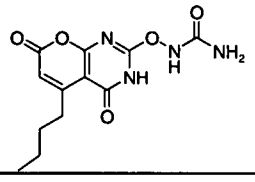
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647		B	448.2
648		B	382.2
649		B	368
650		B	329.2
651		B	520
652		A	280.1
653		C	399.2
654		A	M+Na 391.2

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

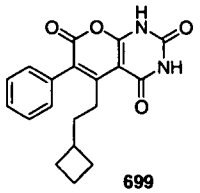
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665		C	304
666		A	332
667		B	346
668		C	304
669		B	319
670		A	319.2
671		A	305
672		B	305

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

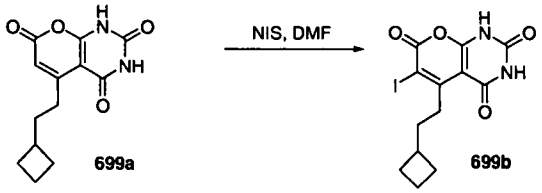
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683		C	360.2
684		A	371.2
685		B	412.2
686		B	279.2
687		B	305.2
688		B	374.2
689		B	400.2

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		--	324.2
698		--	295.2

Preparative example 699

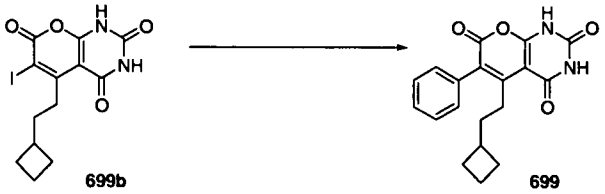


699



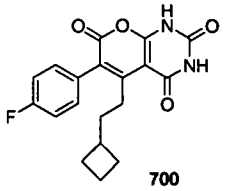
699a 699b

Compound **699a** (0.925 g, 3.53 mmol) was taken in DMF (10 mL) in a 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, H_2O (25 mL) was added. The product was filtered, washed with water followed by ether to give a white powdery mixture (> 95% yield). The product **699b** was used as such for the next step without any further purification.



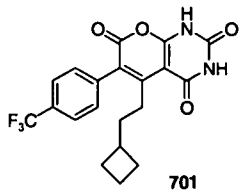
699b 699

Compound **699b** (0.1 g, 0.258 mmol) was taken in 5 mL DME/H_2O (4:1) in a 10 mL round bottomed flask. $PdCl_2(PPh_3)_2$ (0.018 g, 0.0258 mmol), Na_2CO_3 (0.082 g, 0.774 mmol), and phenylboronic acid (0.057 g, 0.464 mmol) 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 (CH_2Cl_2 to 5% MeOH/CH_2Cl_2) to yield compound **699**.



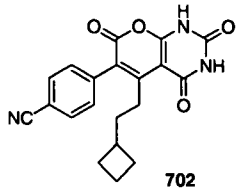
700

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



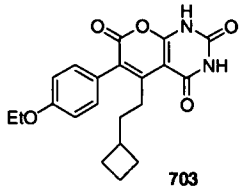
701

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



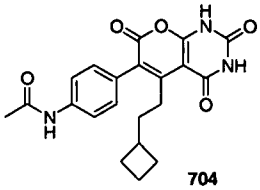
702

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



703

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



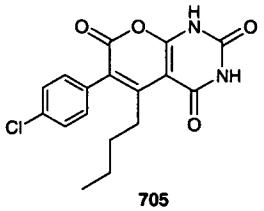
704

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



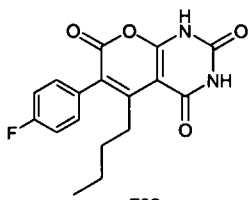
705a 705b

Compound **705b** was prepared in the same manner as in example **699b**.



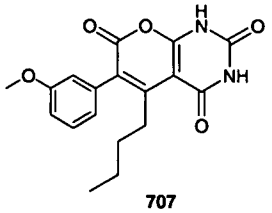
705

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



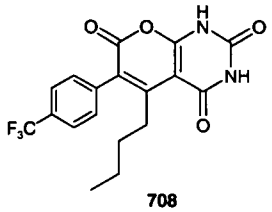
706

The compound **706** was prepared in the same manner of compound **699.**



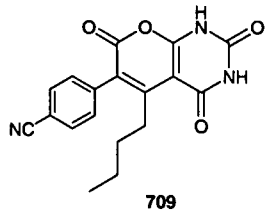
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The compound **707** was prepared in the same manner of compound **699.**



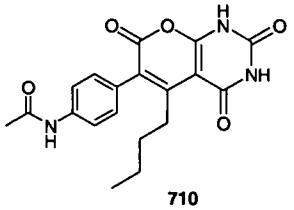
708

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



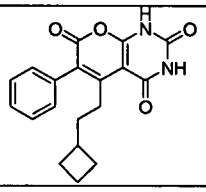
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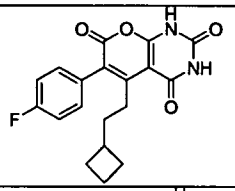
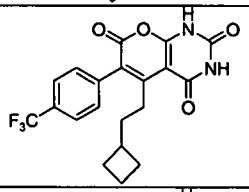
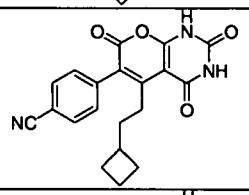
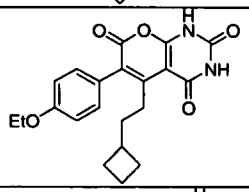
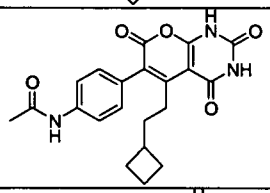
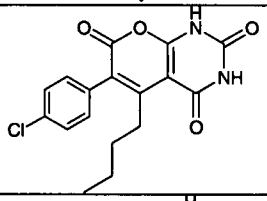
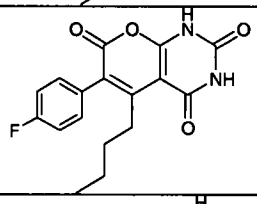
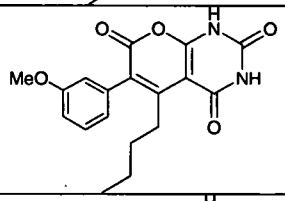
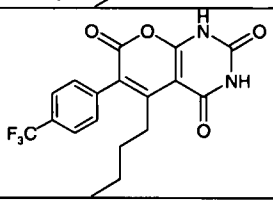
The compound **709** was prepared in the same manner of compound **699.**

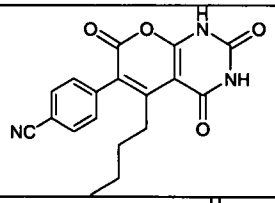
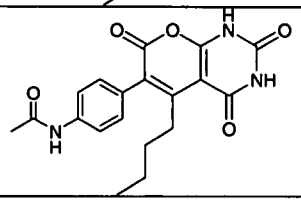


710

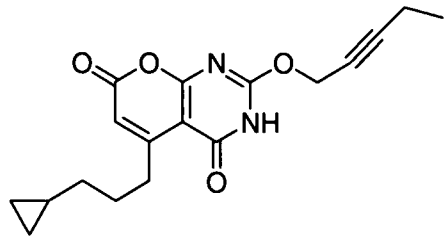
The compound **710** was prepared in the same manner of compound **699.**

Compound No.	STRUCTURE	NA EC_{50} 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

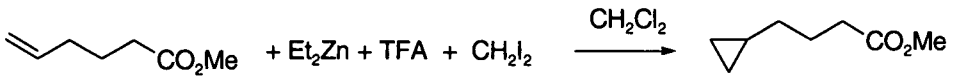
709		C	338.2
710		C	370.2

Preparative example 711



711

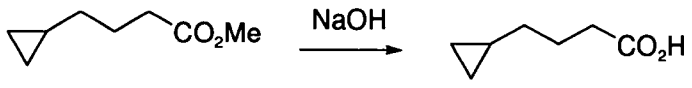
Step A:



711 A

To a solution of diethyl zinc (3.0 eq, 1.0 M in THF) in CH_2Cl_2 (0.2 M) at 0 °C, was added TFA (3.0 equiv, dropwise via an addition funnel). The resulting mixture was allowed to stir at 0 °C for 15 minutes after the addition was complete. CH_2I_2 (3.0 equiv) was then added to the reaction mixture dropwise via syringe and the resulting reaction was allowed to stir at 0 °C for 10 minutes. To the resulting reaction was added hex-5-enoic acid methyl ester (1.0 equiv) and the reaction mixture was stirred for about 15 hours, allowing the mixture to increase to room temperature. The reaction was then quenched by careful addition of aqueous 1 N HCl and the the aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic phases were washed with water, then brine, then dried over $MgSO_4$ and concentrated *in vacuo* to provide compound **711A** in quantitative yield.

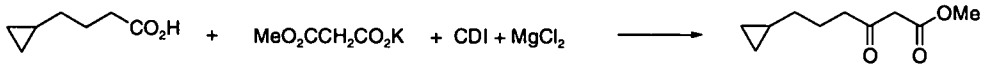
Step B:



711A **711B**

Aqueous NaOH solution (2.0 equiv, 2.0 N) was added to a solution of **711A** (1.0 equiv) in THF and MeOH (v/v = 2/1, 0.2 M) at room temperature. The mixture was allowed to stir for 4 hours and the solvent was then removed *in vacuo*. The resulting aqueous solution was extracted with ether and the resulting solution was then acidified using 5 M HCl. The aqueous layer was extracted with ether (3x) and the combined organic phases were washed with water, then brine, then dried over $MgSO_4$ and concentrated *in vacuo* to provide compound **711B** in quantitative yield.

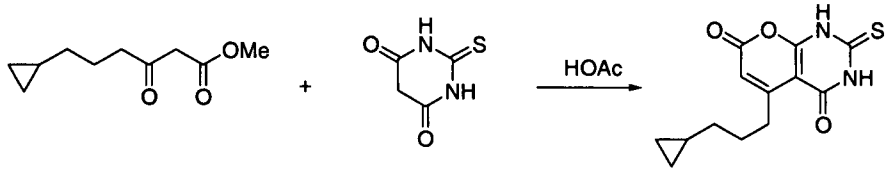
Step C:



711B **711C**

CDI (1.2 equiv) was added to a solution of **711B** in THF (0.5 M) at room temperature. The reaction mixture was allowed to stir for 1 hour, then monomethyl melonate ester potassium salt (1.5 equiv) and $MgCl_2$ (1.0 equiv) were added. The resulting reaction was allowed to stir for about 15 hours and was then quenched with aqueous HCl (1.0 N). The aqueous layer was extracted with EtOAc (3x). The combined organic phases were washed with water, then brine, then dried over $MgSO_4$ and concentrated *in vacuo* to provide compound **711C** in quantitative yield.

Step D:



711C **711D**

A mixture of 4,6-dihydroxy-2-mercapto-pyrimidine (1.0 eq) and **711C** (1.25 equiv) in HOAc (1.0 M) was heated to reflux and allowed to stir at this temperature for about 15 hours. The reaction mixture was then cooled and concentrated *in vacuo* and

the resulting residue was purified using flash column chromatography on silica gel to provide compound **711D** (37% yield).

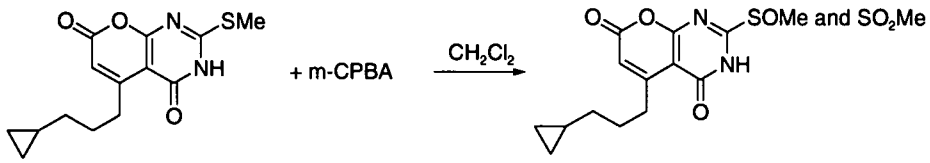
Step E:



711D **711E**

MeI (1.8 equiv) was added to a suspension of **711D** (4.0 g, 17.86 mmol) in DMF (0.3 M) at room temperature. The reaction mixture was allowed to stir at room temperature for about 15 hours, then poured into water and the resulting solution was filtered through a sintered funnel. The collected solid material was washed with water and dried under vacuum to provide compound **711E** (96% yield).

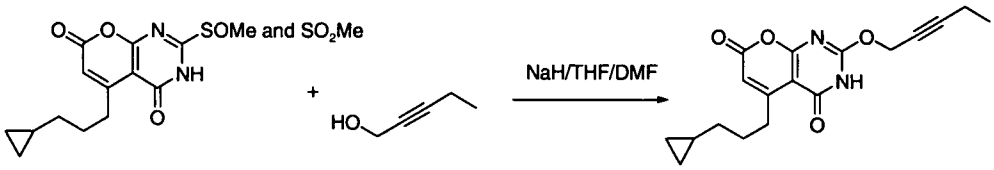
Step F:



711E **711F**

m-CPBA (2.0 equiv) was added to a suspension of **711E** (1.0 equiv) in CH_2Cl_2 (0.15 M) at room temperature. After stirring for 3 hours, the reaction was quenched with Me_2S (3.0 eq) and concentrated *in vacuo* to provide a crude product which was washed with Hexane/EtOAc (v/v = 3/1) to provide compound **711F** as a mixture of sulfone and sulfoxide (90% yield, w/w = 1/2).

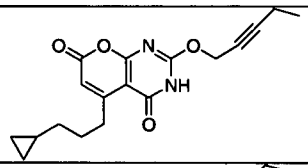
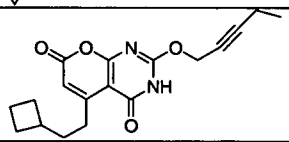
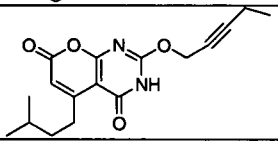
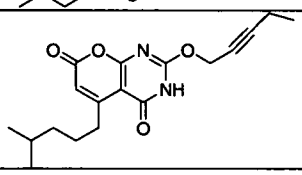
Step G:

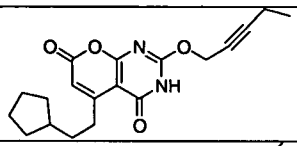
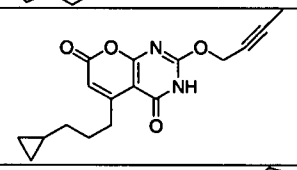
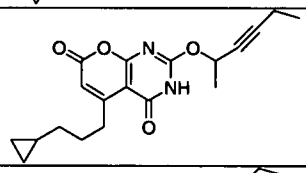
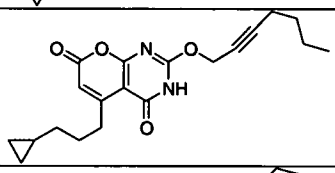
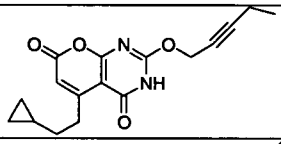
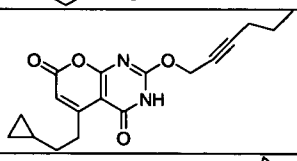
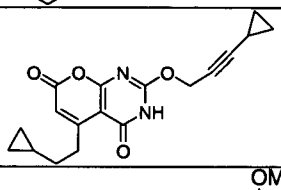
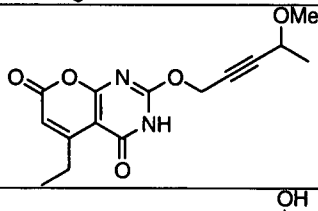
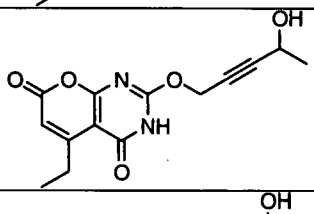
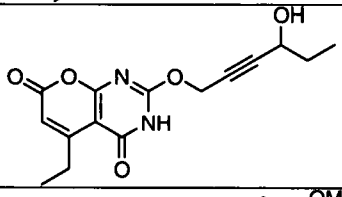
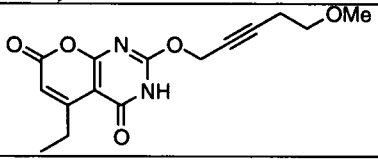


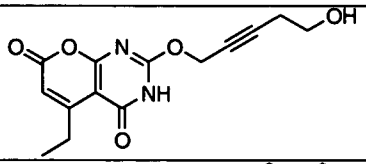
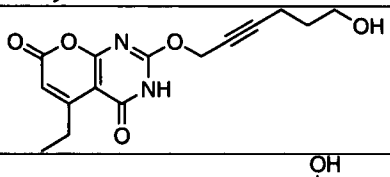
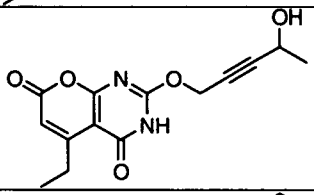
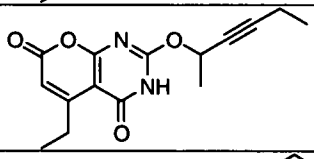
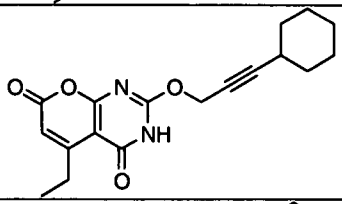
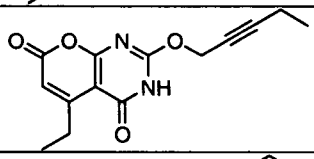
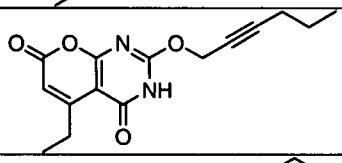
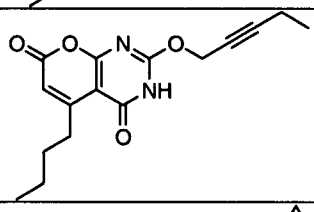
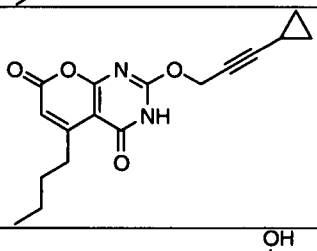
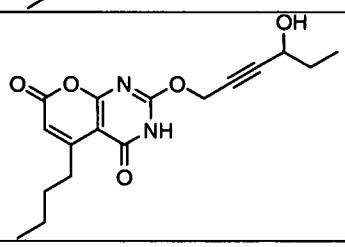
711F **711G**

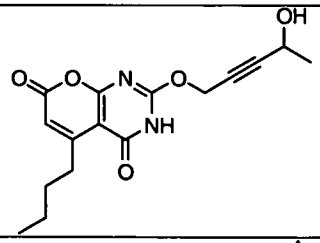
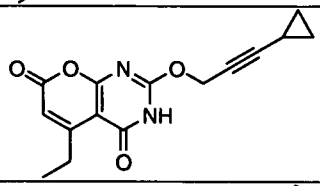
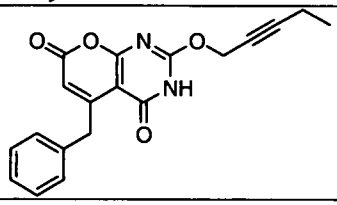
Pent-2-yne-1-ol (2.0 equiv) was added dropwise to a suspension of NaH (2.0 equiv) in THF at room temperature. The reaction mixture was stirred for 1 hour to provide a clear solution to which was then added dropwise a solution of **711F** (1.0 equiv) in DMF. The reaction mixture was stirred for about 2 hours at room temperature and was then quenched with HOAc (2.0 equiv). The resulting solution was diluted with EtOAc and washed sequentially with 0.1 M HCl, water and brine, then dried over $MgSO_4$ and concentrated *in vacuo*. The resulting residue was purified using flash column chromatography on silica gel (eluent: hexane/CH_2Cl_2/EA (v/v/v = 7/3/2)) to provide compound **711** (50% yield). Electrospray MS $[M+1]^+$ 329.2.

