TITLE OF THE INVENTION

PYRIMIDINDIONE DERIVATIVES AS PROKINETICIN RECEPTOR ANTAGONISTS

CROSS-REFERENCE TO RELATED APPLICATIONS

This Application claims priority to United States Provisional Patent Application No. 60/664865 March 24, 2005, which is hereby incorporated by reference in its entirety.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

The research and development of the invention described below was not federally sponsored.

BACKGROUND OF THE INVENTION

Functional bowel disorders involve abnormal motility and secretion within organs of the gastrointestinal (GI) tract, and are characterized by abdominal discomfort/pain. The criteria for these disorders are summarized by gastroenterologists in the 'Rome II criteria'. Based on these criteria the disorders are common and include, but are not limited to, functional dyspepsia, irritable bowel syndrome (IBS), gastroesophageal reflux disease (GERD) and non-erosive reflux disease (NERD), and chronic constipation (including colonic inertia, idiopathic pseudoobstruction). GERD is extremely prevalent, is usually associated with non-cardiac chest pain and may be treated with acid-suppressing agents and prokinetic agents. IBS is characterized by the presence of reoccurring constipation and/or

diarrhea, which can be associated with gaseous distention/bloating and abdominal discomfort/pain (Thompson, W.G. and Heaton, K.W. *Gastroenterology* **1980**, *79*, 283-288). The onset of the pain of IBS is associated with a change in the frequency and/or form of stool and can be relieved by defecation. IBS is an extremely prevalent condition that occurs to varying severity in 10-15% of the population (Saito, Y.A.; Schoenfeld, P.; and Locke, G.R. *Am. J. Gastroenterol.* **2002**, *97*, 1910-1915). The pain may be treated with smooth muscle relaxants and antidepressants (Jackson, J.L.; O'Malley, P.G.; Tomkins, G.; Balden, E.; Santoro, J.; and Kroenke, K.; *Am. J. Med.* **2000**, *108*, 65-72; Jailwala, J.; Imperiale, T.F.; and Kroenke, K.; *Ann. Intern. Med.* **2000**, *133*:136-147; Akehurst, R. and Kaltenthaler, E. *Gut* **2001**, *48*, 272-282; Poynard, T.; Regimbeau, C.; and Benhamou, Y.; *Aliment Pharmacol. Ther.* **2001**, *15*, 355-361). Severe diarrhea predominant IBS is treated by alosetron, whereas constipation predominant IBS is treated by tegaserod. Functional dyspepsia is a disorder of the upper GI tract with symptoms exacerbated by a meal and associated with early satiety, nausea and vomiting. Although its etiology is unknown, prokinetic agents may relieve the symptoms of IBS. In some patients there is overlap in symptoms between GERD/NERD, functional dyspepsia and IBS. Treatments for functional bowel disorders, such as IBS, have low efficacy and are associated with adverse effects. For example, alosetron is approved by the FDA on a risk management program because it is associated with an increase in a serious adverse event, ischemic colitis. No treatments effectively alleviate pain in functional bowel disorders.

In addition to functional disorders, inflammatory bowel diseases (IBD) are common and include ulcerative colitis (UC) and Crohn's disease (CD). Although there may be a genetic component to CD, the etiology of both CD and UC is unknown.

UC is a diffuse mucosal disease of the colon, characterized by inflammation and ulceration, which is associated with diarrhea and abdominal cramping. The mucosal inflammation progresses from the rectal area to eventually extend through the large bowel. CD is a transmural inflammation that most frequently involves the distal small bowel and colon. The inflammation can result in ulcers of varying involvement and in severe cases result in transmural scarring and chronic inflammation. Both infectious and dysregulated immune functions may contribute to disease onset. Therapies for IBD include corticosteroids, immunosuppressives (azathioprine, mercaptopurine, and methotrexate) and aminosalicylates (5-ASA). These therapies involve suppression of the immune system by mimicking corticoids, or unknown mechanisms of action. Oral corticosteroid use is associated with serious adverse effects, whereas immunosuppressives and aminosalicylates are only moderately effective. Infliximab (a chimeric monoclonal anti-tumor necrosis factor antibody) is effective in CD, however, its use is associated with the presence of antibodies, which reduce its efficacy. There are no treatments that target the motility and secretory abnormalities or painful sensation that are associated with gut inflammation.

The cysteine rich proteins known as Prokineticin 1 (PK1) and Prokineticin 2 (PK2), as well as variants, fragments and molecules having PK activity, have been identified. These have been shown to contract gastrointestinal smooth muscle (Li, M.; Bullock, C.M.; Knauer, D.J.; Ehlert, F.J.; and Zhou, Q.Y., *Mol. Pharmacol.* **2001**, *59*, 692-698), and suppress feeding (Negri, L.; Lattanzi, R.; Giannini, E.; De Felice, M.; Colucci, A. and Melchiorri, P. *Brit. J. Pharmacol.* **2004**, *142*, 181-191). PK1 and PK2 act on both PK1 and PK2 receptors, and limited structural changes of C-terminal cysteine-rich regions of these related PKs are tolerated. For example, chimeric PKs, where the cysteine-rich domains of PK 1 and PK 2 were exchanged between the two; and a splice variant of PK2 that included a 21 residue insertion in its C-terminal domain retained activity (Bullock, CM; Li J.D.; Zhou, Q.Y.; *Mol.*

Pharmacol. **2004**, *65(3)*, 582-8). A PK variant binds to receptors of primary sensory neurons, and results in an intense sensitization of peripheral nociceptors to thermal and mechanical stimuli (Mollay, C.; Weschelberger, C.; Mignogna, G.; Negri, L.; Melchiorri, P.; Barra, D.; Kreil, G.; *Eur. J. Pharmacol.* **1999**, *374*, 189-196; Negri, L.; Lattanzi, R.; Giannini, E.; Metere, A.; Colucci, M.; Barra, D.; Kreil, G.; Melchiorri, P.; *Brit. J. Pharmacol.* **2002**, *137(8)*, 1147-54).

Patent application PCT/US2004/087054 A2 provides methods of modulating gastric acid or pepsinogen secretion by administering an amount of a prokineticin receptor antagonist effective to alter one or more indicia of gastric acid secretion.