Using the method described above, and appropriate materials, Compounds **712-739** were prepared:

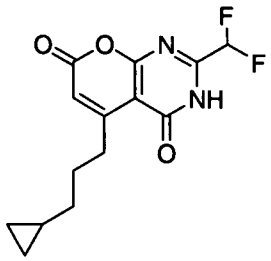
Compound No.	Structure	Electrospray LCMS $[M+1]^+$
712		329.2
713		329.2
714		317.2
715		331.2

716		343.2
717		315.2
718		343.2
719		357.2
720		315.2
721		329.2
722		327.2
723		305
724		305
725		319
726		305

727		291
728		305
729		291
730		289
731		329
732		275
733		289
734		303
735		315
736		333

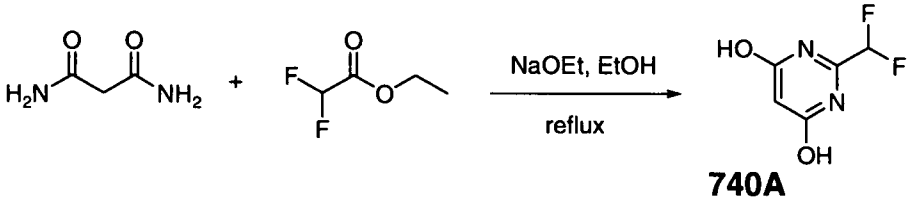
737		319
738		287
739		337.1

Preparative example 740



740

Step:1

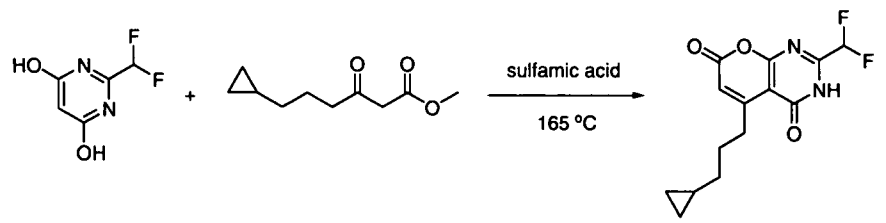


740A

A mixture of malonamide (40.00 g, 392.22 mmol) and NaOEt (21%, 292.00 ml, 784.53 mmol) in MeOH (1 L) was stirred at room temperature for 1 hour. Difluoroacetic acid ethyl ester (58.00 g, 467.74 mmol) was then added to the reaction mixture and the reaction was heated to reflux and allowed to stir at this temperature for about 15 hours. The reaction mixture was cooled to room temperature and the solid product was collected by filtration and washed sequentially with EtOH, EtOAc

and hexane, then sucked dry under vacuum to provide 45.0 g product as white powder (71% yield).

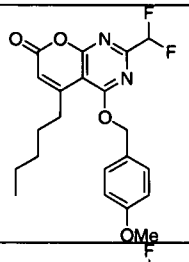
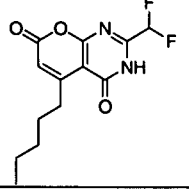
Step:2

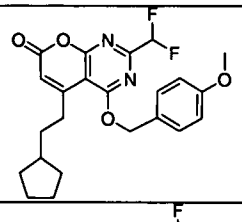
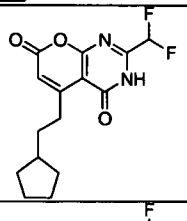
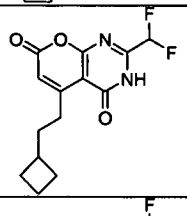
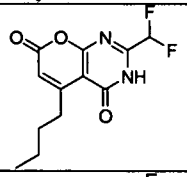
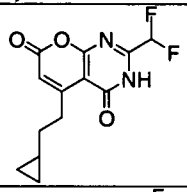
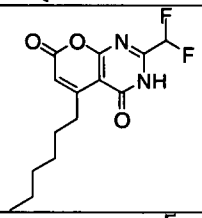
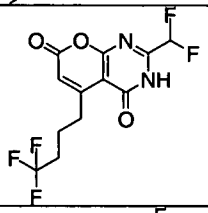
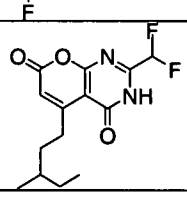


740A **740B** **740**

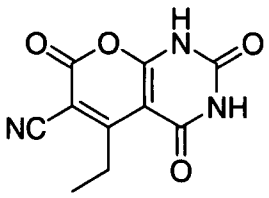
A mixture of compound **740A** (10.50g, 64.81 mmol), compound **740B** (14.90g, 80.98 mmol), and sulfamic acid (6.29g, 64.84 mmol) was heated to 165 °C and allowed to stir at this temperature for 30 minutes. The reaction mixture was then cooled to about 70 °C, then poured into into a mixture of CH_2Cl_2/MeOH (1:1, 50 mL) and the resulting solution was filtered. The solid collected by filtration was then washed repeatedly with CH_2Cl_2/MeOH (1:1) and the eluates were combined and concentrated *in vacuo* to provide compound **740** as white crystals (3.30 g, 17%).

Using the method described above, and appropriate materials, Compounds **742**, **743**, **745**, **746**, **748**, **750**, **752**, **754**, **757** and **812** were prepared:

Compound No.	Structure	Electrospray LCMS $[M+1]^+$
742		405.2
743		285.1

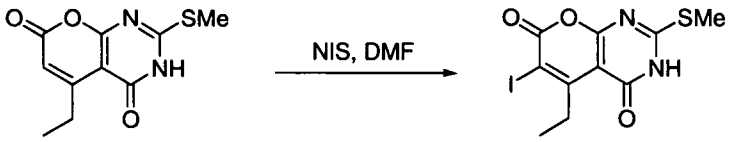
745		431.2
746		311.2
748		297.2
750		271.1
752		283.2
754		299.2
757		325.2
812		299.2

Preparative example 758



758

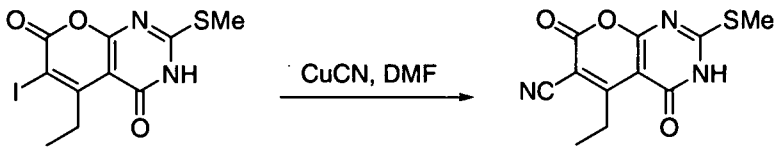
Step A:



758A **758B**

NIS (6.72 g, 29.9 mmol) was added to a solution of **758A** (5 g, 21 mmol) in DMF (70 mL). The reaction mixture was heated to 50 °C and allowed to stir at this temperature for about 15 hours. The reaction mixture was then cooled to room temperature and water (100 mL) was added. The resulting solution was filtered, and the collected solid was washed with water then ether to provide compound **758B** as a yellow powder (65% yield) which was used without further purification.

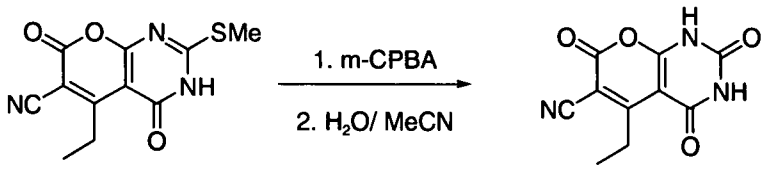
Step B:



758B **758C**

CuCN (0.246 g, 2.75 mmol) was added to a solution of **758B** (1.0 g, 2.75 mmol) in DMF (10 mL). The reaction was refluxed for 2 h, under N_2. After cooling to room temperature, H_2O (50 mL) was added. The precipitated product was filtered, washed with water then ether to afford **16** (95% yield).

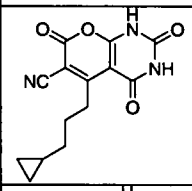
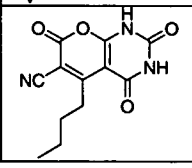
Step C:



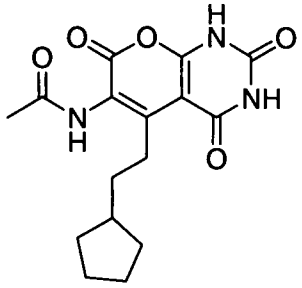
758C **758**

m-CPBA (0.936 g, 4.18 mmol) was added to a solution of **758C** (0.55 g, 2.09 mmol) in CH_2Cl_2 (15 mL). The resulting reaction was allowed to stir at room temperature for 4 hours, then Me_2S was added and the resulting solution was allowed to stir for an additional 10 minutes and concentrated *in vacuo*. The resulting residue was diluted with 10 mL CH_3CN/ H_2O (1:1) and the resulting solution was stirred at room temperature for 12 hours then concentrated *in vacuo* and purified by preparative TLC (15% MeOH/DCM) to provide compound **758**. Electrospray MS: $[MH^+]$ = 262.1

Using the method described above, and appropriate materials, compounds **759** and **760** were prepared:

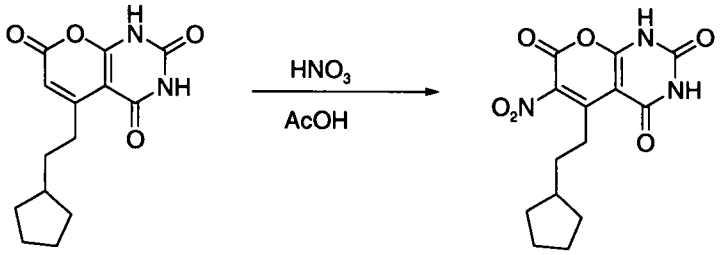
Compound No.	Structure	Electrospray LCMS $[M+1]^+$
759		288.2
760		262.1

Preparative example 761



761

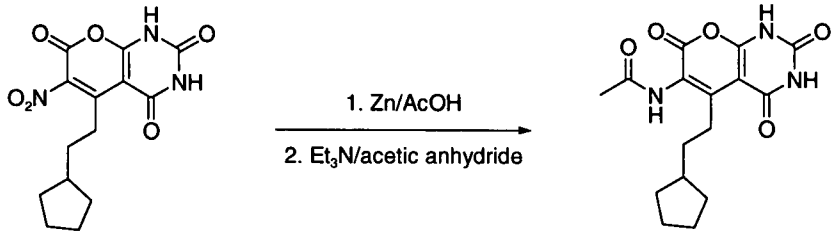
Step A:



761A **761B**

Fuming HNO_3 (0.9 mL) was added drop wise to a solution of **761A** (0.5 g, 1.81 mmol) in HOAc (1.8 mL) under N_2. The reaction was heated to 100 °C and allowed to stir at this temperature for 30 minutes, then the reaction mixture was poured into cold water (5 mL). The precipitate formed was isolated and washed with acetonitrile (1 mL) to afford compound **761B** (0.3 g, 51%). Electrospray MS: $[MH^+]$ = 322.2

Step B:

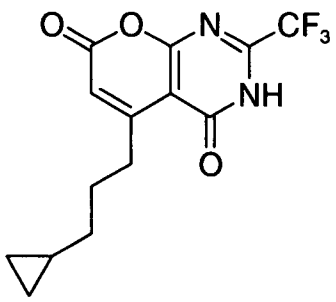


761B **761**

Zn dust (0.47 g, 7.2 mmol) was added to a solution of **761B** (0.23 g, 0.72 mmol) in HOAc (3 mL) and MeOH (2 mL), and the resulting reaction was stirred at room temperature for about 18 hours. The reaction was filtered and the filtrate was concentrated *in vacuo* to provide a residue which was dissolved in CH_2Cl_2 (2 mL). To the resulting solution was added Et_3N (2 mL) followed by acetic anhydride (2 mL). The resulting reaction was allowed to stir at room temperature for 24 hours, then was concentrated *in vacuo* and the resulting residue was purified using flash column chromatography on silica gel (eluent: $MeOH/CH_2Cl_2$ (v/v = 10/97)) to provide compound **761** (0.15 g, 62%). Electrospray MS: $[MH^+]$ = 334.2

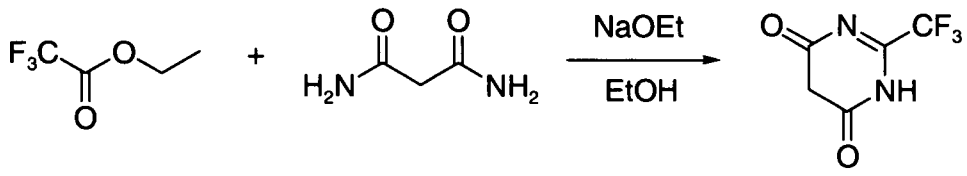
Preparative example 762

220



762

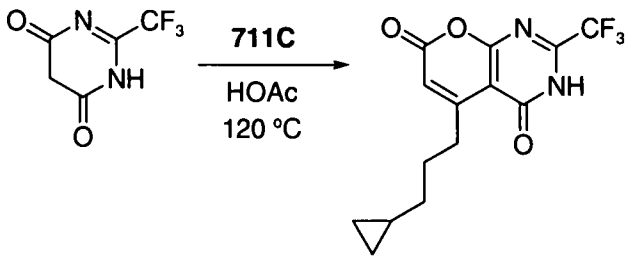
Step A:



762A

Trifluoroacetic acid ethyl ester (8.8 ml, 73.5 mmol) was slowly added to a suspension of malonamide (5 g, 49 mmol) and NaOEt (21% in EtOH, 36.5 ml, 98 mmol) in EtOH (50 mL). The resulting reaction was put under nitrogen atmosphere, heated to reflux, and allowed to stir at this temperature for about 20 hours. The reaction mixture was then filtered and the collected yellow solid was washed with EtOAc, then EtOH to provide compound **762A**.

Step B:

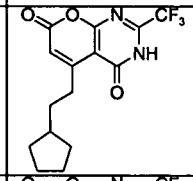
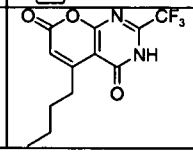


762A **762**

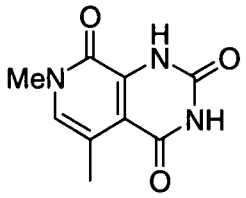
Compound **711C** (0.8g, 4.2 mmol, prepared as described above in preparative example 711, step C) was added to a solution of **762A** (0.5g, 2.8 mmol) in HOAc (1.5 mL). The resulting reaction was heated to 120 °C and allowed to stir at this temperature for 20 hours, then the reaction was cooled to room temperature and concentrated *in vacuo*. The resulting residue was purified using flash column

chromatography on silica gel (eluent: 3% MeOH/CH_2Cl_2) followed by preparative TLC (5% MeOH/CH_2Cl_2) to to provide compound **762**.

Using the method described above, and appropriate materials, compounds **763** and **764** were prepared:

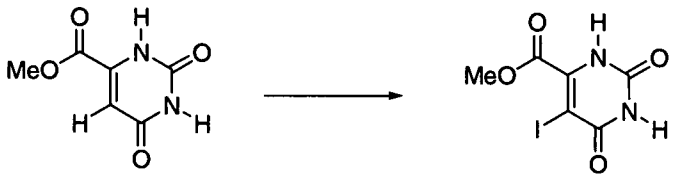
Compound No.	Structure	Electrospray LCMS $[M+1]^+$
763		329.2
764		289.2

Preparative example 765



765

Step A:

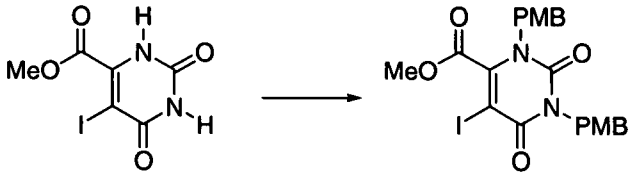


765A **765B**

N-iodosuccinimide (40 g, 177 mmol) was added to a solution of **765A** (15 g, 88 mmol) in a mixture of TFA-TFAA (300 mL, 30 mL) and the resulting reaction was heated heated to 85 °C and allowed to stir at this temperature for about 15 hours. The reaction was then cooled to room temperature and concentrated in vacuo. The resulting residue was partitioned between 200 mL of H_2O and 100 mL of EtOAc. The

precipitate was collected and washed with H_2O and EtOAc, then dried *in vacuo* to afford compound **765B** (20.2 g, 78%).

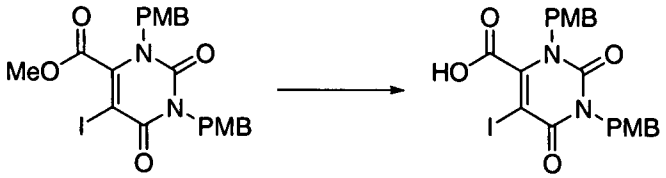
Step B:



765B **765C**

Na_2CO_3 (27g, 300 mmol) and PMBCl (34 mL, 300 mmol) were added to a solution of **765B** (20 g, 100 mmol) in DMF (300 mL). The resulting slurry was heated to 50 °C and allowed to stir at this temperature for about 15 hours. The reaction was then cooled to room temperature and partitioned between H_2O (250 mL) and EtOAc (500 mL). The organic layer was separated and washed with H_2O, then brine, then dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting residue was filtered through a pad of silica gel, eluted with EtOAc-heaxanes (1:10) followed by EtOAc-hexanes (1:1). The filtrate was concentrated *in vacuo* and the residue was recrystalized from DCM and hexanes to afford **765C** (16.6 g, 31%).

Step C:

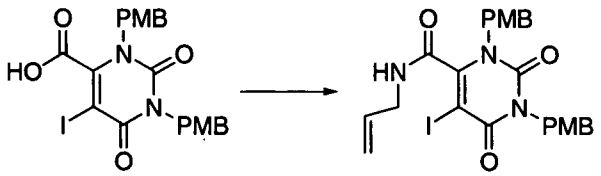


765C **765D**

Lithium iodide (15.3 g, 114 mmol) was added to a solution of **765C** (15.3 g, 28.5 mmol) in EtOAc (300 mL). The resulting slurry was stirred heated to 85 °C and allowed to stir at this temperature for about 15 hours. The reaction mixture was cooled to room temperature; then water (100 mL) was added and the resulting solution was transferred to a separatory funnel. The aqueous layer was separated and brought to a basic pH by the addition of 1 N NaOH, then the basified solution was washed with ether. The aqueous layer was then adjusted to pH = 1 by addition of 1 N HCl and the resulting acidic solution was extracted with EtOAc. The combined

organic extracts were washed with 1 N sodium thiosulfate solution, dried over $MgSO_4$, then filtered and concentrated *in vacuo* to provide compound **765D** (13.5 g, 90%).

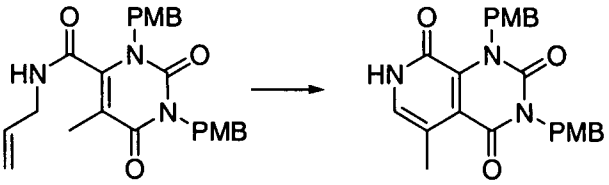
Step D:



765D **765E**

Oxalyl chloride (0.2 mL, 2.32 mmol) was added to a solution of **765D** (1.0 g, 1.91 mmol) in CH_2Cl_2 (10 mL), followed by addition of a drop of DMF. The resulting mixture was allowed to stir at room temperature for 30 minutes, then concentrated *in vacuo*. The resulting residue was dissolved in CH_2Cl_2 (10 mL), and to the resulting solution was added allylamine (0.2 mL, 19.8 mmol) . The resulting reaction was allowed to stir at room temperature for about 15 hours, then the reaction mixture was diluted with CH_2Cl_2 (10 mL) and washed with 1 N HCl. The organic layer was separated, washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The resulting residue was purified using flash column chromatography on silica gel (eluent: EtOAc-hexanes, 1:1), to provide compound **765E** (0.61 g, 60%).

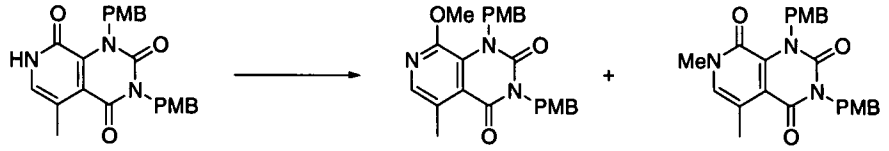
Step E:



765E **765F**

In a sealed tube, Et_3N (0.42 ml, 2.99 mmol) and $Pd(OAc)_2$ (38 mg, 0.17 mmol) were added to a solution of **765E** (1.0 g, 1.91 mmol) in DMF (6 mL). The resulting reaction was heated at 85 °C and allowed to stir at this temperature for about 15 hours, then cooled to room temperature and filtered through Celite. The filtrate was concentrated *in vacuo* and the resulting residue was purified using flash column chromatography on silica gel (eluent: EtOAc-hexanes, 1:1) to provide compound **765F** (0.27 g, 36%).

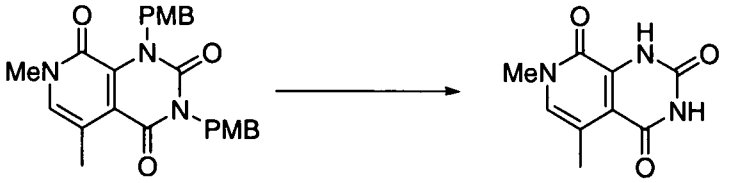
Step F:



765F 765G 765H

A solution of **765F** (262 mg, 0.60 mmol) in DMF/THF (1:1, 12 mL) was cooled to 0 °C and NaH (30 mg, 1.18 mmol, 95% oil dispersion) was added. The resulting reaction was allowed to stir at 0 °C was stirred for about 30 minutes, then iodomethane (0.1 mL, 1.60 mmol) was added and the reaction was allowed to stir at room temperature for about 15 hours. The reaction was quenched with water, and the aqueous layer was separated and extracted with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The resulting residue was purified using flash column chromatography on silica gel (eluent: EtOAc-hexanes, 1:1) to provide compounds **765G** (5 mg, 4% yield) and **765H** (121 mg, 90%).

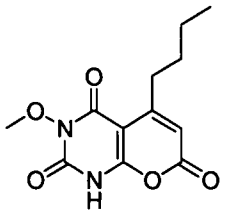
Step G:



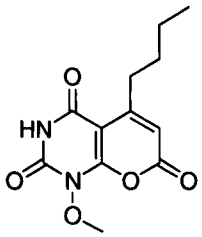
765H 765

TFA (0.5 mL) and TfOH (0.1 mL) were added to a solution of **765H** (100 mg, 0.22 mmol) in CH_2Cl_2 (6 mL). The resulting reaction was allowed to stir at room temperature for about 15 hours, then concentrated in vacuo to provide a crude residue which was purified using preparatory TLC (eluent: acetic acid/CH_2Cl_2/EtOAc, 1:10:10) to provide compound **765** (12 mg, 26%). Electrospray MS $[M+1]^+$ 208.1

Preparative examples 766 and 767

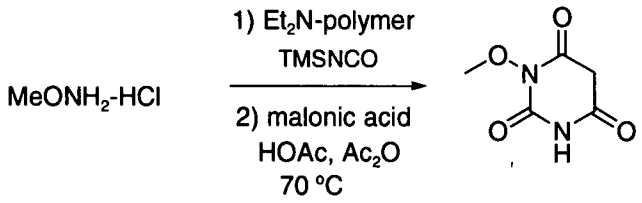


766



767

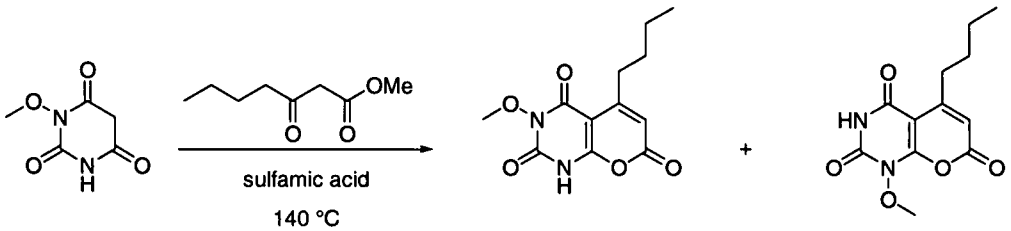
Step A:



766A

Diethylaminomethyl-polystyrene (40 g, 3.2 mmol/g,128 mmol) was added to a solution of methoxylamine hydrochloride (5.0 g, 60 mmol) in MeOH (300 mL). The reaction mixture was stirred for 1 h. Then, TMSNCO (8.1 mL, 60 mmol) was added and the solution was stirred for 4 h. The polymer was filtered and washed twice with MeOH (50 mL, each). The volatiles were removed and the residue was dissolved in acetic acid (40 mL) then malonic acid (5.1 g, 60 mmol) and Ac_2O (40 mL) were added. The mixture was heated at 70 °C for 10h. The reaction was concentrated in vacuo and the residue was dissolved in MeOH (100 mL), stirred for 10 min. and concentrated. The resulting residue was triturated in 1:1 EtOAc/Et2O and filtered to obtain **34** (4.2 g).

Step B:

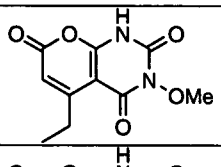
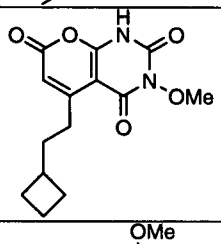
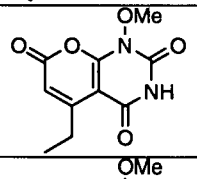
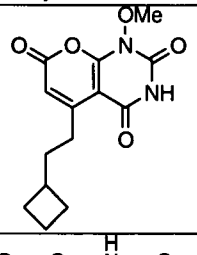
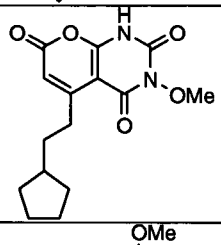
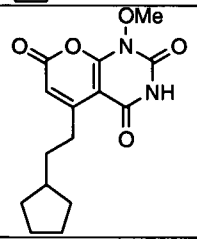


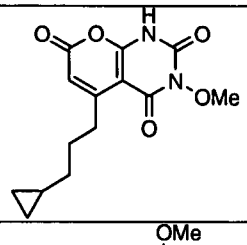
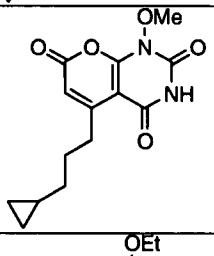
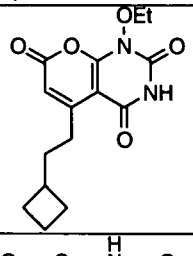
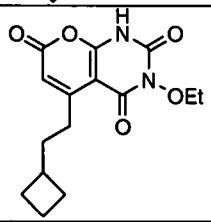
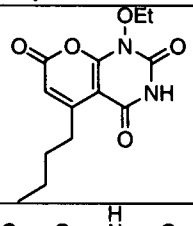
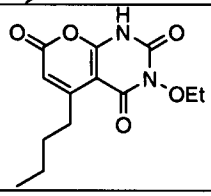
766A **766** **767**

Sulfamic acid (613 mg, 6.32 mmol) was added to a mixture of 3-oxo-heptanoic acid methyl ester (2.0 g, 12.6 mmol) and **766A** (1.0 g, 6.32 mmol). The mixture was

heated at 140 °C for 4 hours. The resulting residue was dissolved in 10 mL of MeOH, filtered and separated using a Gilson HPLC to obtain pure **766** and **767**. Electrospray MS $[M+1]^+$ 267.1

Using the method described above, and appropriate materials, compounds **768-779** were prepared:

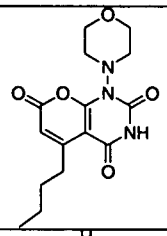
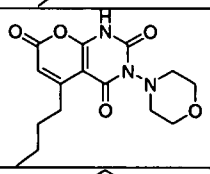
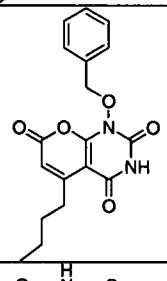
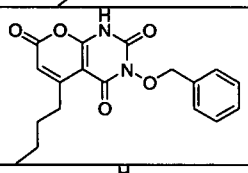
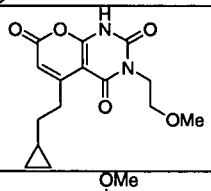
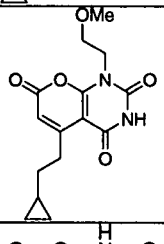
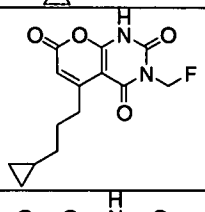
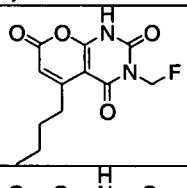
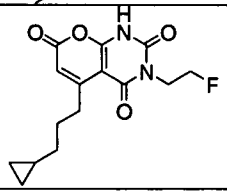
Compound No.	Structure	Electrospray LCMS $[M+1]^+$
768		239.1
769		293.1
770		293.1
771		292.2
772		306.3
773		306.31

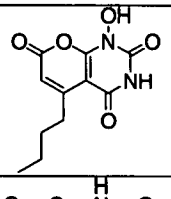
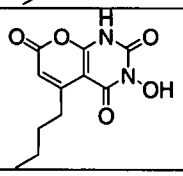
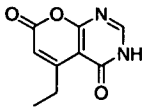
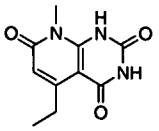
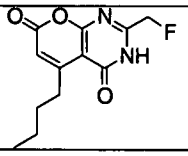
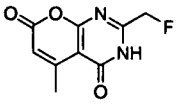
774		NA
775		NA
776		307.1
777		307.1
778		281.1
779		281.1

NA = not available

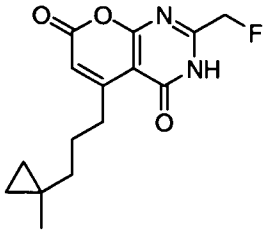
Other illustrative compounds of formula (I), include but are not limted to compounds **796-810**, which are depicted below:

Compound No.	**Structure**	**Electrospray LCMS $[M+1]^+$**

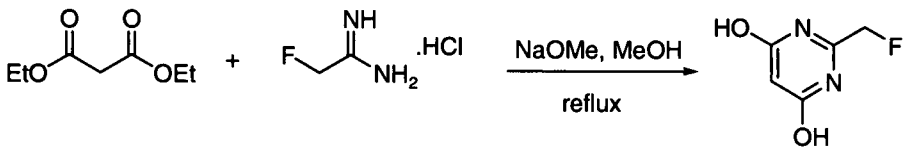
796		322.2
797		322.2
798		343.2
799		343.2
800		307.2
801		307.2
802		295.2
803		269.1
804		309.2

805		253.1
806		253.1
807		193.1
808		222.2
809		253.1
810		211.1

Preparative example 811



811



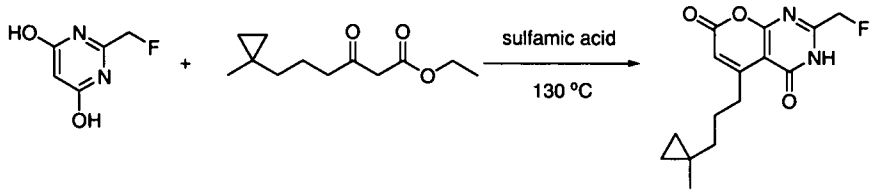
811A

Step A:

A solution of diethylmalonate (2.96 g, 18.48 mmol) and NaOMe (25 wt % in MeOH, 10.75 g, 49.76 mmol) was added to a solution of 2-fluoroacetamidine hydrochloride (2.0 g, 17.77 mmol) in MeOH (20 mL). The resulting reacton was heated to reflux and allowed to stir at this temperature for about 15 hours. The

reaction mixture was cooled to room temperature, concentrated in *vacuo*, and the resulting residue was diluted with water (20 mL). The resulting solution was neutralized using concentrated HCl and the solid formed was collected by filtration, washed sequentially with H_2O and Et_2O, then sucked dry to provide compound **811A** as a pale brown powder (1.8 g, 69%).

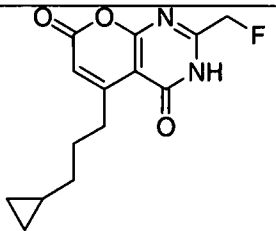
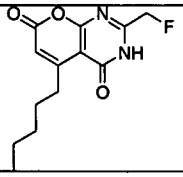
Step B

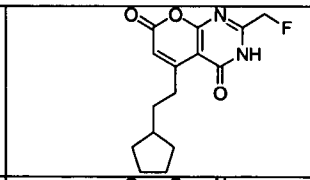
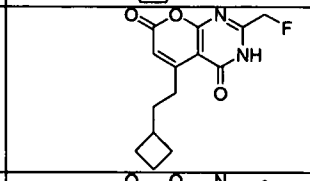
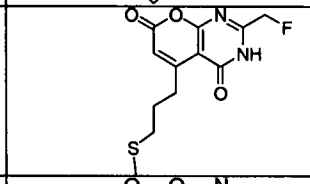
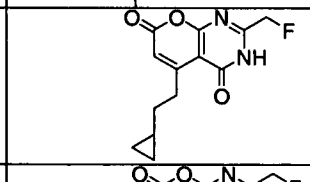
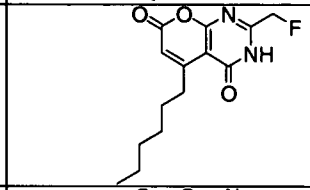
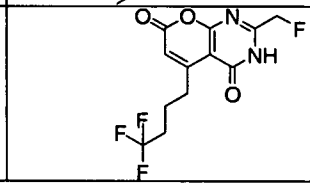


811A **811B** **811**

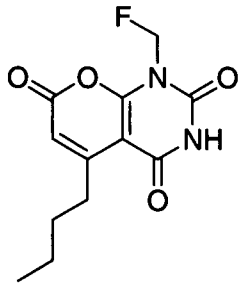
A mixture of compound **811A** (0.1 g, 0.694 mmol), compound **811B** (0.295 g, 1.39 mmol) and sulfamic acid (0.034 g, 0.347 mmol) was heated to 130 °C and allowed to stir at this temperature for about 2 hours. The reaction mixtures was then cooled to room temperature and poured into into a mixture of CH_2Cl_2/MeOH (1:1, 1 mL). The resulting solution was purified using flash column chromatography (eluent: gradient of from 20% to 50% EtOAc/hexanes) to provide compound **811** product as a white solid.