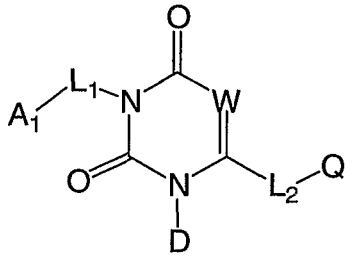
PK1 induces proliferation, migration and fenestration in capillary endothelial cells derived from endocrine glands. The expression of PK mRNA is restricted to the steroidogenic glands, ovary, testis, adrenal and placenta (LeCouter, J.; Kowalski, J.; Foster, J.; Hass, P., Zhang, Z.; Dillard-Telm, L., Frantz, G., Rangell, L.; DeGuzman, L.; Keller, G.A.; Peale, F.; Gurney, A.; Hillan, K.J.; Ferrara, N. *Nature* **2001**, *412 (6850)*, 877-84). In 2002 the identification of the PK1 receptor provided a novel molecular basis for the regulation of angiogenesis in endocrine glands (Masuda, Y.; Takatsu, Y.; Terao, Y.; Kumano, S.; Ishibashi, Y.; Suenaga, M.; Abe, M.; Fukusumi, S.; Watanabe, T.; Shintani, Y.; Yamada, T.; Hinuma, S.; Inatomi, N.; Ohtaki, T.; Onda, H.; Fujino, M.; *Biochem. Biophys. Res. Commun.* **2002**, *293(1)*, 396-402;LeCouter, J.; Lin, R.; Ferrara, N.; *Cold Spring Harb Symp Quant Biol.* **2002**, *67*, 217-21). For example, adenoviral delivery of PK1 to the mouse testis results in a potent angiogenic response (LeCouter, J.; Lin, R.; Tejada, M.; Frantz, G.; Peale, F.; Hillan, K.J.; Ferrara, N. *Proc. Natl. Acad. Sci. U S A.* **2003**, *100,* 2685-90). Recently, it was shown that PK1 mRNA is not normally expressed in colorectal normal mucosa but is detected in colorectal cancer cells (Goi, T.; Fujioka, M.; Satoh, Y.; Tabata, S.; Koneri, K.; Nagano, H.; Hirono, Y.; Katayama, K.; Hirose, K. and Yamaguchi., *Cancer Res.* **2004**, *64*,1906-1910).

Prokineticin 2 receptor antagonists are useful in the treatment and prevention of various mammalian disease states, for example, visceral pain that is associated with IBS and IBD. Additionally, PK2 receptor antagonists are useful for the treatment of GERD or other forms of secretory diarrhea. And, PK2 receptor antagonists are useful in treating cancer-specific angiogenesis factor in the large intestine and reproductive organs.

It is an object of the present invention to provide prokineticin 2 receptor antagonists. It is also an object of the invention to provide a method of treating or ameliorating a condition mediated by prokineticin 2 receptor. And, it is an object of the invention to provide a useful pharmaceutical composition comprising a compound of the present invention useful as a prokineticin 2 receptor antagonist.

SUMMARY OF THE INVENTION

The present invention is directed to a compound of Formula (I):



Formula (I)

wherein:

A_1 is hydrogen; aryl; heteroaryl; C_{5-8}cycloalkyl; or heterocyclyl; provided that A_1 is other than piperidin-4-yl, *N*-t-butoxycarbonyl-piperidin-4-yl, or *N*-methyl-piperidin-3-yl; and wherein substituents of A_1 other than hydrogen are optionally

substituted with one to three substituents independently selected from the group consisting of C_{1-6}alkyl, hydroxy(C_{1-6})alkyl, C_{1-6}alkoxy, halogen, nitro, halogenated C_{1-6}alkyl, halogenated C_{1-6}alkoxy, C_{1-6}alkylthio, C_{1-6}alkoxycarbonyl, amino, C_{1-6}alkylamino, di(C_{1-6}alkyl)amino, cyano, hydroxy, aminocarbonyl, C_{1-6}alkylaminocarbonyl, di(C_{1-6}alkyl)aminocarbonyl, C_{1-6}alkoxycarbonylamino, C_{1-6}alkylcarbonyl, C_{1-6}alkylthiocarbonyl, formyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, aminosulfonyl, C_{1-6}alkylaminosulfonyl, and di(C_{1-6}alkyl)aminosulfonyl;

L_1 is $-(CH_2)_r-$ or $-CH_2CH_2X(CH_2)_s-$, optionally substituted with one to three subsitutuents independently selected from the group consisting of C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, and halogen; provided that when A_1 is hydrogen, r is greater than or equal to 4;

r is an integer of 1 to 5;

s is an integer of 1 to 3;

X is O or S;

D is $-P-A_2$; wherein when A_2 is hydrogen, P is $-(CH_2)_{4-6}-$, and when A_2 is other than hydrogen, P is $-(CH_2)_{1-2}-$ or $-CH_2CH=CH-$;

A_2 is hydrogen; benzodioxalyl; heteroaryl other than unsubstituted pyridin-2-yl; C_{3-8}cycloalkyl; or phenyl optionally substituted at the meta and para positions with one to three substituents independently selected from the group consisting of C_{1-6}alkyl, C_{1-6}alkoxy, halogen, halogenated C_{1-6}alkyl, halogenated C_{1-6}alkoxy, aryl(C_{1-6})alkoxy, phenyl, C_{1-6}alkylthio, C_{1-6}alkoxycarbonyl, amino, C_{1-6}alkylamino, di(C_{1-6}alkyl)amino, cyano, hydroxy, nitro, C_{1-6}alkylcarbonyl, C_{1-6}alkylthiocarbonyl, aminocarbonyl, C_{1-6}alkylaminocarbonyl, di(C_{1-6}alkyl)aminocarbonyl, C_{1-6}alkylcarbonylamino, and a non fused C_{3-6}cycloalkyloxy; wherein benzodioxalyl, heteroaryl, and C_{3-8}cycloalkyl are optionally substituted with one to three substituents independently selected from the group consisting of C_{1-6}alkyl, C_{1-6}alkoxy, halogen, halogenated C_{1-6}alkyl, halogenated C_{1-6}alkoxy, aryl(C_{1-6})alkoxy, phenyl, C_{1-6}alkylthio, C_{1-6}alkoxycarbonyl, amino, C_{1-6}alkylamino, di(C_{1-6}-

$_6$alkyl)amino, cyano, hydroxy, nitro, C_{1-6}alkylcarbonyl, C_{1-6}alkylthiocarbonyl, aminocarbonyl, C_{1-6}alkylaminocarbonyl, di(C_{1-6}alkyl)aminocarbonyl, C_{1-6}alkylcarbonylamino, and a non fused C_{3-6}cycloalkyloxy;

provided that no more than two substituents on A_2 are aryl(C_{1-6})alkoxy, phenyl, or a non fused C_{3-6}cycloalkyloxy;

provided that when A_1 is unsubstituted phenyl and L_2 is $-X_1-CH(R^x)-(CR^yR^z)-$ wherein X_1 is NH, and R^x, R^y, and R^z are each hydrogen, A_2 is other than unsubstituted phenyl; phenyl substituted with aryl(C_{1-6})alkoxy or phenyl; or phenyl substituted at the meta position with cyano;

and, further provided that when A_1 is unsubstituted phenyl and L_2 is $-X_1-CH(R^x)-(CR^yR^z)_2-$ wherein X_1 is NH and R^x, R^y, and R^z are each hydrogen, A_2 is other than phenyl substituted with methoxy;

and, provided that when A_1 is 3,4-dichloro-phenyl and P is $-CH_2-$, A_2 is other than phenyl substituted at the meta position with trifluoromethyl or trifluoromethoxy;

and, further provided that when A_1 is 3,4-dichloro-phenyl and P is $-(CH_2)_2-$, A_2 is other than 4-methoxy-phenyl;

W is N or C(R_W); wherein R_W is H or C_{1-2}alkyl;

L_2 is a bivalent radical selected from the group consisting of

pyrrolidinyl or piperidinyl attached to the triazine ring of Formula (I) via its nitrogen atom, wherein said pyrrolidinyl or piperidinyl is substituted on a carbon atom with $-(CH_2)_{0-2}-$;

$-NH-C_{5-7}$cycloalkyl$-(CH_2)_{0-2}-$; such that when C_{5-7}cycloalkyl is cyclohexyl, Q is attached at either the 2- or cis-4-position relative to the position of –NH-;

$-X_1-(CH_2)_u-X_2-(CH_2)_v-$; wherein u is an integer of 1 to 3; and wherein v is an integer of 1 to 4; provided that when X_1 is a direct bond and W is C(R_W), then u is 1 and v is 2 to 4;

$-X_2-(CH_2)_{0-4}-$;

$-X_1-(CH_2)_{2-3}-X_3-(CH_2)_{2-3}-$;

$-NH(CH_2)_{1-4}C(=O)-$, provided that at least one of R^b, R^c, or R^d is other than hydrogen and m is 0;

$-NHC(=O)-(CH_2)_{1-4}-$;

$-C(=O)NH(CR^yR^z)_{2-5}-$;

and

$-X_1-CH(R^x)-(CR^yR^z)_{1-5}-$; such that when X_1 is a direct bond and W is $C(R_w)$, then R^x is hydrogen;

wherein X_1 is –NH-, O, S, or a direct bond, such that X_1 is other than O when W is N;

X_2 is –CH=CH-;

X_3 is O, S, NH, or C=O;

R^x, R^y, and R^z are independently H or C_{1-4}alkyl;

and provided that L_2 in any instance does not exceed 7 atoms in length;

and further provided that when L_2 is $-X_2-(CH_2)_{0-4}-$ or $-C(=O)NH(CR^yR^z)_{2-5}-$, then R_W is hydrogen;

Q is $-(O)_mN(R^a)-G$; and m is 0 or 1;

G is $-C(=NR^b)NR^cR^d$;

R^a and R^d are independently hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, or C_{3-6}alkynyl, wherein substituents of R^a and R^d other than hydrogen are optionally substituted with one to three substituents independently selected from the group consisting of hydroxy, C_{1-4}alkoxy, fluoro, amino, C_{1-4}alkylamino, diC_{1-4}alkylamino, and C_{1-4}alkylcarbonyl; or R^a and R^c are taken together with the atoms to which they are attached to form a 5-8 membered monocyclic ring optionally substituted with oxo;

R^b is hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-6}alkynyl, C_{2-6}alkoxycarbonyl, or cyano; or, R^b and R^c are taken together with the atoms to which they are attached to form a 5-8 membered monocyclic ring optionally substituted with oxo;

R^c is hydrogen, C_{1-10}alkyl, C_{2-10}alkenyl, C_{3-10}alkynyl, C_{3-7}cycloalkyl, adamantyl, amino, C_{1-6}alkylamino, di(C_{1-6}alkyl)amino, C_{1-6}alkylcarbonyl, C_{1-6}alkoxycarbonyl, arylcarbonyl, heteroarylcarbonyl, heterocyclylcarbonyl, aryl, heteroaryl, or

heterocyclyl; wherein C_{1-10}alkyl, C_{2-10}alkenyl, and C_{2-10}alkynyl are optionally substituted with one to three substituents independently selected from the group consisting of hydroxy, C_{1-6}alkoxy, trifluoromethyl, aryl, heteroaryl, and heterocyclyl; and wherein any aryl- or heteroaryl-containing substituents of R^c are optionally substituted with one to three substituents independently selected from the group consisting of C_{1-6}alkyl, C_{1-6}alkoxy, halogen, fluorinated C_{1-6}alkyl, fluorinated C_{1-6}alkoxy, C_{1-6}alkylcarbonyl, C_{1-6}alkoxycarbonyl, aminocarbonyl, C_{1-6}alkylaminocarbonyl, di(C_{1-6}alkyl)aminocarbonyl, C_{1-6}alkoxycarbonylamino, formyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, aminosulfonyl, C_{1-6}alkylaminosulfonyl, and di(C_{1-6}alkyl)aminosulfonyl, nitro, methylthio, hydroxy, and cyano; or, R^c and R^d are taken together with the atoms to which they are attached to form a 5-8 membered monocyclic ring that optionally includes 1 to 2 O or S heteroatoms within the ring, and said ring is optionally substituted with oxo;

with the proviso that in any instance, only one ring optionally exists between R^a and R^b, R^b and R^c, or R^c and R^d;

and enantiomers, diastereomers, tautomers, solvates, and pharmaceutically acceptable salts thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows a MALDI-TOF ANALYSIS of a Prokineticin-1 ligand preparation mixture. The mixture includes a four C-terminal residue truncated product (MW= 9172), and a full-length prokineticin-1 ligand (MW= 9668).

DETAILED DESCRIPTION OF THE INVENTION

As used herein, the following terms are intended to have the following meanings:

"C_{a-b}" (where *a* and *b* are integers) refers to a radical containing from *a* to *b* carbon atoms inclusive. For example, C_{1-3} denotes a radical containing 1, 2 or 3 carbon atoms.

With reference to substituents, the term "independently" means that when more than one of such substituent is possible, such substituents may be the same or different from each other. Therefore, designated numbers of carbon atoms (e.g. C_{1-8}) shall refer independently to the number of carbon atoms in an alkyl or cycloalkyl moiety or to the alkyl portion of a larger substituent in which alkyl appears as its prefix root.

As used herein, unless otherwise noted, "alkyl" whether used alone or as part of a substituent group refers to straight and branched carbon chains having 1 to 8 carbon atoms or any number within this range. The term "alkoxy" refers to an -Oalkyl substituent group, wherein alkyl is as defined supra. Similarly, the terms "alkenyl" and "alkynyl" refer to straight and branched carbon chains having 2 to 8 carbon atoms or any number within this range, wherein an alkenyl chain has at least one double bond in the chain and an alkynyl chain has at least one triple bond in the chain. An alkyl and alkoxy chain may be substituted on a carbon atom. In substituent groups with multiple alkyl groups such as $(C_{1-6}alkyl)_2amino$- the $C_{1-6}alkyl$ groups of the dialkylamino may be the same or different.