Using the method described above, and appropriate materials, Compounds **741**, **744**, **747**, **749**, **751**, **753**, **755** and **756** were prepared:

Compound No.	Structure	Electrospray LCMS $[M+1]^+$
741		279
744		267.1

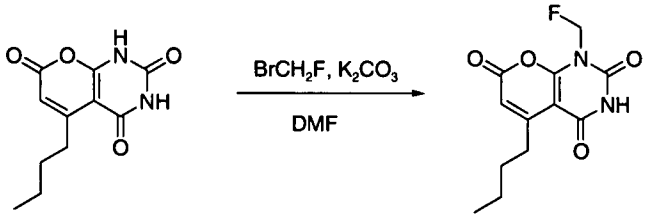
747		293.2
749		279.2
751		285.2
753		265.1
755		281.2
756		307.2

Preparative example 813



813

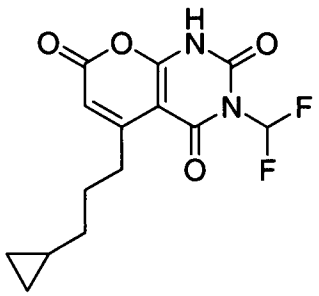
Step A:



102 **813**

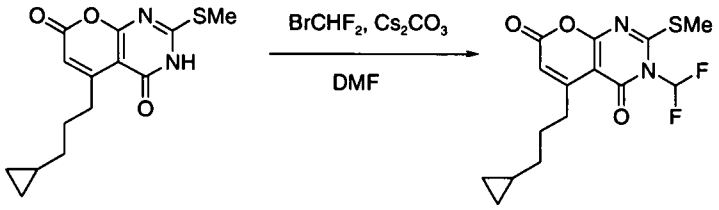
K_2CO_3 (0.35 g, 2.54 mmol) was added to a solution of compound **102** (0.4 g, 1.69 mmol) and $BrCH_2F$ (0.21 g, 1.86 mmol) in DMF (5.0 mL) at room temperature. The resulting mixture was stirred overnight. The reaction mixture was diluted with ethyl acetate and neutralized with aqueous HCl solution (0.5 N). The organic phase was washed with water (3x), dried (Mg_2SO_4), and concentrated *under vacuo* to provide crude product which was purified with PTLC (CH2Cl2/MeOH = 20/1) to give product **813** (5 mg), Electrospray MS $[M+1]^+$ 269.1.

Preparative example 814



814

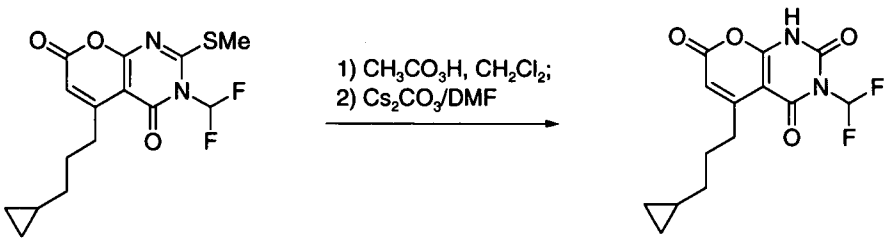
Step A:



711E **814A**

Cs_2CO_3 (1.30 g, 3.99 mmol) was added to a solution of compound **711E** (0.39 g, 1.33 mmol) and $BrCHF_2$ (0.79 g, 6.05 mmol) in DMF (5.0 mL) at room temperature. The resulting mixture was stirred overnight. The reaction mixture was diluted with ethyl acetate and neutralized with aqueous HCl solution (0.5 N). The organic phase was washed with water (3x), dried (Mg_2SO_4), and concentrated *under vacuo* to provide crude product which was purified with silica gel column chromatography (EtOAc/hexane gradient) to provide compound **814A** (0.15 g).

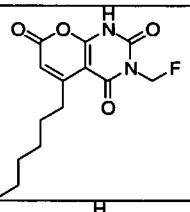
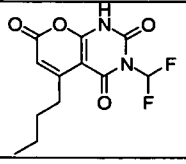
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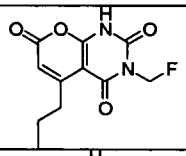
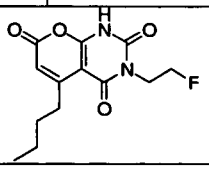
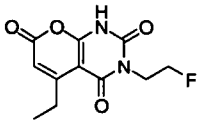
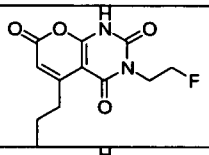
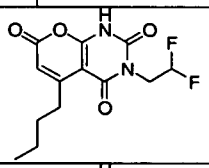
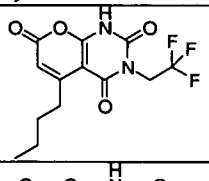
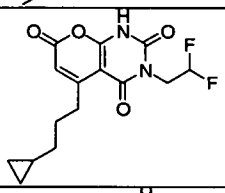
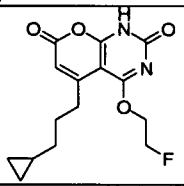
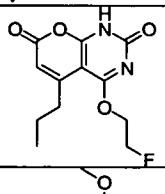
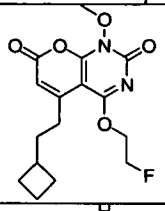
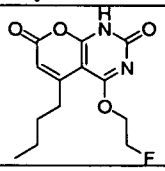


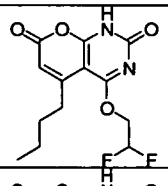
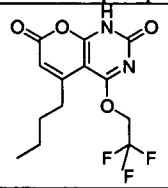
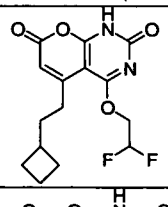
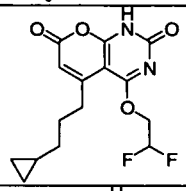
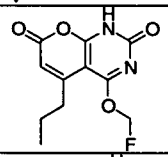
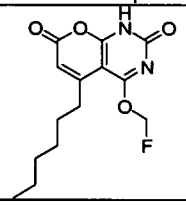
814A **814**

CH_3CO_3H (0.30 mL, 1.4 mmol) was added at room temperature to a solution of **814A** (80 mg, 0.234 mmol) in CH_2Cl_2 (2.0 mL). The mixture was stirred for 3 hours before it was quenched with Me_2S (10.0 eq.). The reaction mixture was diluted with ethyl acetate and washed with water (3x). The organic phase was washed with brine, dried (Mg_2SO_4), and concentrated *under vacuo* to provide crude product which was taken up in DMF (2.0 mL) and treated with Cs_2CO_3 (91.6 mg, 0.281 mmol). The mixture was stirred for 1 hour before it was diluted with ethyl acetate and neutralized with aqueous HCl solution (0.5 N). The organic phase was washed with water (3x), dried (Mg_2SO_4), and concentrated *under vacuo* to provide crude product which was purified with reverse phase Gilson separation to provide compound **814** (60 mg), Electrospray MS $[M+1]^+$ 313.2.

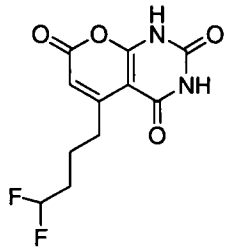
Using the method described above in Preparative Examples 813 and 814, and substituting the appropriate bromo compound in Step A, Compounds **815-833** were prepared:

Compound No.	Structure	Electrospray LCMS $[M+1]^+$
815		297.2
816		287.2

817		255.1
818		283.2
819		255.1
820		269.1
821		301.2
822		319.2
823		327.2
824		309.2
825		269.1
826		339.2
827		283.2

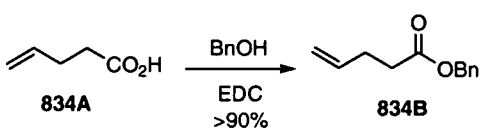
828		301.2
829		319.2
830		327.2
831		327.2
832		255.1
833		297.2

Preparative Example 834



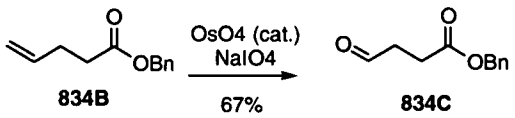
834

Step1:



To a solution of 4-pentenoic acid (**834A**, 60 g, 0.594 mol) and benzyl alcohol (56 mL, 0.54 mol) in dichloromethane (1 L) was added EDC (207 g, 1.08 mol) at 0°C and the reaction was stirred until homogeneous (~5 min). DMAP (6.7 g, 0.054 mol) was then added and reaction mixture was allowed to warm to room temperature, then stirred under nitrogen for an additional 2 hours. The reaction mixture was washed with 1N HCl (aq.), then saturated $NaHCO_3$ (aq.), then dried over sodium sulfate and concentrated *in vacuo* to provide compound **834B** in nearly quantitative yield (>95%).

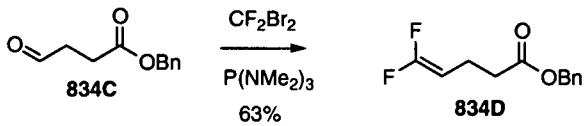
Step2:



834B **834C**

To a solution of compound **834B** (2.3 g, 0.012 mol) and 4% osmium tetraoxide in water (3 mL, 0.04 eq) in 3:1 (v/v) THF/H_2O (45 mL:15 mL) was added sodium periodate (7.7 g, 0.036 mol) and the resulting reaction was stirred under nitrogen at room temperature overnight. Sodium periodate was then added and a precipiate formed from the resulting exotherm. The reaction mixture was filtered, dried over sodium sulfate and concentrated *in vacuo*. The resulting residue was purified using flash column chromatograpy on silica gel (0-20% EtOAc/Hexane) to provide compound **834C** (1.6 g, 0.083 mol, 67%).

Step 3:

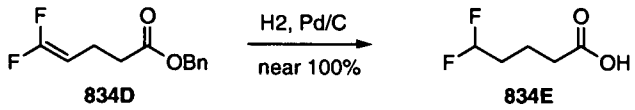


834C **834D**

To a solution of hexamethyl phosphorous triamide (25.4 g, 0.156 mol) in THF (300 mL) at -78°C was added dibromodifluoromethane (16.4 g, 0.078 mol) and the resulting suspension was allowed to warm to room temperature. Compound **834C** (7.5 g, 0.039 mol) was added and RM refluxed at 66°C under nitrogen overnight. The

reaction mixture was filtered, dried over sodium sulfate and concentrated *in vacuo*. The resulting residue was purified using flash column chromatograpy on silica gel (0-10% EtOAc/Hexane) to provide compound **834D** (5.5 g, 0.024 mol, 62 %).

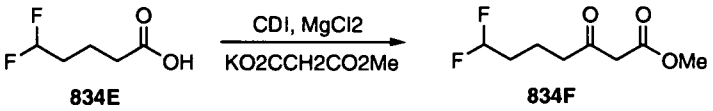
Step 4:



834D 834E

To a solution of compound **834D** (5.5 g, 0.024 mol) in EtOAc (120 mL) was added 10% Pd/C (1.3 g, 0.05 eq) and the resulting solution was placed on Parr shaker under 50 psi hydrogen gas overnight. The reaction mixture was then filtered and the filtrate was concentrated *in vacuo* to provide compound **834E** (3.3 g, 0.024 mol, >99%).

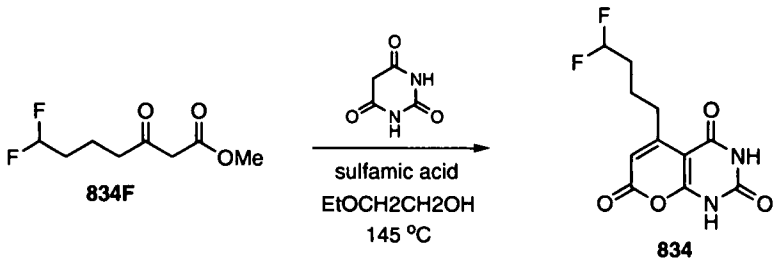
Step 5



834E 834F

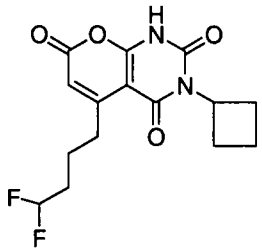
To solution of compound **834E** (6 g, 0.0434 mol) in THF (150 mL) was added CDI (8.5 g, 1.2 eq) and the resulting reaction was stirred at room temperature under nitrogen for 1 hour. MgCl2 (4.1 g, 1 eq) and monomethyl malonate potassium salt (10.2 g, 1.5 eq) were than added and the resulting reaction was stirred at room temperature under nitrogen overnight. The reaction mixture was then partitioned between 1N HCl (aq.) (200 mL) and EtOAc (200 mL). The aqueous layer was collected and extracted with EtOAc (3 x 100 mL) and the combined organic layers were washed with brine (50 mL), dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude residue obtained was purified using flash chromatography on silica gel (0-20% EtOAc/Hexane) to provide compound **834F** (6.7 g, 0.0347, 80%)

Step 6:

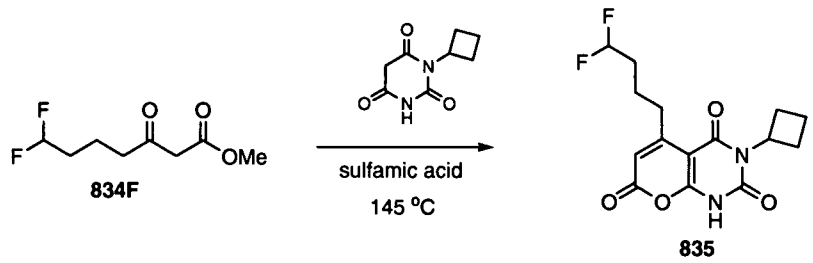


To a solution of barbituric acid (7 g, 1.1 eq) and compound **834F** (9.7 g, 0.05 mol) in EtOEtOH (15 mL) was added sulfamic acid (2.4 g, 0.5 eq) and the resulting reaction was stirred at 147°C for 4 hours. The reaction mixture was concentrated *in vacuo* and the resulting residue triturated with hot water three times to provide compound **834** (2 g, 0.007 mol, 15 %).

Preparative Example 835

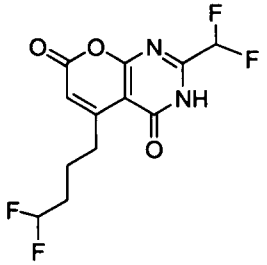


835

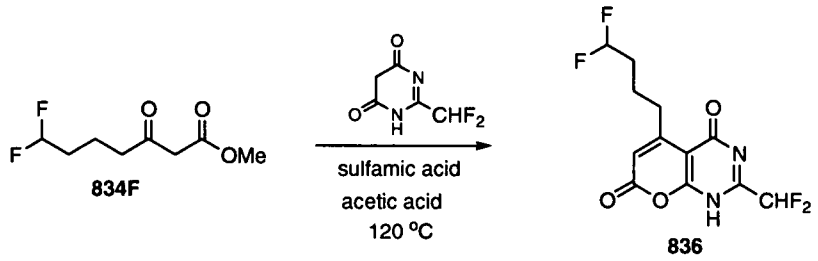


N-cyclobutyl barbituric acid (782, 4.3 mmol) and compound **834F** (1 g, 1.2 eq) were heated at 140°C for 2 hours in the presence of sulfamic acid (417 mg, 1 eq). The mixture was suspended in 10 mL DMF and the suspension was then filtered. The filtrate was injected into a Gilson HPLC in twenty injections and purified on a C18 column eluted with 0.1% TFA in water/acetonitrile (gradient 10-100% water/acetonitrile at a flow rate of 25 mL/min) to provide compound **835** (retention time: 10.1 min; 120 mg, 0.037 mmol, 9%).

Preparative Example 836

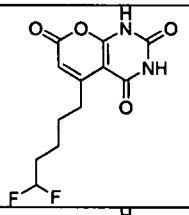
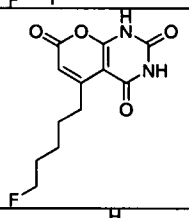
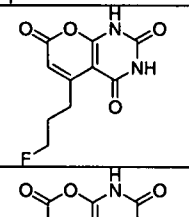
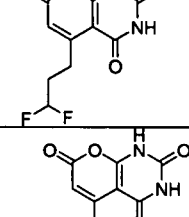
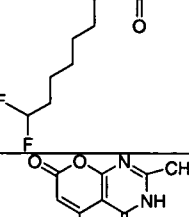
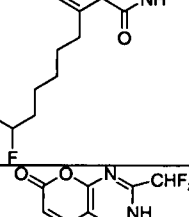
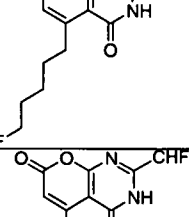
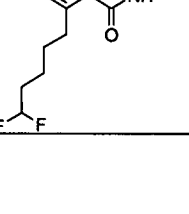


836



To a mixture of difluorobarbituric acid (1 g) and compound **834F** (1 g) in a 15 mL microwave vial was added acetic acid (3 mL). The vial was sealed and the resuting solution was microwaved at 180 °C for 20 minutes. The reaction mixture was then concentrated *in vacuo* and purified using flash chromatography on silica gel (gradient elution of 0-80% EtOAC/Hexane). The blue UV band that eluted off the column was collected and concentrated in vacuo and the resulting residue was purified using preparative TLC (2:1 EtOAc/Hexane) to provide compound **836** (40 mg, 3%).

Using the methods described above in Preparative Examples **834-836** with the approrpriate difluoro β-keto ester and barbituric acid or barbituric acid derivative, Compounds **837-844** were prepared:

Compound No.	Structure
837	
838	
839	
840	
841	
842	
843	
844	

Nicotinic Acid Receptor Assay

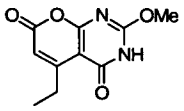
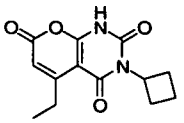
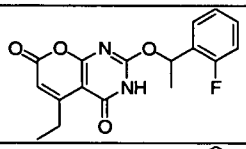
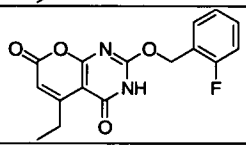
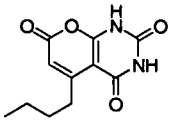
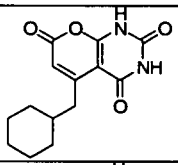
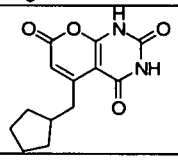
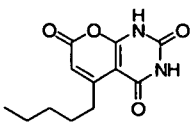
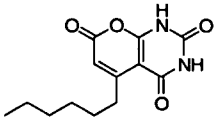
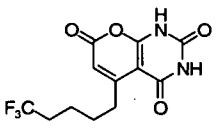
The nicotinic acid receptor agonist activity of the inventive compounds was determined by following the inhibition of forskolin-stimulated cAMP accumulation in cells using the MesoScale Discovery cAMP detection kit following the manufacturer's protocol. Briefly, Chinese Hamster Ovary (CHO) cells expressing 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 $3x10^6$ 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.