"Halogenated alkyl" refers to a saturated branched or straight chain alkyl radical derived by removal of 1 hydrogen atom from the parent alkyl; the parent alkyl chain contains from 1 to 8 carbon atoms with 1 or more hydrogen atoms substituted with halogen atoms up to and including substitution of all hydrogen atoms with

halogen. Preferred halogenated alkyl groups include include trifluoromethyl substituted alkyls and perfluorinated alkyls; more preferred fluorinated alkyls include trifluoromethyl.

"Halogenated alkoxy" refers to a radical derived from a halogenated alkyl, radical attached to an oxygen atom with the oxygen atom having one open valence for attachment to a parent structure.

The term "cycloalkyl" refers to saturated or partially unsaturated, moncyclic or polycyclic hydrocarbon rings of from 3 to 20 carbon atom members (preferably from 3 to 14 carbon atom members). Examples of such rings include, and are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or adamantyl. The term cycloalkyl includes a cycloalkyl ring fused to a benzene ring (benzo fused cycloalkyl), a 5 or 6 membered heteroaryl ring (containing one of O, S or N and, optionally, one additional nitrogen) to form a heteroaryl fused cycloalkyl.

The term "heterocyclyl" refers to a nonaromatic cyclic ring of 5 to 10 members in which 1 to 4 members are nitrogen or a nonaromatic cyclic ring of 5 to 10 members in which zero, one or two members are nitrogen and up to two members is oxygen or sulfur; wherein, optionally, the ring contains zero, one or two unsaturated bonds. The term heterocyclyl includes a heterocyclyl ring fused to a benzene ring (benzo fused heterocyclyl), a 5 or 6 membered heteroaryl ring (containing one of O, S or N and, optionally, one additional nitrogen), a 5 to 7 membered cycloalkyl or cycloalkenyl ring, a 5 to 7 membered heterocyclyl ring (of the same definition as above but absent the option of a further fused ring) or fused with the carbon of attachment of a cycloalkyl, cycloalkenyl or heterocyclyl ring to form a spiro moiety. For instant compounds of the invention, the carbon atom ring members that form the heterocyclyl ring are fully saturated. Other compounds of the invention may have a partially saturated heterocyclyl ring. Additionally, heterocyclyl includes a heterocyclic ring bridged to form

bicyclic rings. Preferred partially saturated heterocyclyl rings may have from one to two double bonds. Such compounds are not considered to be fully aromatic and are not referred to as heteroaryl compounds. Examples of heterocyclyl groups include, and are not limited to, pyrrolinyl (including 2*H*-pyrrole, 2-pyrrolinyl or 3-pyrrolinyl), pyrrolidinyl, 2-imidazolinyl, imidazolidinyl, 2-pyrazolinyl, pyrazolidinyl, piperidinyl, morpholinyl, thiomorpholinyl and piperazinyl.

The term "aryl" refers to an unsaturated, aromatic monocyclic ring of 6 carbon members or to an unsaturated, aromatic polycyclic ring of from 10 to 14 carbon members. Examples of such aryl rings include, and are not limited to, phenyl, naphthalenyl or anthracenyl. Preferred aryl groups for the practice of this invention are phenyl and naphthalenyl.

The term "heteroaryl" refers to an aromatic ring of 5 or 6 members wherein the ring consists of carbon atoms and has at least one heteroatom member. Suitable heteroatoms include nitrogen, oxygen or sulfur. In the case of 5 membered rings, the heteroaryl ring contains one member of nitrogen, oxygen or sulfur and, in addition, may contain up to three additional nitrogens. In the case of 6 membered rings, the heteroaryl ring may contain from one to three nitrogen atoms. For the case wherein the 6 membered ring has three nitrogens, at most two nitrogen atoms are adjacent. The term heteroaryl includes a heteroaryl ring fused to a benzene ring (benzo fused heteroaryl), a 5 or 6 membered heteroaryl ring (containing one of O, S or N and, optionally, one additional nitrogen), a 5 to 7 membered cycloalkyl ring or a 5 to 7 membered heterocyclic ring (as defined supra but absent the option of a further fused ring). Examples of heteroaryl groups include, and are not limited to, furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, thiadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl or pyrazinyl; fused heteroaryl groups include indolyl, isoindolyl, indolinyl, benzofuryl; benzothienyl, indazolyl, benzimidazolyl, benzthiazolyl, benzoxazolyl, benzisoxazolyl,

benzothiadiazolyl, benzotriazolyl, quinolizinyl, quinolinyl, isoquinolinyl or quinazolinyl.

The term "arylalkyl" means an alkyl group substituted with an aryl group (e.g., benzyl, phenethyl). Similarly, the term "arylalkoxy" indicates an alkoxy group substituted with an aryl group (e.g., benzyloxy).

The term "halogen" refers to fluorine, chlorine, bromine and iodine. Substituents that are substituted with multiple halogens are substituted in a manner that provides compounds, which are stable.

The term "oxo" whether used alone or as part of a substituent group refers to an O= to either a carbon or a sulfur atom. For example, phthalimide and saccharin are examples of compounds with oxo substituents.

Whenever the term "alkyl" or "aryl" or either of their prefix roots appear in a name of a substituent (*e.g.*, arylalkyl, alkylamino) it shall be interpreted as including those limitations given above for "alkyl" and "aryl." Designated numbers of carbon atoms (e.g., C_1-C_6) shall refer independently to the number of carbon atoms in an alkyl moiety or to the alkyl portion of a larger substituent in which alkyl appears as its prefix root. For alkyl, and alkoxy substituents the designated number of carbon atoms includes all of the independent member included in the range specified individually and all the combination of ranges within in the range specified. For example C_{1-6} alkyl would include methyl, ethyl, propyl, butyl, pentyl and hexyl individually as well as sub-combinations thereof (e.g. C_{1-2}, C_{1-3}, C_{1-4}, C_{1-5}, C_{2-6}, C_{3-6}, C_{4-6}, C_{5-6}, C_{2-5}, etc.).

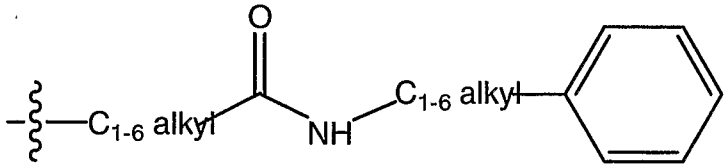
The term "subject" as used herein, refers to an animal, preferably a mammal, most preferably a human, who has been the object of treatment, observation or experiment.

The term "therapeutically effective amount" as used herein, means that amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician, which includes alleviation of the symptoms of the disease or disorder being treated.

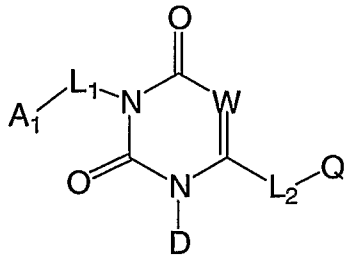
As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combinations of the specified ingredients in the specified amounts.

As used herein, the term "acyl" refers to alkylcarbonyl substituents.

Throughout this disclosure, the terminal portion of the designated side chain is described first, followed by the adjacent functionality toward the point of attachment. Thus, for example, a "phenylC_{1-6}alkylaminocarbonylC_{1-6}alkyl" substituent refers to a group of the formula



The present invention is directed to a compound of Formula (I):



Formula (I)

wherein:

A_1 is hydrogen; aryl; heteroaryl; C_{5-8}cycloalkyl; or heterocyclyl; provided that A_1 is other than piperidin-4-yl, *N*-t-butoxycarbonyl-piperidin-4-yl, or *N*-methyl-piperidin-3-yl; and wherein substituents of A_1 other than hydrogen are optionally substituted with one to three substituents independently selected from the group consisting of C_{1-6}alkyl, hydroxy(C_{1-6})alkyl, C_{1-6}alkoxy, halogen, nitro, halogenated C_{1-6}alkyl, halogenated C_{1-6}alkoxy, C_{1-6}alkylthio, C_{1-6}alkoxycarbonyl, amino, C_{1-6}alkylamino, di(C_{1-6}alkyl)amino, cyano, hydroxy, aminocarbonyl, C_{1-6}alkylaminocarbonyl, di(C_{1-6}alkyl)aminocarbonyl, C_{1-6}alkoxycarbonylamino, C_{1-6}alkylcarbonyl, C_{1-6}alkylthiocarbonyl, formyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, aminosulfonyl, C_{1-6}alkylaminosulfonyl, and di(C_{1-6}alkyl)aminosulfonyl;

L_1 is $-(CH_2)_r-$ or $-CH_2CH_2X(CH_2)_s-$, optionally substituted with one to three substituents independently selected from the group consisting of C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, and halogen; provided that when A_1 is hydrogen, r is greater than or equal to 4;

r is an integer of 1 to 5;

s is an integer of 1 to 3;

X is O or S;

D is $-P-A_2$; wherein when A_2 is hydrogen, P is $-(CH_2)_{4-6}-$, and when A_2 is other than hydrogen, P is $-(CH_2)_{1-2}-$ or $-CH_2CH=CH-$;

A_2 is hydrogen; benzodioxalyl; heteroaryl other than unsubstituted pyridin-2-yl; C_{3-8}cycloalkyl; or phenyl optionally substituted at the meta and para positions with one to three substituents independently selected from the group consisting of C_{1-6}alkyl, C_{1-6}alkoxy, halogen, halogenated C_{1-6}alkyl, halogenated C_{1-6}alkoxy, aryl(C_{1-6})alkoxy, phenyl, C_{1-6}alkylthio, C_{1-6}alkoxycarbonyl, amino, C_{1-6}alkylamino, di(C_{1-6}alkyl)amino, cyano, hydroxy, nitro, C_{1-6}alkylcarbonyl, C_{1-6}alkylthiocarbonyl, aminocarbonyl, C_{1-6}alkylaminocarbonyl, di(C_{1-6}alkyl)aminocarbonyl, C_{1-}

$_6$alkylcarbonylamino, and a non fused C_{3-6}cycloalkyloxy; wherein benzodioxalyl, heteroaryl, and C_{3-8}cycloalkyl are optionally substituted with one to three substituents independently selected from the group consisting of C_{1-6}alkyl, C_{1-6}alkoxy, halogen, halogenated C_{1-6}alkyl, halogenated C_{1-6}alkoxy, aryl(C_{1-6})alkoxy, phenyl, C_{1-6}alkylthio, C_{1-6}alkoxycarbonyl, amino, C_{1-6}alkylamino, di(C_{1-6}alkyl)amino, cyano, hydroxy, nitro, C_{1-6}alkylcarbonyl, C_{1-6}alkylthiocarbonyl, aminocarbonyl, C_{1-6}alkylaminocarbonyl, di(C_{1-6}alkyl)aminocarbonyl, C_{1-6}alkylcarbonylamino, and a non fused C_{3-6}cycloalkyloxy;

provided that no more than two substituents on A_2 are aryl(C_{1-6})alkoxy, phenyl, or a non fused C_{3-6}cycloalkyloxy;

provided that when A_1 is unsubstituted phenyl and L_2 is $-X_1-CH(R^x)-(CR^yR^z)-$ wherein X_1 is NH, and R^x, R^y, and R^z are each hydrogen, A_2 is other than unsubstituted phenyl; phenyl substituted with aryl(C_{1-6})alkoxy or phenyl; or phenyl substituted at the meta position with cyano;

and, further provided that when A_1 is unsubstituted phenyl and L_2 is $-X_1-CH(R^x)-(CR^yR^z)_2$ -- wherein X_1 is NH and R^x, R^y, and R^z are each hydrogen, A_2 is other than phenyl substituted with methoxy;

and, provided that when A_1 is 3,4-dichloro-phenyl and P is $-CH_2-$, A_2 is other than phenyl substituted at the meta position with trifluoromethyl or trifluoromethoxy;

and, further provided that when A_1 is 3,4-dichloro-phenyl and P is $-(CH_2)_2-$, A_2 is other than 4-methoxy-phenyl;

W is N or C(R_W); wherein R_W is H or C_{1-2}alkyl;

L_2 is a bivalent radical selected from the group consisting of

pyrrolidinyl or piperidinyl attached to the triazine ring of Formula (I) via its nitrogen atom, wherein said pyrrolidinyl or piperidinyl is substituted on a carbon atom with $-(CH_2)_{0-2}-$;

$-NH-C_{5-7}$cycloalkyl$-(CH_2)_{0-2}-$; such that when C_{5-7}cycloalkyl is cyclohexyl, Q is attached at either the 2- or cis-4-position relative to the position of –NH-;

$-X_1-(CH_2)_u-X_2-(CH_2)_v-$; wherein u is an integer of 1 to 3; and wherein v is an integer of 1 to 4; provided that when X_1 is a direct bond and W is $C(R_w)$, then u is 1 and v is 2 to 4;