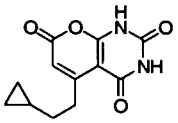
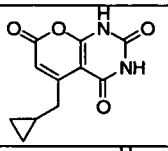
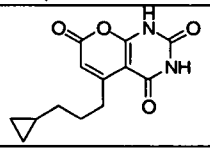
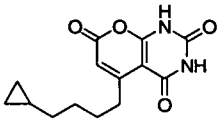
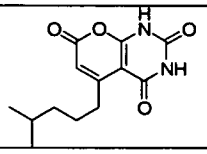
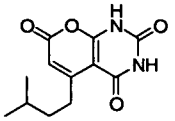
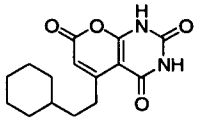
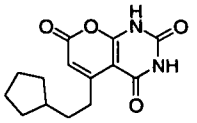
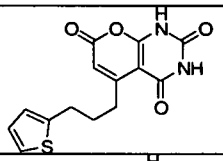
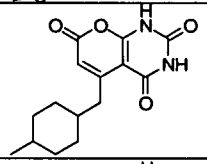
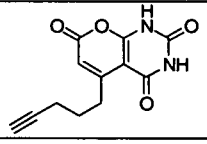
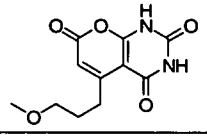
Compounds of Formula (I) of the present invention, and salts, solvates, or esters thereof, have cAMP EC_{50} values of less than about 10,000 nM, preferably about 1000 nM or less, more preferably about 500 nM or less, even more preferably about 100 nM or less.

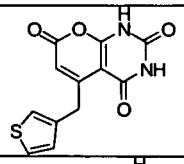
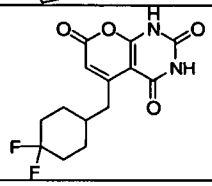
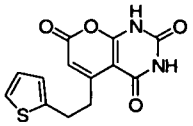
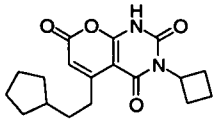
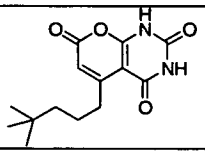
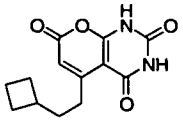
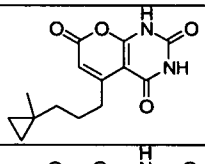
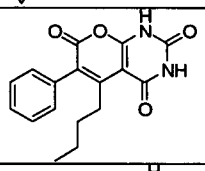
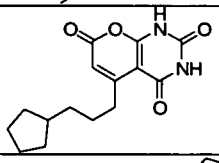
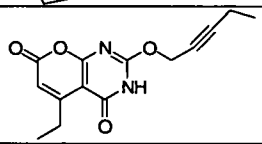
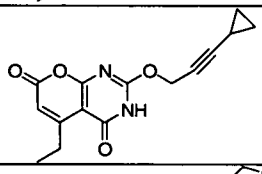
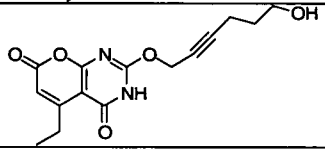
Examples 1, 5, 10, 29, 39, 71, 101-116, and 118-135 have cAMP EC_{50} values of 100 nM or less.

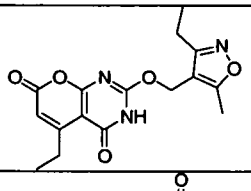
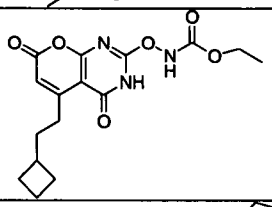
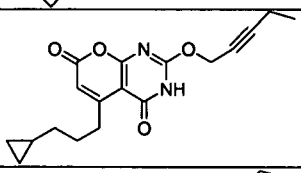
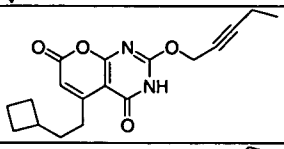
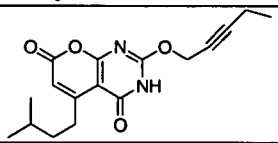
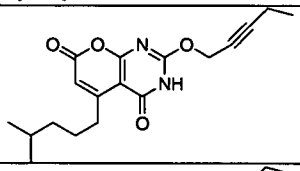
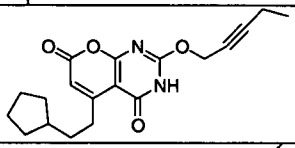
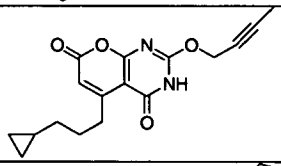
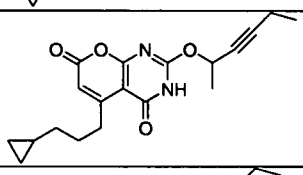
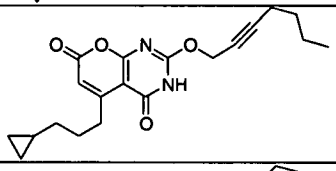
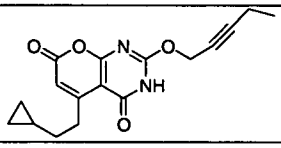
The activity of selected illustrative compounds of the invention as determined using the above-described assay is presented in the following Table:

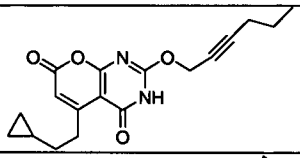
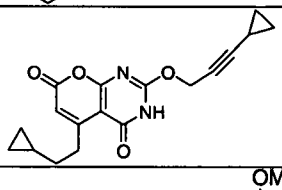
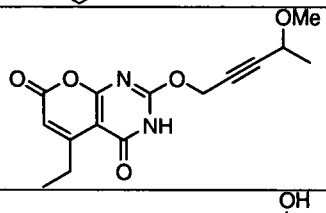
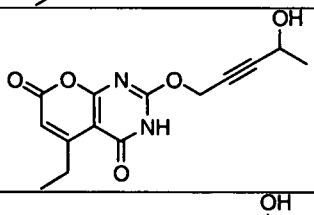
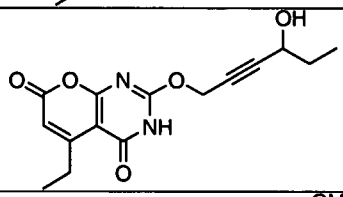
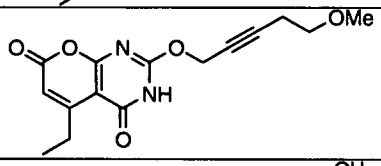
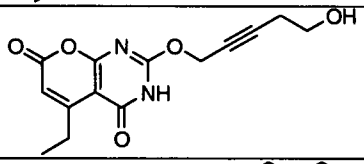
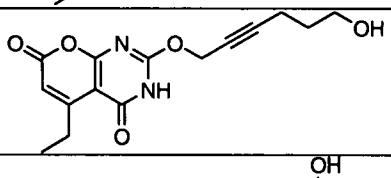
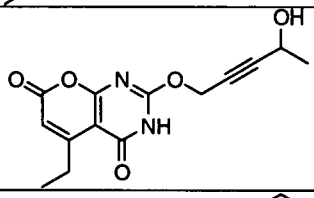
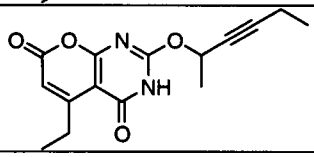
Nicotinic Recepor Agonist Activity of Selected Illustrative Compounds of the Invention

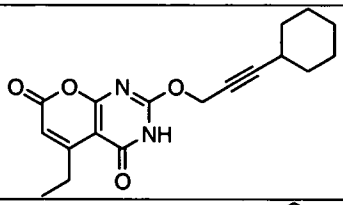
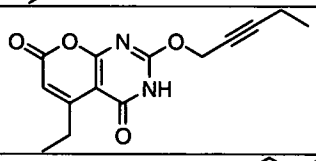
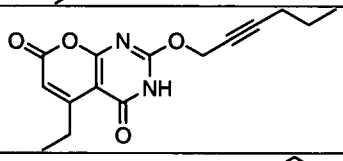
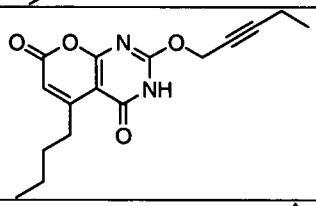
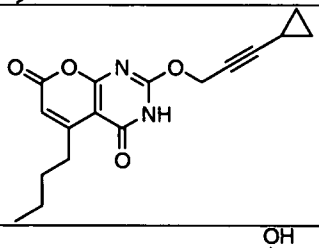
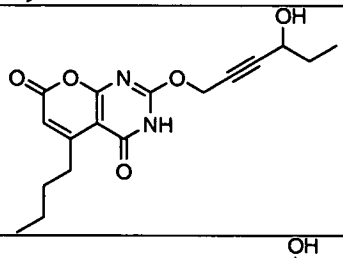
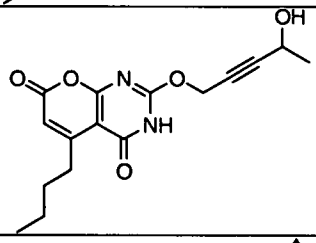
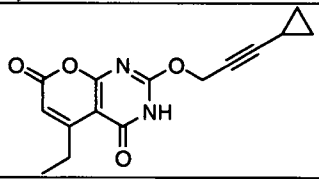
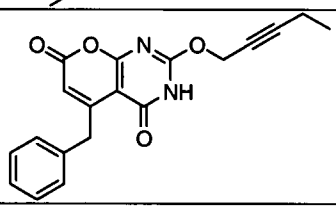
Compound No.	Structure	NA EC_{50} camp (nM)
11		125.0
35		9.0
90		475.3
74		183.0
102		31.0
103		74.3
104		47.0
107		18.7
108		28.0
112		14.4

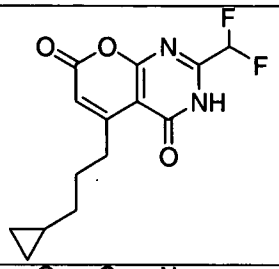
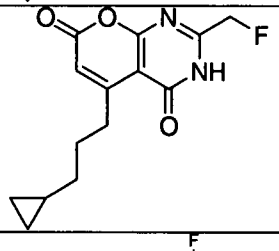
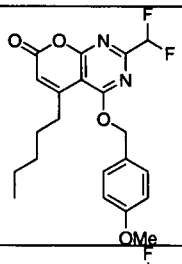
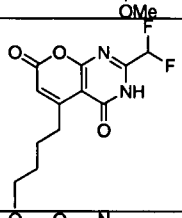
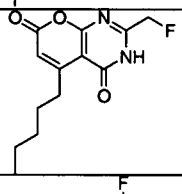
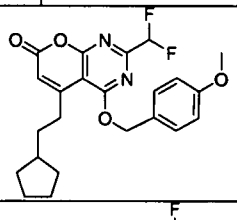
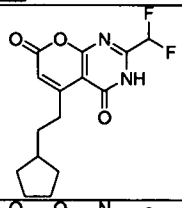
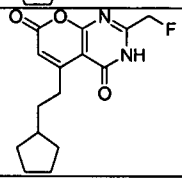
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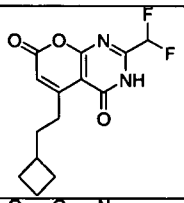
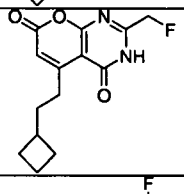
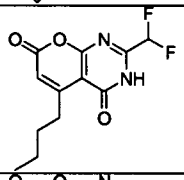
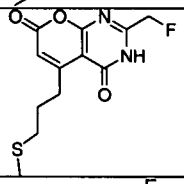
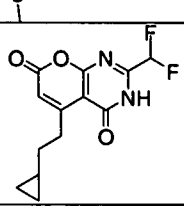
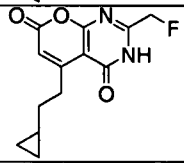
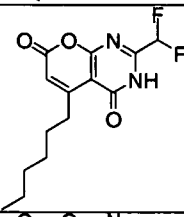
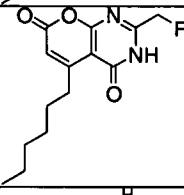
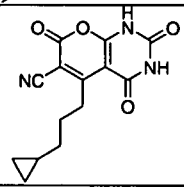
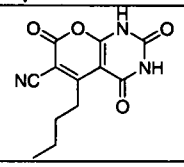
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229		47.4
241		12.95
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268		2.1
292		300
297		56.75
512		95.5
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645		26.2

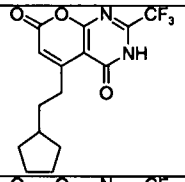
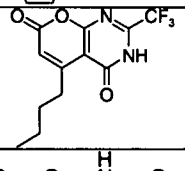
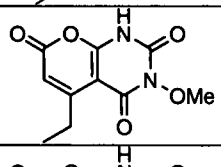
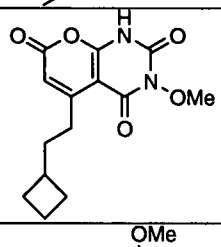
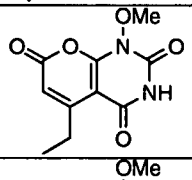
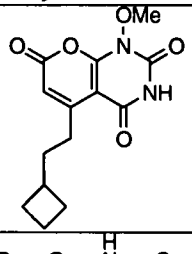
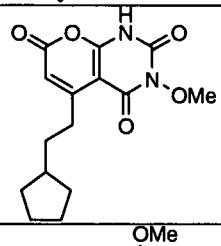
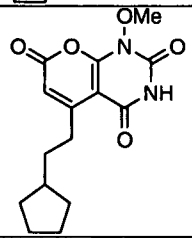
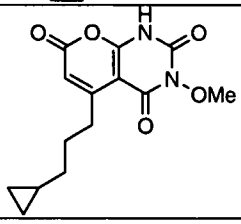
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713		22.0
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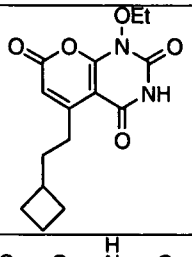
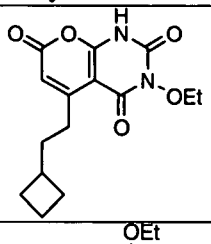
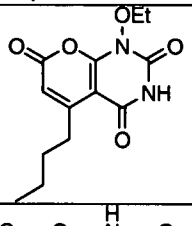
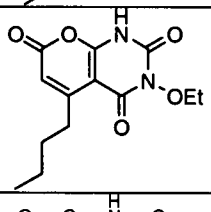
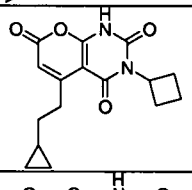
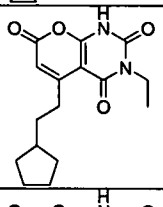
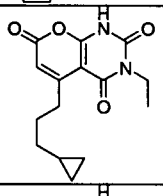
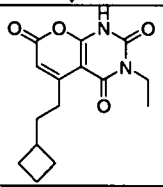
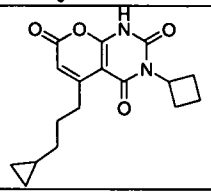
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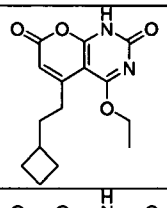
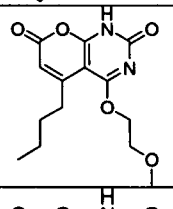
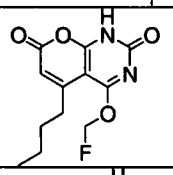
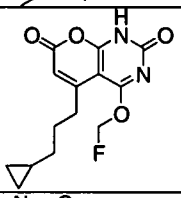
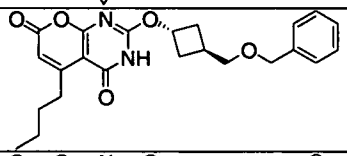
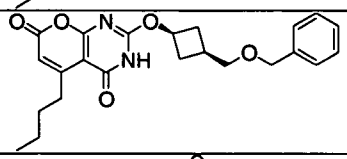
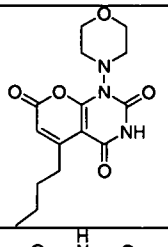
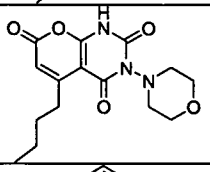
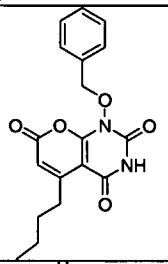
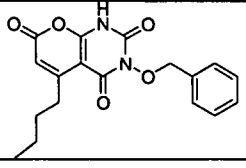
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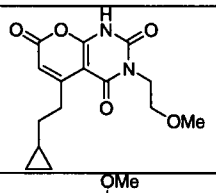
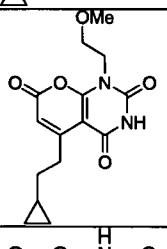
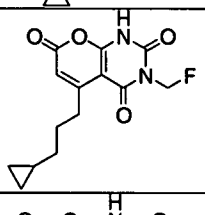
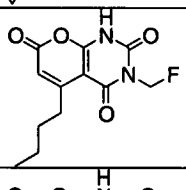
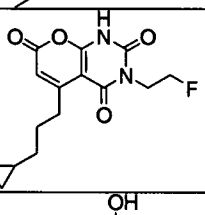
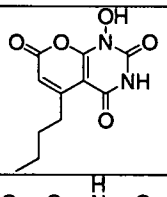
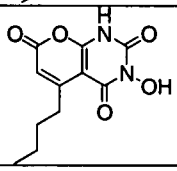
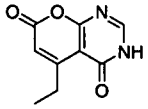
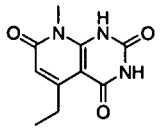
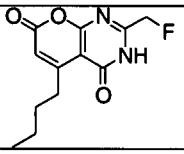
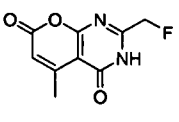
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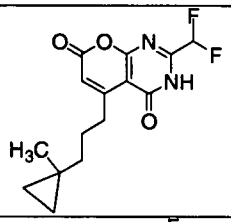
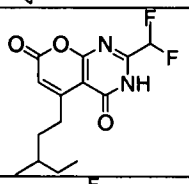
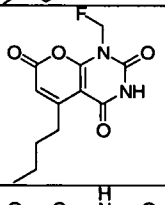
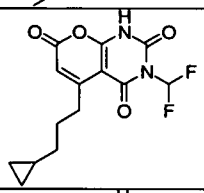
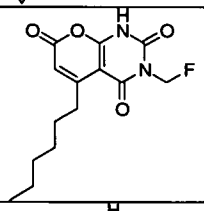
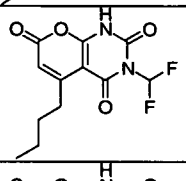
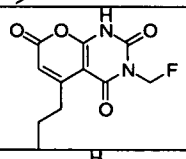
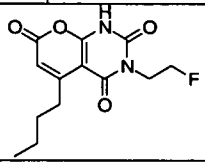
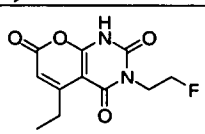
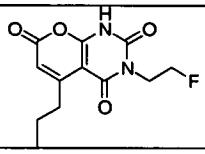
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752		248
753		228
754		308
755		286
759		2326
760		10000

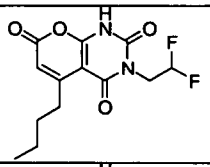
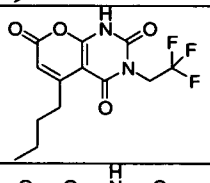
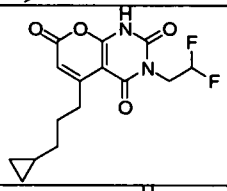
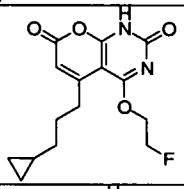
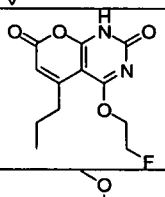
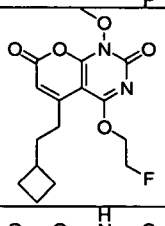
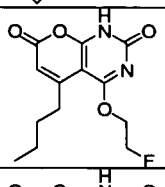
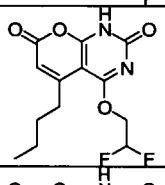
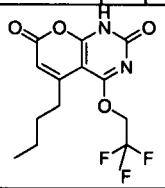
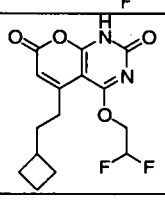
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768		383.5
769		19
770		908
771		17
772		39
773		48.5
774		28.0

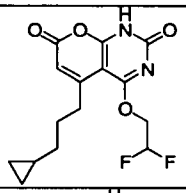
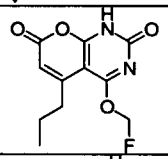
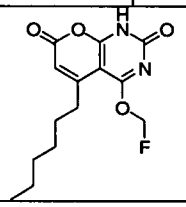
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777		5600
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779		2851
780		36
781		68
782		94
783		64
784		17.9

786		5331
787		681.5
788		38.5
789		88
791		50
792		44
796		>10000
797		>1000
798		>10000
799		>10000

800		>10000
801		>10000
802		12
803		3450
804		178
805		2063
806		256
807		>10000
808		>10000
809		187
810		>10000

811		22
812		40
813		256
814		161
815		10000
816		291
817		1450
818		308
819		1536
820		10000

821		142
822		10000
823		10000
824		91
825		616
826		3251
827		690
828		407
829		882
830		112

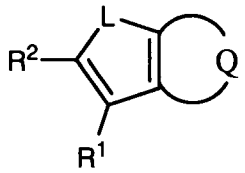
831		531
832		304
833		511

The activity of compounds **834-844** was also determined using the above-described assay and the EC_{50} values measured ranged from about 3 nM to about 1600 nM. Several selected compounds demonstrated EC_{50} values ranging from about 3 nM to about 100 nM.

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.

What is claimed is:

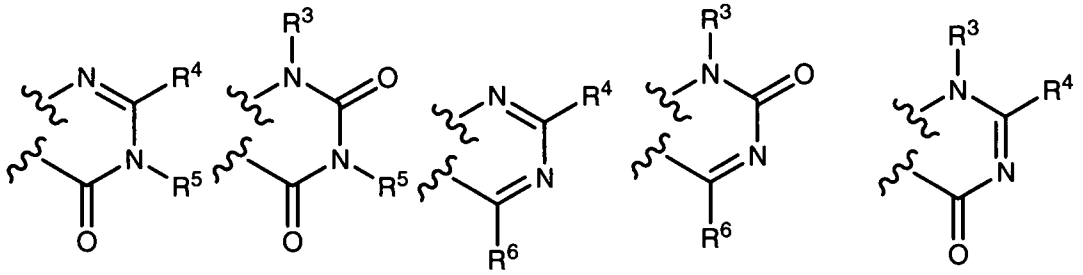
1. A compound having the formula:



(I)

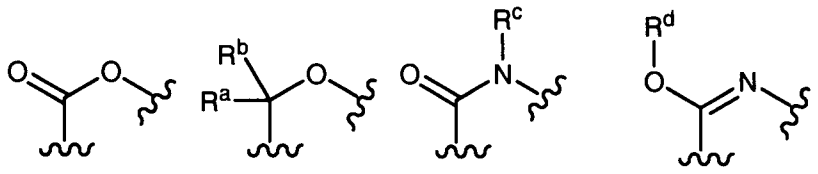
or a pharmaceutically acceptable salt, solvate, ester, or tautomer thereof, wherein:

Q is selected from the group consisting of:



(a) , (b) , (c) , (d) and (e) ;

L is selected from the group consisting of:



(f) , (g) , (h) , and (i) ;

R^1 is selected from the group consisting of H, alkyl, arylalkyl, -alkylene-S-alkyl, alkenyl, alkynyl, haloalkyl, wherein an alkyl group can be optionally substituted with one or more of the following groups, which can be the same or different: -OH, cycloalkyl, -C(O)-alkyl, -alkylene-C(O)-O-alkyl, -O-R^{10}, -alkylene-O-alkyl, aryl, -alkylene-aryl, heteroaryl, -alkylene-heteroaryl, halogen, -$(CH_2)_n$-$N(R^7)_2$, -alkylene-cycloalkyl, or -alkylene-cycloalkenyl,

wherein the cycloalkyl or the cycloalkyl portion of said -alkylene-cycloalkyl of R^1 is unsubstituted or substituted with one or more X groups, said aryl or the aryl portion of said -alkylene-aryl of R^1 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 the 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, haloalkyl, -O-cycloalkyl, -O-alkynyl, -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, -N_3, and -O-C(O)-alkyl;

R^5 is selected from the group consisting of H, alkyl, -OH, haloalkyl, arylalkyl, -O-alkyl, -O-aryl, cycloalkyl, heterocyclyl, -O-cycloalkyl, -O-heterocyclyl, -O-arylalkyl or -alkylene-O-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 the 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)$_2$,

wherein the 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,

wherein the 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;

R^8 is selected from the group consisting of aryl, -OH, and heterocyclyl,

wherein the 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, 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

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, cycloalkyl, arylalkyl, haloalkyl, -alkylene-O-alkyl, -alkylene-aryl, -alkenylene-aryl, -alkylene-heteroaryl, alkenyl, -C(O)-alkyl, alkynyl, and -alkylene-cycloalkyl,

wherein an the alkynyl portion of an –O-alkynyl group can be optionally subsituted with –OH or alkoxy; the cycloalkyl portion of an –O-cycloalkyl group can be optionally substituted with an –alkylene-O-alkylene-aryl

group; 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 the 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 a heterocyclyl;

each R^{12} is independently selected from the group consisting of alkyl, aryl, and heteroaryl,

wherein the aryl of R^{12} is unsubstituted or substituted with one or more Y groups and said heteroaryl of R^{12} is unsubstituted or substituted with one or more Z groups; or wherein both R^{12} groups, together with the carbon atom to which they are attached, combine to form a heterocyclyl group;

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

wherein the 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,

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;

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, $-NO_2$, -OH, $-S(O_2)$-alkyl, $-S(O_2)$-aryl,

$-S(O_2)-NH_2$, $-S(O_2)-NH$-alkyl, $-S(O_2)-NH$-aryl, $-S(O_2)-N(alkyl)_2$, $-S(O_2)-N(aryl)_2$, $-S(O_2)-N(alkyl)(aryl)$, and aryl;

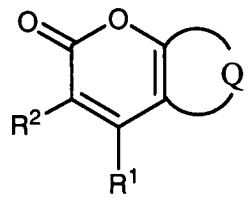
each Z is independently selected from the group consisting of alkyl, haloalkyl, halogen, -O-alkyl, -O-haloalkyl, -CN, -OH, aryl, and N-oxide;

n is 0, 1, 2, or 3;

m is 0, 1, or 2; and

with the proviso that when L is (f), and R^2, R^3 and R^5 are each H, then R^1 is not $-CH_3$.

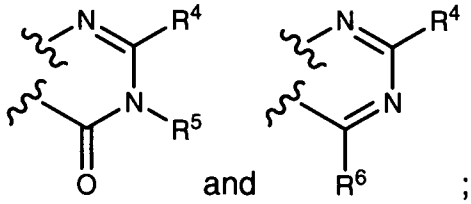
2. The compound of claim 1, having the formula:



(II)

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

Q is selected from the group consisting of:



;

R^1 is –H, alkyl, haloalkyl, arylalkyl, -alkylene-S-alkyl or -alkylene-cycloalkyl;

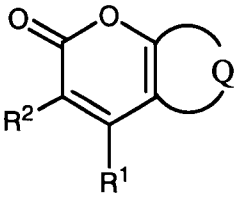
R^2 is –H, -CN, or -NHC(O)-alkyl;

R^4 is -O-cycloalkyl, –O-alkynyl, -O-alkynylene-cycloalkyl, haloalkyl or –O-$N=C(R^{12})_2$, wherein both R^{12} groups, together with the carbon atom to which they are attached, combine to form a heterocyclyl group, and wherein the alkynyl portion of an –O-alkynyl group can be optionally subsituted with –OH or alkoxy; and wherein the cycloalkyl portion of an –O-cycloalkyl group can be optionally substituted with an –alkylene-O-alkylene-aryl group;

R^5 is –H, -OH, alkyl, haloalkyl, arylalkyl, -O-alkyl, -O-aryl, cycloalkyl, heterocyclyl, -O-cycloalkyl, -O-heterocyclyl, -O-arylalkyl or -alkylene-O-alkyl; and

R^6 is alkoxy, -O-alkylene-O-alkyl, -O-arylalkyl or –O-haloalkyl.

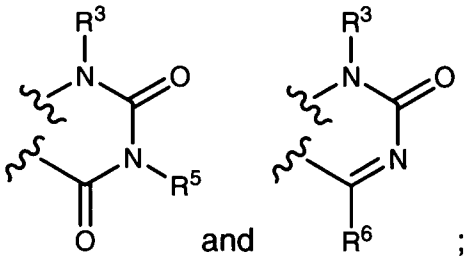
3. The compound of claim 1, having the formula:



(III)

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

Q is selected from the group consisting of:



and ;

R^1 is –H, alkyl, haloalkyl, arylalkyl, -alkylene-S-alkyl or -alkylene-cycloalkyl;

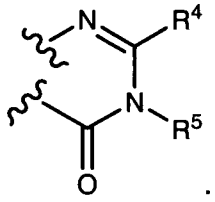
R^2 is –H, -CN, or -NHC(O)-alkyl;

R^3 is –H, -OH, alkyl, haloalkyl, arylalkyl, -O-alkyl, -O-aryl, cycloalkyl, heterocyclyl, -O-cycloalkyl, -O-heterocyclyl, -O-arylalkyl or -alkylene-O-alkyl;

R^5 is –H, -OH, alkyl, haloalkyl, arylalkyl, -O-alkyl, -O-aryl, cycloalkyl, heterocyclyl, -O-cycloalkyl, -O-heterocyclyl, -O-arylalkyl or -alkylene-O-alkyl; and

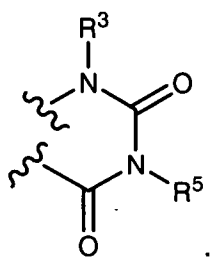
R^6 is alkoxy, -O-alkylene-O-alkyl, -O-arylalkyl or –O-haloalkyl.

4. The compound of claim 1, wherein Q is:



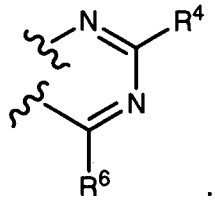
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5. The compound of claim 1, wherein Q is:

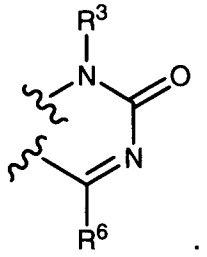


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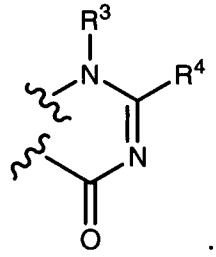
6. The compound of claim 1, wherein Q is:



7. The compound of claim 1, wherein Q is:



8. The compound of claim 1, wherein Q is:



9. The compound of claim 1, wherein

R^1 is –H, alkyl, haloalkyl, arylalkyl, -alkylene-S-alkyl or -alkylene-cycloalkyl;

R^2 is –H, -CN, or -NHC(O)-alkyl;

R^3 is –H, -OH, alkyl, haloalkyl, arylalkyl, -O-alkyl, -O-aryl, cycloalkyl, heterocyclyl, -O-cycloalkyl, -O-heterocyclyl, -O-arylalkyl or -alkylene-O-alkyl;

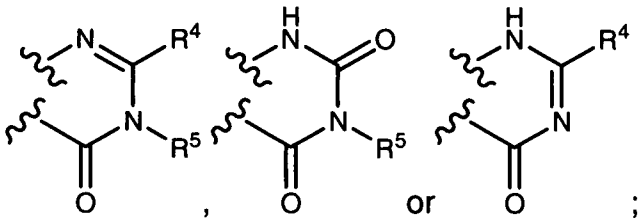
R^4 is -O-cycloalkyl, –O-alkynyl, -O-alkynylene-cycloalkyl, haloalkyl or –O-N=C(R^{12})$_2$, wherein both R^{12} groups, together with the carbon atom to which they are attached, combine to form a heterocyclyl group, and wherein the alkynyl portion of an –O-alkynyl group can be optionally subsituted with –OH or alkoxy; and wherein the cycloalkyl portion of an –O-cycloalkyl group can be optionally substituted with an –alkylene-O-alkylene-aryl group; and

R^5 is –H, -OH, alkyl, haloalkyl, arylalkyl, -O-alkyl, -O-aryl, cycloalkyl, heterocyclyl, -O-cycloalkyl, -O-heterocyclyl, -O-arylalkyl or -alkylene-O-alkyl; and

R^6 is alkoxy, -O-alkylene-O-alkyl, -O-arylalkyl or –O-haloalkyl.

10. The compound of claim 9, wherein

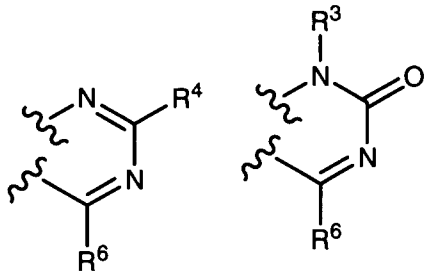
Q is:



; R^1 is alkyl, haloalkyl or -alkylene-cycloalkyl; R^2 is –H; and R^5 is –H or alkyl.

11. The compound of claim 9, wherein

Q is:

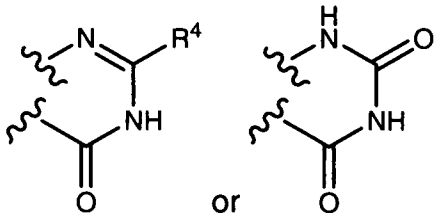


(c) or (d) ;

R^1 is alkyl, haloalkyl or -alkylene-cycloalkyl; and R^2 is –H.

12. The compound of claim 10, wherein

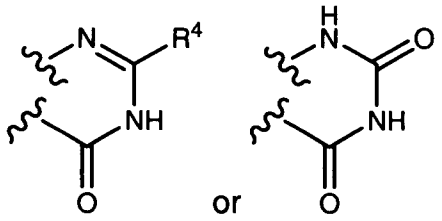
Q is:



and R^4 is –O-alkynyl or -O-alkynylene-cycloalkyl, wherein the alkynyl portion of an –O-alkynyl group can be optionally subsituted with –OH or alkoxy.

13. The compound of claim 10, wherein

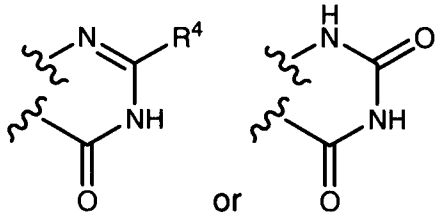
Q is:



and R^4 is haloalkyl.

14. The compound of claim 10, wherein

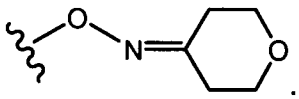
Q is:



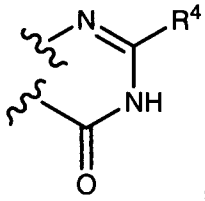
and R^4 is -O-N=C(R^{12})$_2$, wherein both R^{12} groups, together with the carbon atom to which they are attached, combine to form a heterocyclyl group.

15. The compound of claim 13, wherein R^4 is $-CH_2F$ or $-CH(F)_2$.

16. The compound of claim 14, wherein R^4 is:



17. The compound of claim 2, wherein Q is:



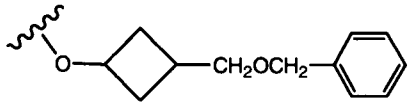
R^1 is alkyl, haloalkyl, or -alkylene-cycloalkyl, and R^2 is –H.

18. The compound of claim 17, wherein R^4 is –O-alkynyl or -O-alkynylene-cycloalkyl, wherein the alkynyl portion of an –O-alkynyl group can be optionally subsituted with –OH or alkoxy.

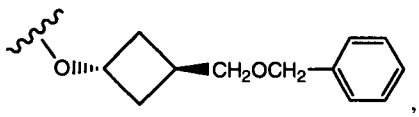
19. The compound of claim 17, wherein R^4 is haloalkyl.