$-X_2-(CH_2)_{0-4}-$;

$-X_1-(CH_2)_{2-3}-X_3-(CH_2)_{2-3}-$;

$-NH(CH_2)_{1-4}C(=O)-$, provided that at least one of R^b, R^c, or R^d is other than hydrogen and m is 0;

$-NHC(=O)-(CH_2)_{1-4}-$;

$-C(=O)NH(CR^yR^z)_{2-5}-$;

and

$-X_1-CH(R^x)-(CR^yR^z)_{1-5}-$; such that when X_1 is a direct bond and W is $C(R_w)$, then R^x is hydrogen;

wherein X_1 is –NH-, O, S, or a direct bond, such that X_1 is other than O when W is N;

X_2 is –CH=CH-;

X_3 is O, S, NH, or C=O;

R^x, R^y, and R^z are independently H or C_{1-4}alkyl;

and provided that L_2 in any instance does not exceed 7 atoms in length; and further provided that when L_2 is $-X_2-(CH_2)_{0-4}-$ or $-C(=O)NH(CR^yR^z)_{2-5}-$, then R_W of W is hydrogen;

Q is $-(O)_mN(R^a)-G$; and m is 0 or 1;

G is $-C(=NR^b)NR^cR^d$;

R^a and R^d are independently hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, or C_{3-6}alkynyl, wherein substituents of R^a and R^d other than hydrogen are optionally substituted with one to three substituents independently selected from the group consisting of hydroxy, C_{1-4}alkoxy, fluoro, amino, C_{1-4}alkylamino, diC_{1-4}alkylamino, and C_{1-4}alkylcarbonyl; or R^a and R^c are taken together with the atoms to which they are attached to form a 5-8 membered monocyclic ring optionally substituted with oxo;

R^b is hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-6}alkynyl, C_{2-6}alkoxycarbonyl, or cyano; or, R^b and R^c are taken together with the atoms to which they are attached to form a 5-8 membered monocyclic ring optionally substituted with oxo;

R^c is hydrogen, C_{1-10}alkyl, C_{2-10}alkenyl, C_{3-10}alkynyl, C_{3-7}cycloalkyl, adamantyl, amino, C_{1-6}alkylamino, di(C_{1-6}alkyl)amino, C_{1-6}alkylcarbonyl, C_{1-6}alkoxycarbonyl, arylcarbonyl, heteroarylcarbonyl, heterocyclylcarbonyl, aryl, heteroaryl, or heterocyclyl; wherein C_{1-10}alkyl, C_{2-10}alkenyl, and C_{2-10}alkynyl are optionally substituted with one to three substituents independently selected from the group consisting of hydroxy, C_{1-6}alkoxy, trifluoromethyl, aryl, heteroaryl, and heterocyclyl; and wherein any aryl- or heteroaryl-containing substituents of R^c are optionally substituted with one to three substituents independently selected from the group consisting of C_{1-6}alkyl, C_{1-6}alkoxy, halogen, fluorinated C_{1-6}alkyl, fluorinated C_{1-6}alkoxy, C_{1-6}alkylcarbonyl, C_{1-6}alkoxycarbonyl, aminocarbonyl, C_{1-6}alkylaminocarbonyl, di(C_{1-6}alkyl)aminocarbonyl, C_{1-6}alkoxycarbonylamino, formyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, aminosulfonyl, C_{1-6}alkylaminosulfonyl, and di(C_{1-6}alkyl)aminosulfonyl, nitro, methylthio, hydroxy, and cyano; or, R^c and R^d are taken together with the atoms to which they are attached to form a 5-8 membered monocyclic ring that optionally includes 1 to 2 O or S heteroatoms within the ring, and said ring is optionally substituted with oxo;

with the proviso that in any instance, only one ring optionally exists between R^a and R^b, R^b and R^c, or R^c and R^d;

and further provided that a compound of Formula (I) is other than a compound wherein A_1 is phenyl, L is -CH_2-, D is -CH_2-(4-methoxy-phenyl), W is N, L_2 is -$NH(CH_2)_2$-, and Q is -$NHC(=NH)NH_2$.

and enantiomers, diastereomers, tautomers, solvates, and pharmaceutically acceptable salts thereof.

Embodiments of the present invention include compounds of Formula (I) wherein:

a) A_1 is hydrogen; aryl; heteroaryl; or C_{5-8}cycloalkyl; wherein substituents of A_1 other than hydrogen are optionally substituted with one to three substituents independently selected from the group consisting of C_{1-6}alkyl, hydroxy(C_{1-6})alkyl, C_{1-6}alkoxy, halogen, nitro, halogenated C_{1-6}alkyl, halogenated C_{1-6}alkoxy, C_{1-6}alkylthio, C_{1-6}alkoxycarbonyl, amino, C_{1-6}alkylamino, di(C_{1-6}alkyl)amino, cyano, hydroxy, aminocarbonyl, C_{1-6}alkylaminocarbonyl, di(C_{1-6}alkyl)aminocarbonyl, C_{1-6}alkoxycarbonylamino, C_{1-6}alkylcarbonyl, C_{1-6}alkylthiocarbonyl, formyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, aminosulfonyl, C_{1-6}alkylaminosulfonyl, and di(C_{1-6}alkyl)aminosulfonyl;

b) A_1 is hydrogen; aryl; heteroaryl; C_{5-8}cycloalkyl; or heterocyclyl; provided that A_1 is other than piperidin-4-yl, *N*-t-butoxycarbonyl-piperidin-4-yl, or *N*-methyl-piperidin-3-yl; and wherein substituents of A_1 other than hydrogen are optionally substituted with one to three substituents independently selected from the group consisting of C_{1-6}alkyl, hydroxy(C_{1-6})alkyl, C_{1-6}alkoxy, halogen, nitro, halogenated C_{1-6}alkyl, halogenated C_{1-6}alkoxy, C_{1-6}alkylthio, C_{1-6}alkoxycarbonyl, amino, cyano, hydroxy, aminocarbonyl, C_{1-6}alkylaminocarbonyl, di(C_{1-6}alkyl)aminocarbonyl, and C_{1-6}alkylcarbonyl;

c) A_1 is hydrogen; aryl; heteroaryl; C_{5-8}cycloalkyl; or heterocyclyl other than piperidinyl; wherein substituents of A_1 other than hydrogen are optionally substituted with one to three substituents independently selected from the group consisting of C_{1-6}alkyl, hydroxy(C_{1-6})alkyl, C_{1-6}alkoxy, halogen, nitro, halogenated C_{1-6}alkyl, halogenated C_{1-6}alkoxy, C_{1-6}alkylthio, C_{1-6}alkoxycarbonyl, amino,