20. The compound of claim 17, wherein R^4 is -O-N=C(R^{12})$_2$, wherein both R^{12} groups, together with the carbon atom to which they are attached, combine to form a heterocyclyl group.

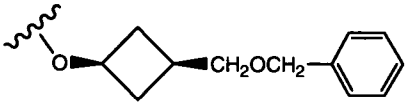
21. The compound of claim 17, wherein R^4 is –CH_2F, –$CH(F)_2$, –CF_3, –$OCH_2C{\equiv}CCH_2CH_3$, –$OCH_2C{\equiv}C(CH_2)_3CH_3$, –$OCH_2C{\equiv}CCH_2CH_2CH_3$, –$OCH_2C{\equiv}C$-cyclopropyl, –$OCH_2C{\equiv}CCH(OCH_3)CH_3$, –$OCH_2C{\equiv}CCH(OH)CH_3$, –$OCH_2C{\equiv}CCH(OH)CH_2CH_3$,–$OCH_2C{\equiv}CCH_2CH_2OCH_3$, –$OCH_2C{\equiv}CCH_2CH_2OH$, –$OCH_2C{\equiv}C(CH_2)_3OH$, –$OCH(CH_3)C{\equiv}CCH_2CH_3$, –$OCH_2C{\equiv}C$-cyclohexyl, –O-cyclobutyl,



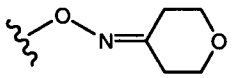
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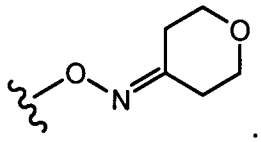


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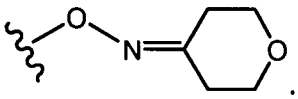
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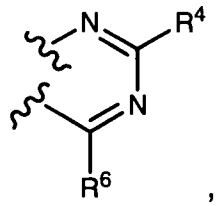
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22. The compound of claim 21, wherein R^4 is –CH_2F, –$CH(F)_2$ or



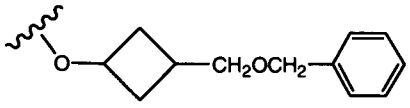
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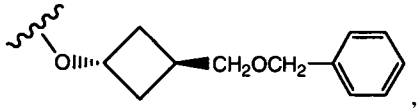
23. The compound of claim 2, wherein Q is:

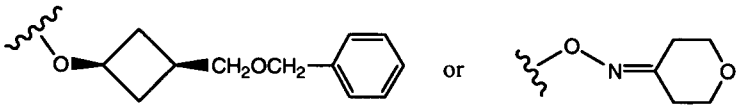


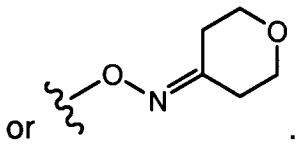
R^1 is alkyl, haloalkyl, or -alkylene-cycloalkyl, and R^2 is –H.

24. The compound of claim 23, wherein R^4 is $-CH_2F$, $-CH(F)_2$, $-CF_3$, $-OCH_2C{\equiv}CCH_2CH_3$, $-OCH_2C{\equiv}C(CH_2)_3CH_3$, $-OCH_2C{\equiv}CCH_2CH_2CH_3$, $-OCH_2C{\equiv}C$-cyclopropyl, $-OCH_2C{\equiv}CCH(OCH_3)CH_3$, $-OCH_2C{\equiv}CCH(OH)CH_3$, $-OCH_2C{\equiv}CCH(OH)CH_2CH_3$,$-OCH_2C{\equiv}CCH_2CH_2OCH_3$, $-OCH_2C{\equiv}CCH_2CH_2OH$, $-OCH_2C{\equiv}C(CH_2)_3OH$, $-OCH(CH_3)C{\equiv}CCH_2CH_3$, $-OCH_2C{\equiv}C$-cyclohexyl, –O-cyclobutyl,

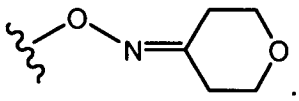








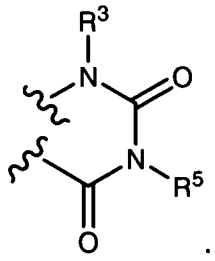
25. The compound of claim 24, wherein R^4 is $-CH_2F$, $-CH(F)_2$ or



26. The compound of claim 24, wherein R^1 is a straight chain alkyl having from 1 to 6 carbon atoms.

27. The compound of claim 24, wherein R^1 is $-(CH_2)_3$-cyclopropyl or $-(CH_2)_2$cyclobutyl.

28. The compound of claim 3, wherein Q is:



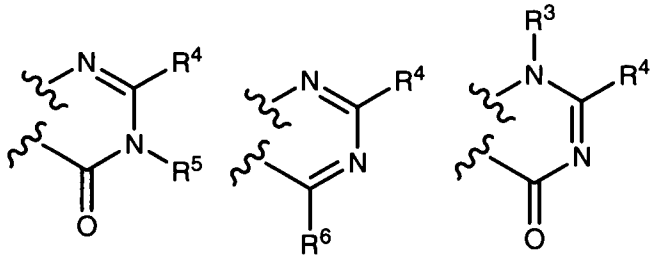
29. The compound of claim 28, wherein R^1 is alkyl, haloalkyl, or -alkylene-cycloalkyl; and R^2, R^3 and R^5 are each –H.

30. The compound of claim 28, wherein R^1 is alkyl, haloalkyl, or -alkylene-cycloalkyl; R^2 is –H and one, but not both of R^3 and R^5 are –H.

31. The compound of claim 29, wherein R^1 is a straight chain alkyl having from 1 to 6 carbon atoms.

32. The compound of claim 1, wherein

Q is:



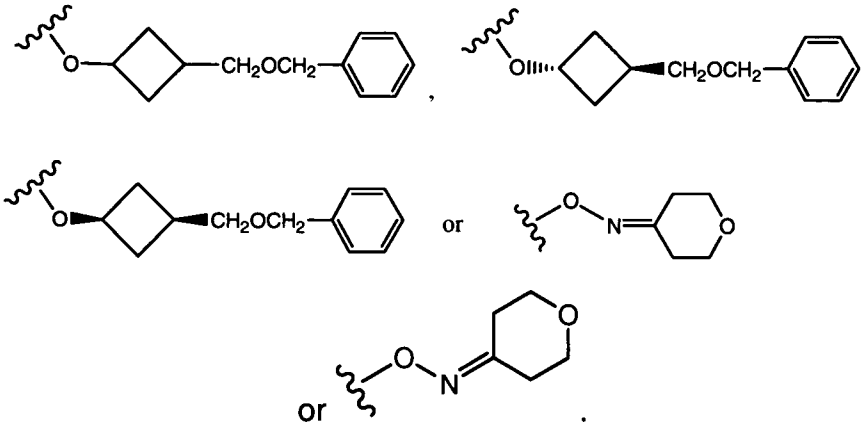
(a) (c) or (e) ,

R^1 is alkyl or -alkylene-cycloalkyl and R^2 is –H.

33. The compound of claim 32, wherein R^4 is haloalkyl or -O-N=C(R^{12})$_2$, wherein both R^{12} groups, together with the carbon atom to which they are attached, combine to form a heterocyclyl group.

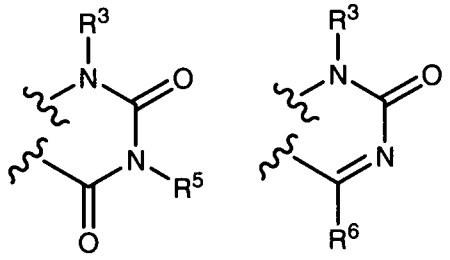
34. The compound of claim 33, wherein R^4 is –CH_2F or –$CH(F)_2$.

35. The compound of claim 30, wherein R^1 is methyl, ethyl, n-butyl, n-phenyl, -$(CH_2)_3$-cyclopropyl or -$(CH_2)_2$-cyclobutyl, R^2 is –H, and R^4 is $-CH_2F$, $-CH(F)_2$, $-CF_3$, $-OCH_2C{\equiv}CCH_2CH_3$, $-OCH_2C{\equiv}C(CH_2)_3CH_3$, $-OCH_2C{\equiv}CCH_2CH_2CH_3$, $-OCH_2C{\equiv}C$-cyclopropyl, $-OCH_2C{\equiv}CCH(OCH_3)CH_3$, $-OCH_2C{\equiv}CCH(OH)CH_3$, $-OCH_2C{\equiv}CCH(OH)CH_2CH_3$, $-OCH_2C{\equiv}CCH_2CH_2OCH_3$, $-OCH_2C{\equiv}CCH_2CH_2OH$, $-OCH_2C{\equiv}C(CH_2)_3OH$, $-OCH(CH_3)C{\equiv}CCH_2CH_3$, $-OCH_2C{\equiv}C$-cyclohexyl, –O-cyclobutyl,



36. The compound of claim 1, wherein

Q is:



(b) or (d) ,

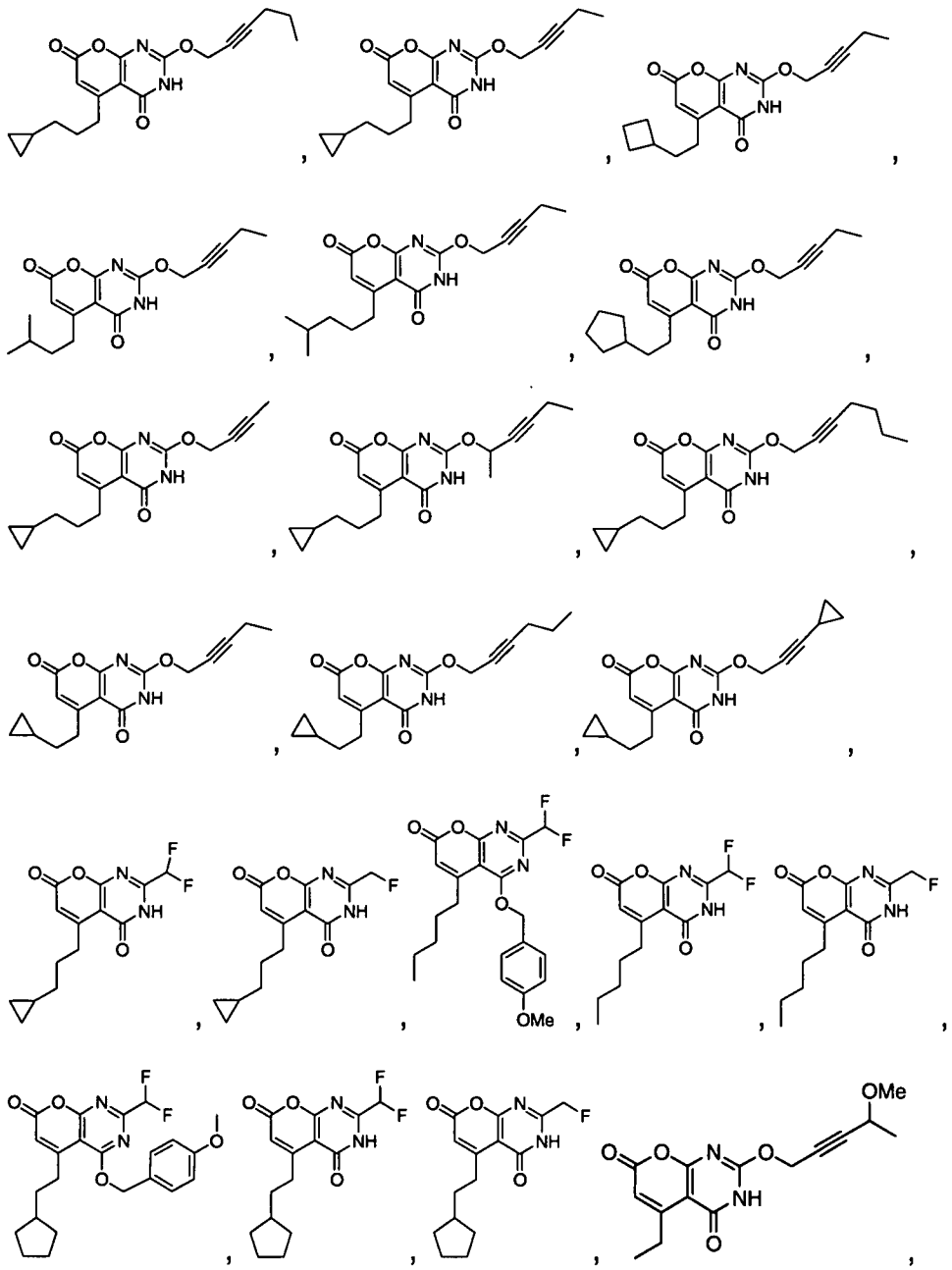
R^1 is alkyl or -alkylene-cycloalkyl and R^2 is –H.

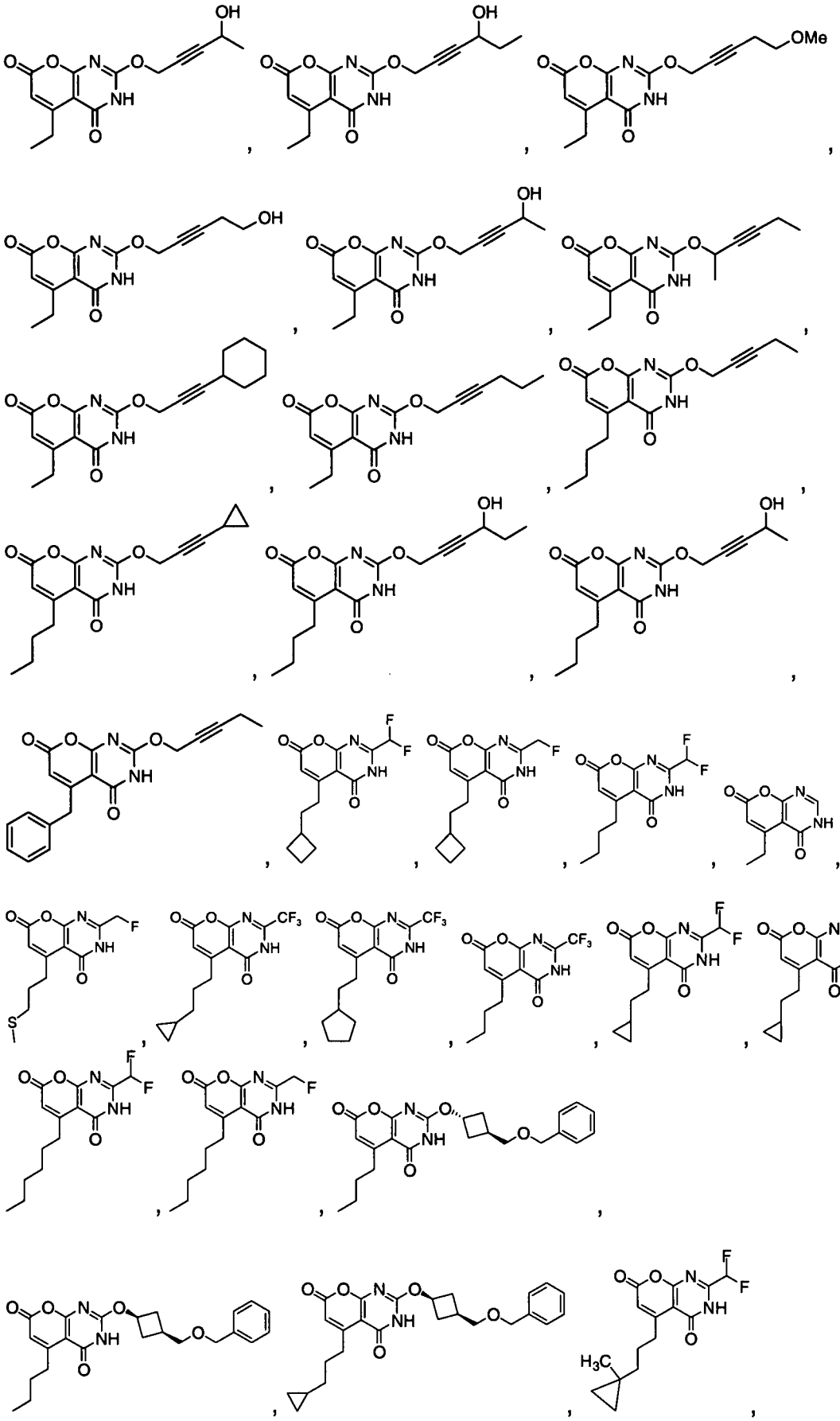
37. The compound of claim 36, wherein one, but not both, of R^3 and R^5 is –H.

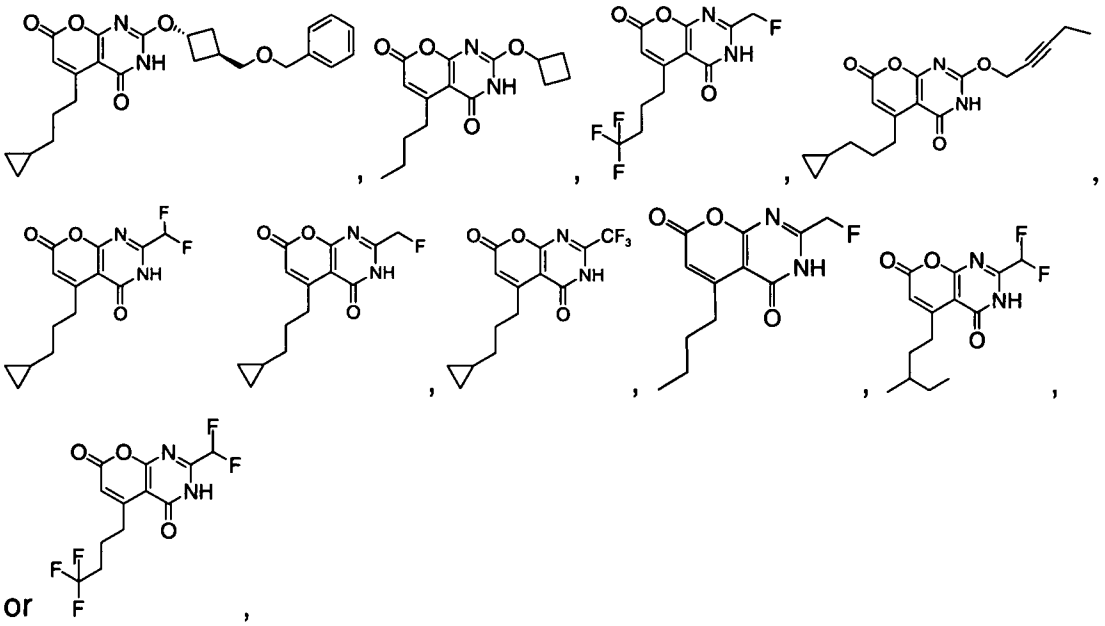
38. The compound of claim 37, wherein one of R^3 and R^5 is –H and the other is -OH, alkyl, haloalkyl, arylalkyl, -O-alkyl, -O-aryl, cycloalkyl, heterocyclyl, -O-cycloalkyl, -O-heterocyclyl, -O-arylalkyl or -alkylene-O-alkyl.

39. The compound of claim 38, wherein one of R^3 and R^5 is –H and the other is –OCH_3, cyclobutyl, ethyl, *N*-morpholinyl, –O-benzyl, –$CH_2CH_2OCH_3$, –OCH_2CH_3, –CH_2F, –CH_2CH_2F or –OH.

40. A compound having the structure:

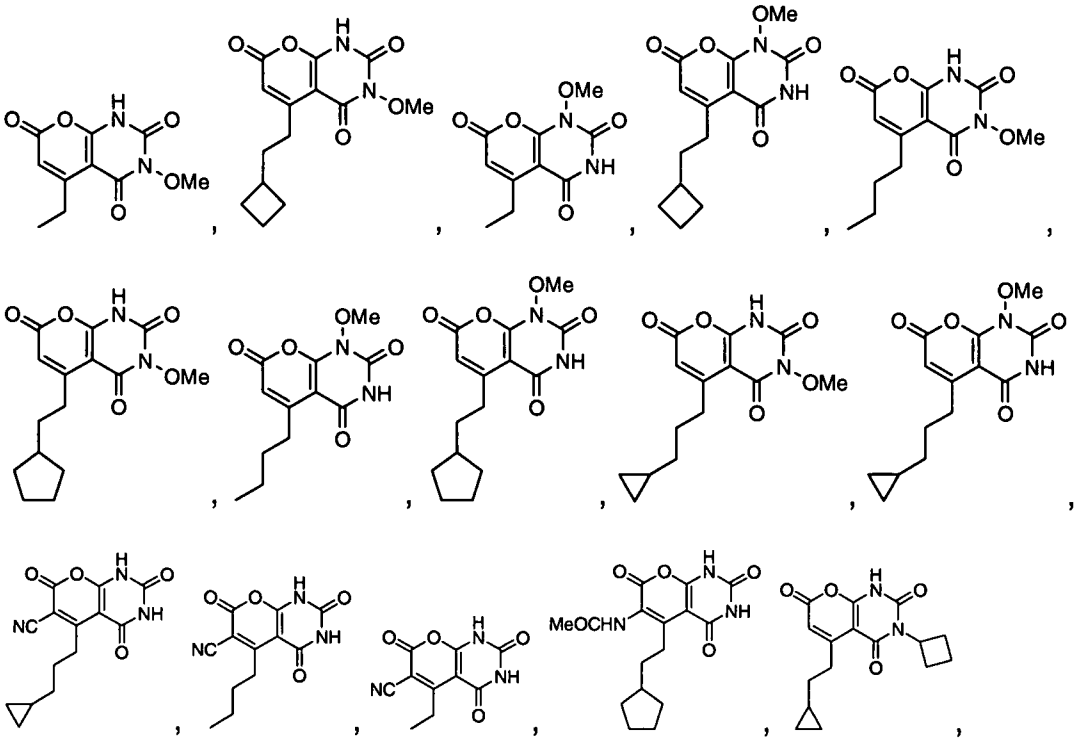


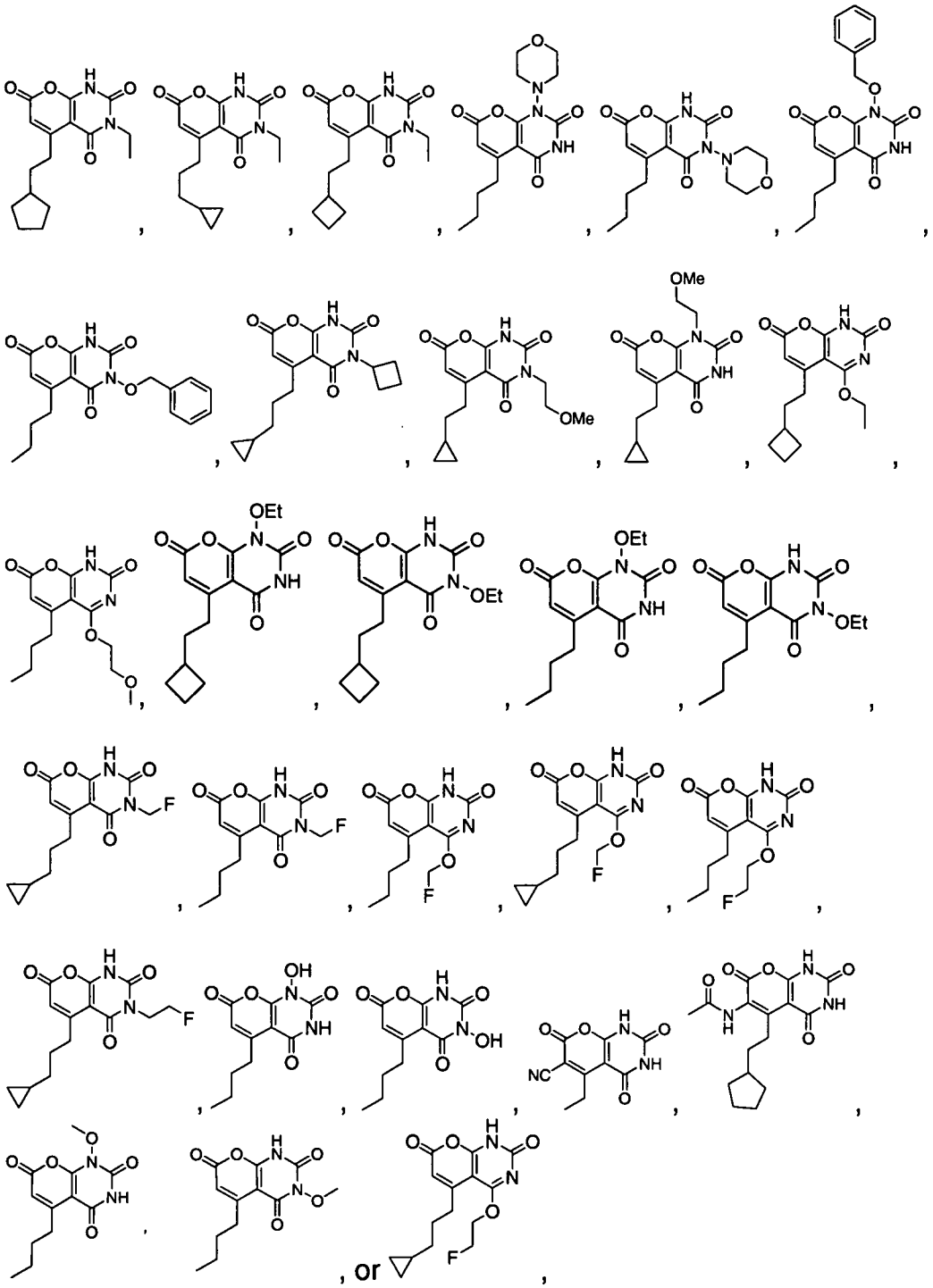




or a pharmaceutically acceptable salt, solvate, ester, or tautomer thereof.

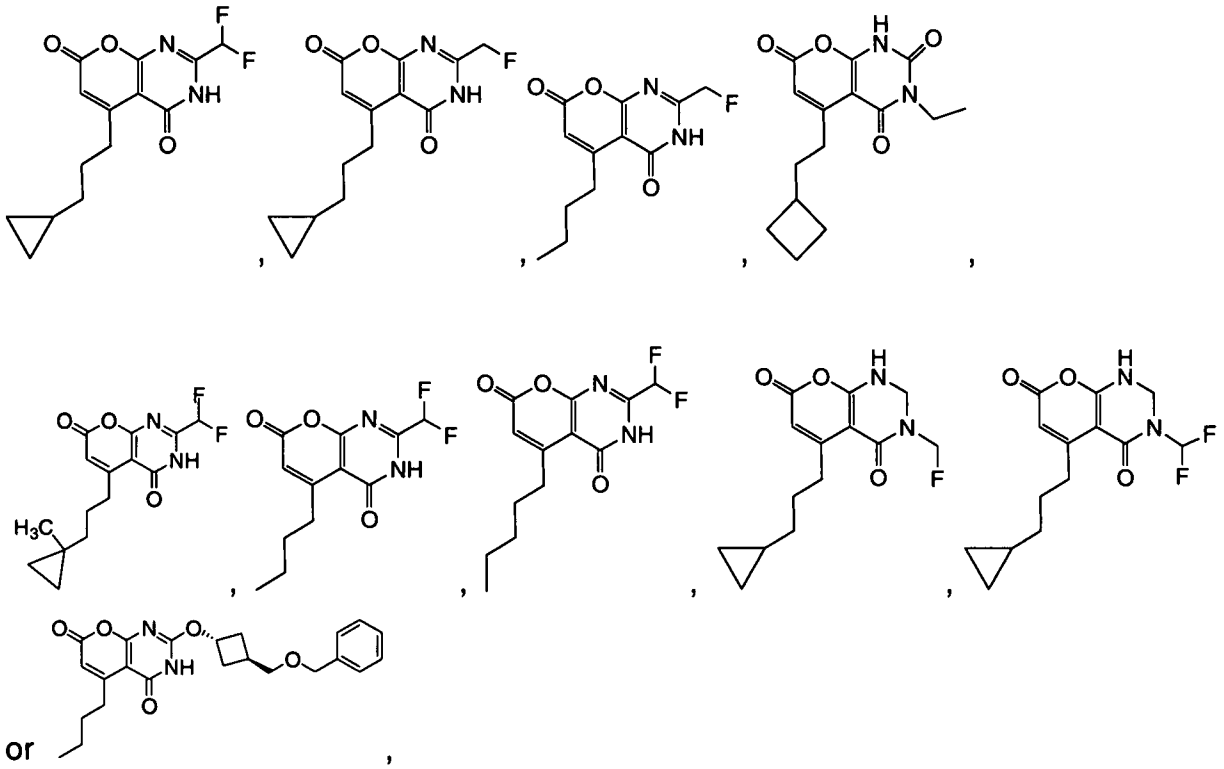
41. A compound having the structure:





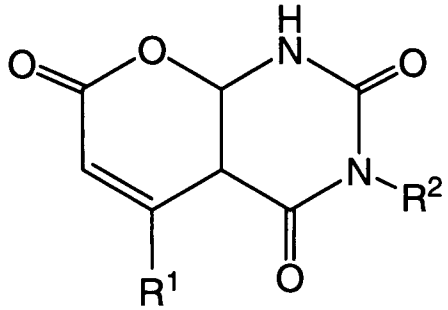
or a pharmaceutically acceptable salt, solvate, ester, or tautomer thereof.

42. A compound having the structure:



or a pharmaceutically acceptable salt, solvate, ester, or tautomer thereof.

43. A compound having the formula:



(IV)

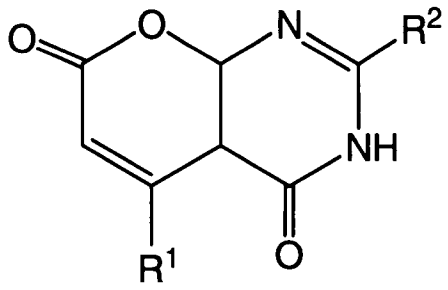
or a pharmaceutically acceptable salt or solvate thereof,

wherein:

R^1 is haloalkyl; and

R^2 is H or cycloalkyl.

44. A compound having the formula:



(V)

or a pharmaceutically acceptable salt or solvate thereof,

wherein:

R^1 and R^2 are each, independently, haloalkyl.

45. The compound of claim 43, wherein R^1 is fluoroalkyl.

46. The compound of claim 44, wherein R^1 is –alkylene-CF_2.

47. The compound of claim 44, wherein R^1 is –alkylene-F.

48. The compound of claim 46, wherein R^1 is $-(CH_2)_3-CF_2$, $-(CH_2)_4-CF_2$ or $-(CH_2)_5-CF_2$.

49. The compound of claim 43, wherein R^2 is H.

50. The compound of claim 43, wherein R^2 is cycloalkyl.

51. The compound of claim 50, wherein R^2 is cyclobutyl.

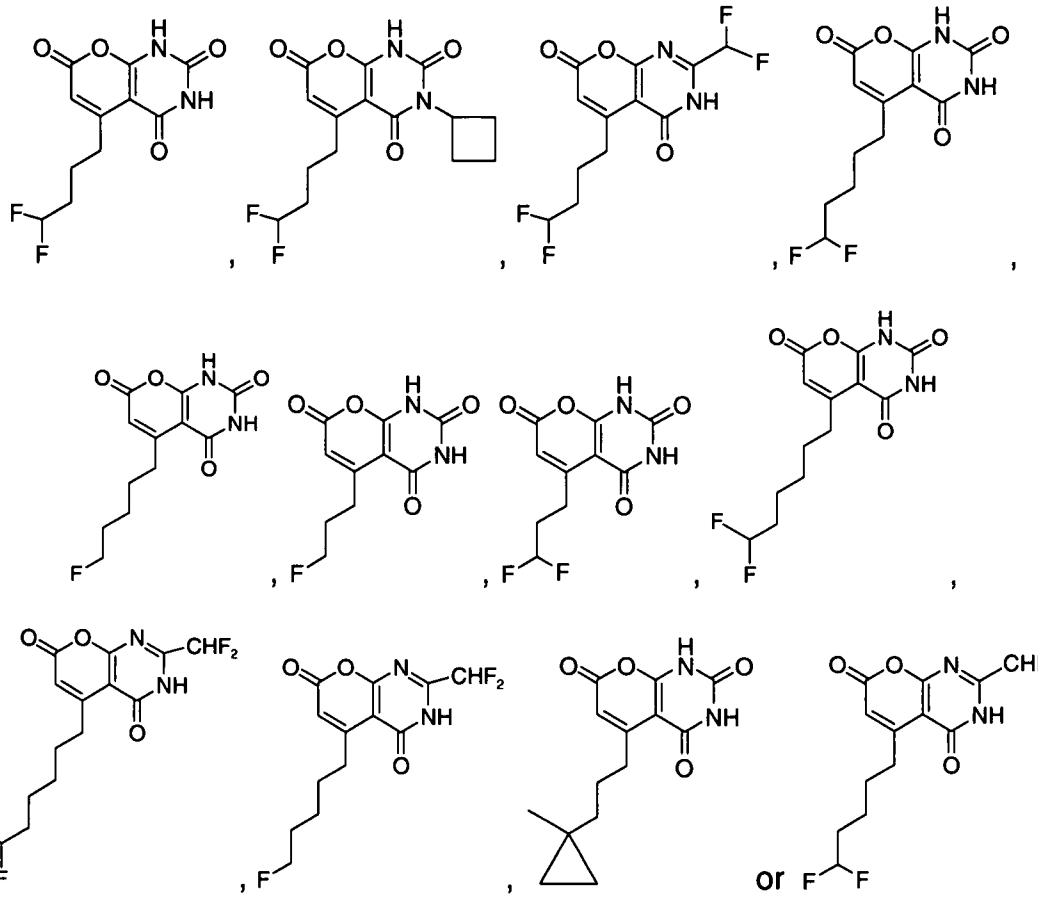
52. The compound of claim 44, wherein R^2 is H.

53. The compound of claim 45, wherein R^2 is H.

54. The compound of claim 44, wherein R^2 is cycloalkyl.

55. The compound of claim 45, wherein R^2 is cycloalkyl.

56. A compound having the structure:



or a pharmaceutically acceptable salt or solvate thereof.

57. A composition comprising at least one compound of claim 1 and a pharmaceutically acceptable carrier.

58. A composition comprising at least one compound of claim 40 and a pharmaceutically acceptable carrier.

59. A composition comprising at least one compound of claim 41 and a pharmaceutically acceptable carrier.

60. A composition comprising at least one compound of claim 42 and a pharmaceutically acceptable carrier.

61. A composition comprising at least one compound of claim 43 and a pharmaceutically acceptable carrier.

62. A composition comprising at least one compound of claim 44 and a pharmaceutically acceptable carrier.

63. A composition comprising at least one compound of claim 56 and a pharmaceutically acceptable carrier.

64. The composition of any one of claims 57-63, further comprising at least one additional therapeutic agent selected from the group consisting of anti-flushing agents, 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, aspirin, NSAID agents, Vytorin®, ezetimibe, inorganic cholesterol sequestrants, AcylCoA:Cholesterol *O*-acyltransferaseinhibitors, 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 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, CB_1 antagonists/inverse agonists, ghrelin antagonists, H_3 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, 5HT2c agonists, Mc4r agonists, monoamine reuptake inhibitors, serotonin reuptake inhibitors, GLP-1 mimetics, phentermine, topiramate, phytopharm compound 57, ghrelin antibodies, Mc3r agonists, ACC inhibitors, β3 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, 11β 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, DPP-IV inhibitors, 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, 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 milano reverse cholesterol transport inhibitors, fatty acid binding protein inhibitors (FABP), and fatty acid transporter protein inhibitors (FATP).

65. The composition of claim 64, wherein the at least one additional therapeutic agent is an HMG CoA reductase inhibitor selected from the group consisting of lovastatin, simvastatin, pravastatin, atorvastatin, fluvastatin, cerivastatin, rivastatin, rosuvastatin calcium, and pitavastatin.

66. The composition of claim 65, wherein the at least one additional therapeutic agent is simvastatin.

67. The composition of claim 64, wherein the at least one additional therapeutic agent is a cholesteryl ester transfer protein inhibitor.

68. The composition of claim 67, wherein the at least one additional therapeutic agent is an anti-flushing agent.

69. The composition of claim 64, wherein the at least one additional therapeutic agent is Vytorin®, ezetimibe, aspirin, ibuprofen or acetaminophen or a combination thereof.

70. The composition of claim 64, wherein the at least one additional therapeutic agent is DPP-IV inhibitor or a GLP-1 mimetic.