cyano, hydroxy, aminocarbonyl, C_{1-6}alkylaminocarbonyl, di(C_{1-6}alkyl)aminocarbonyl, and C_{1-6}alkylcarbonyl;

d) A_1 is hydrogen, substituted phenyl, benzofuranyl, furanyl, thiazolyl, thiophenyl, or cyclopentyl; wherein substituents of A_1 other than hydrogen are optionally substituted and phenyl is substituted with one to two substituents independently selected from the group consisting of C_{1-4}alkyl, C_{1-4}alkoxy, halogen, nitro, halogenated C_{1-4}alkyl, halogenated C_{1-4}alkoxy, methylthio, C_{1-4}alkoxycarbonyl, amino, cyano, hydroxy, aminocarbonyl, and C_{1-4}alkylcarbonyl;

e) A_1 is substituted phenyl, benzofuranyl, thiazolyl, or thiophenyl; wherein phenyl is substituted with, and benzofuranyl, thiazolyl, and thiophenyl are optionally substituted with one to two substituents independently selected from the group consisting of C_{1-4}alkyl, C_{1-4}alkoxy, halogen, nitro, halogenated C_{1-4}alkyl, halogenated C_{1-4}alkoxy, methylthio, amino, cyano, and C_{1-4}alkylcarbonyl;

f) A_1 is phenyl or benzofuranyl; wherein phenyl is substituted at either the para-position or meta and para-positions with one to two substituents independently selected from the group consisting of ethyl, methoxy, fluoro, chloro, nitro, difluoromethoxy, and methylthio;

g) L_1 is $-(CH_2)_r-$, optionally substituted with one to three substituents independently selected from the group consisting of C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, and halogen; provided that when A_1 is hydrogen, r is greater than or equal to 4;

h) L_1 is $-(CH_2)_r-$, optionally substituted with a substituent selected from the group consisting of C_{1-4}alkyl, C_{2-4}alkenyl, and C_{2-4}alkynyl, provided that r is 1 to 3 when A_1 is other than hydrogen; or r is greater than or equal to 4 when A_1 is hydrogen;

i) L_1 is $-(CH_2)_r-$ optionally substituted with a substituent selected from the group consisting of methyl and allyl, provided that r is 1 to 3 when A_1 is other than hydrogen;

j) L_1 is $-CH_2-$ optionally substituted with methyl or allyl;

k) P is $-CH_2-$

l) A_2 is hydrogen, heteroaryl other than unsubstituted pyridin-2-yl, C_{3-8}cycloalkyl, or phenyl optionally substituted at the meta and para positions with one to three substituents independently selected from the group consisting of C_{1-6}alkyl, C_{1-6}alkoxy, halogen, halogenated C_{1-6}alkyl, halogenated C_{1-6}alkoxy, aryl(C_{1-6})alkoxy, phenyl, C_{1-6}alkylthio, C_{1-6}alkoxycarbonyl, amino, cyano, hydroxy, nitro, aminocarbonyl, C_{1-6}alkylcarbonylamino, and a non fused C_{3-6}cycloalkyloxy; wherein heteroaryl other than unsubstituted pyridin-2-yl and C_{3-8}cycloalkyl are optionally substituted with one to three substituents independently selected from the group consisting of C_{1-6}alkyl, C_{1-6}alkoxy, halogen, halogenated C_{1-6}alkyl, halogenated C_{1-6}alkoxy, aryl(C_{1-6})alkoxy, phenyl, C_{1-6}alkylthio, C_{1-6}alkoxycarbonyl, amino, cyano, hydroxy, nitro, aminocarbonyl, C_{1-6}alkylcarbonylamino, and a non fused C_{3-6}cycloalkyloxy;

provided that no more than two substituents on A_2 are aryl(C_{1-6})alkoxy, phenyl, or a non fused C_{3-6}cycloalkyloxy;

provided that when A_1 is unsubstituted phenyl and L_2 is $-X_1-CH(R^x)-(CR^yR^z)-$ wherein X_1 is NH and R^x, R^y, and R^z are each hydrogen, A_2 is other than unsubstituted phenyl; phenyl substituted with aryl(C_{1-6})alkoxy or phenyl; or phenyl substituted at the meta position with cyano;

and, further provided that when A_1 is unsubstituted phenyl and L_2 is $-X_1-CH(R^x)-(CR^yR^z)_2-$ wherein X_1 is NH and R^x, R^y, and R^z are each hydrogen, A_2 is other than phenyl substituted with methoxy;

and, provided that when A_1 is 3,4-dichloro-phenyl and P is $-CH_2-$, A_2 is other than phenyl substituted at the meta position with trifluoromethyl or trifluoromethoxy;

and, further provided that when A_1 is 3,4-dichloro-phenyl and P is $-(CH_2)_2-$, A_2 is other than 4-methoxy-phenyl;

in addition, when A_2 is hydrogen, P is $-(CH_2)_{4-6}-$, and when A_2 is other than hydrogen, P is $-(CH_2)_{1-2}-$ or $-CH_2CH=CH-$;

m) A_2 is heteroaryl other than unsubstituted pyridin-2-yl, a non fused C_{3-8}cycloalkyl, or phenyl optionally substituted at the meta and para positions with one to three substituents independently selected from the group consisting of C_{1-6}alkyl, C_{1-6}alkoxy, halogen, halogenated C_{1-6}alkyl, halogenated C_{1-6}alkoxy, C_{1-6}alkylthio, C_{1-6}alkoxycarbonyl, amino, hydroxy, nitro, aminocarbonyl, C_{1-6}alkylcarbonylamino, and a non fused C_{3-6}cycloalkyloxy; wherein heteroaryl other than unsubstituted pyridin-2-yl and a non fused C_{3-8}cycloalkyl are optionally substituted with one to three substituents independently selected from the group consisting of C_{1-6}alkyl, C_{1-6}alkoxy, halogen, halogenated C_{1-6}alkyl, halogenated C_{1-6}alkoxy, C_{1-6}alkylthio, C_{1-6}alkoxycarbonyl, amino, hydroxy, nitro, aminocarbonyl, C_{1-6}alkylcarbonylamino, and a non fused C_{3-6}cycloalkyloxy; provided that no more than two substituents on A_2 are non fused C_{3-6}cycloalkyloxy;

provided that when A_1 is unsubstituted phenyl and L_2 is $-X_1-CH(R^x)-(CR^yR^z)-$ wherein X_1 is NH and R^x, R^y, and R^z are each hydrogen, A_2 is other than unsubstituted phenyl;

and, further provided that when A_1 is unsubstituted phenyl and L_2 is $-X_1-CH(R^x)-(CR^yR^z)_2-$ wherein X_1 is NH and R^x, R^y, and R^z are each hydrogen, A_2 is other than phenyl substituted with methoxy;

and, provided that when A_1 is 3,4-dichloro-phenyl, A_2 is other than phenyl substituted at the meta position with trifluoromethyl or trifluoromethoxy;

and, further provided that when A_1 is 3,4-dichloro-phenyl and P is $-(CH_2)_2-$, A_2 is other than 4-methoxy-phenyl;

n) A_2 is furanyl, pyridin-3-yl, pyridin-4-yl, or phenyl optionally substituted at the meta and para positions with one to three substituents independently selected from the group consisting of C_{1-4}alkyl, C_{1-4}alkoxy, halogen, halogenated C_{1-3}alkoxy, C_{1-3}alkylthio, hydroxy, amino, aminocarbonyl, C_{1-3}alkylcarbonylamino, and a non fused C_{3-6}cycloalkyloxy; and wherein furanyl, pyridin-3-yl, and pyridin-4-yl are optionally substituted with one to three substituents independently selected from

the group consisting of C_{1-4}alkyl, C_{1-4}alkoxy, halogen, halogenated C_{1-3}alkoxy, C_{1-3}alkylthio, hydroxy, amino, aminocarbonyl, C_{1-3}alkylcarbonylamino, and a non fused C_{3-6}cycloalkyloxy;

provided that no more than two substituents on A_2 are non fused C_{3-6}cycloalkyloxy;

provided that when A_1 is unsubstituted phenyl and L_2 is $-X_1-CH(R^x)-(CR^yR^z)-$ wherein X_1 is NH and R^x, R^y, and R^z are each hydrogen, A_2 is other than unsubstituted phenyl;

and, further provided that when A_1 is unsubstituted phenyl and L_2 is $-X_1-CH(R^x)-(CR^yR^z)_2-$ wherein X_1 is NH and R^x, R^y, and R^z are each hydrogen, A_2 is other than phenyl substituted with methoxy;

and, provided that when A_1 is 3,4-dichloro-phenyl, A_2 is other than phenyl substituted in the meta position with trifluoromethoxy;

o) A_2 is pyridin-3-yl pyridin-4-yl, or phenyl optionally substituted at the meta and para positions with one to two substituents independently selected from the group consisting of methyl, ethyl, methoxy, ethoxy, isopropyloxy, trifluoromethoxy, difluoromethoxy, hydroxy, aminocarbonyl, and methylcarbonylamino; wherein pyridin-3-yl and pyridin-4-yl are optionally substituted with one to two substituents independently selected from the group consisting of methyl, ethyl, methoxy, ethoxy, isopropyloxy, trifluoromethoxy, difluoromethoxy, hydroxy, aminocarbonyl, and methylcarbonylamino;

provided that when A_1 is unsubstituted phenyl and L_2 is $-X_1-CH(R^x)-(CR^yR^z)-$ wherein X_1 is NH and R^x, R^y, and R^z are each hydrogen, A_2 is other than unsubstituted phenyl;

and, further provided that when A_1 is unsubstituted phenyl and L_2 is $-X_1-CH(R^x)-(CR^yR^z)_2-$ wherein X_1 is NH and R^x, R^y, and R^z are each hydrogen, A_2 is other than phenyl substituted with methoxy;

and, provided that when A_1 is 3,4-dichloro-phenyl, A_2 is other than phenyl substituted in the meta position with trifluoromethoxy;

p) A_2 is phenyl substituted at the para position with a substituent selected from the group consisting of methoxy, ethoxy, isopropyloxy, difluoromethoxy, hydroxy, and aminocarbonyl; or A_2 is pyridin-3-yl or pyridin-4-yl substituted with methoxy;

q) W is N or $C(R_w)$ wherein R_w is H;

r) L_2 is a bivalent radical selected from the group consisting of

$-NH-C_{5-7}$cycloalkyl$-(CH_2)_{0-2}-$; provided that when C_{5-7}cycloalkyl is cyclohexyl, Q is attached at either the 2- or cis-4-position relative to the position of –NH-;

$-X_2-(CH_2)_{0-4}-$;

$-X_1-(CH_2)_{2-3}-X_3-(CH_2)_{2-3}-$;

$-NH(CH_2)_{1-4}C(=O)-$ provided that at least one of R^b, R^c, or R^d is not hydrogen and m is 0;

$-NHC(=O)-(CH_2)_{1-4}-$;

$-C(=O)NH(CR^yR^z)_{2-5}-$;

and

$-X_1-CH(R^x)-(CR^yR^z)_{1-5}-$; such that when X_1 is a direct bond and W is $C(R_w)$, then R^x of $CH(R^x)$ is hydrogen;

wherein X_1 is –NH-, O, S, or a direct bond; such that X_1 is other than O when W is N;

X_2 is –CH=CH-;

X_3 is O, S, NH, or C=O;

R^x, R^y, and R^z are independently H or C_{1-4}alkyl;

and provided that L_2 in any instance does not exceed 7 atoms in length; and further provided that when L_2 is $-X_2-(CH_2)_{0-4}-$ or $-C(=O)NH(CR^yR^z)_{2-5}-$, then R_W is hydrogen;

s) L_2 is a bivalent radical selected from the group consisting of

$-NH-C_{5-6}$cycloalkyl$-(CH_2)_{0-2}-$; provided that when C_{5-6}cycloalkyl is cyclohexyl, Q is attached at either the 2- or cis-4-position relative to the position of –NH-;

$-X_1-CH(R^x)-(CR^yR^z)_{1-5}-$, wherein X_1 is -NH–, O, or S and R^x, R^y, and R^z are each hydrogen; such that X_1 is other than O when W is N;

-C(=O)NH(CH_2)$_2$-;

and

-X_1-(*R,R*-CH(R^x)CR^y(R^z))-; wherein X_1 is -NH–, and R^x and R^z are methyl, and R^y is hydrogen;

provided that when L_2 is -C(=O)NH(CH_2)$_2$-, then R_W is hydrogen

t) L_2 is a bivalent radical selected from the group consisting of

-NH-cyclohexyl–(CH_2)$_{0-2}$– and Q is attached at either the 2- or cis-4-position relative to the position of –NH-;

-X_1-CH(R^x)-(C$R^y R^z$)$_{1-5}$-; wherein X_1 is –NH- or S; and R^x, R^y, and R^z are each hydrogen;

and

-X_1-(*R,R*-CH(R^x)CR^y(R^z))-; wherein X_1 is -NH–, and R^x and R^z are methyl, and R^y is hydrogen;

u) L_2 is a bivalent radical selected from the group consisting of

-NH-cyclohexyl–(CH_2)$_{0-2}$– and Q is attached at either the 2- or cis-4-position relative to the position of –NH-;

-X_1-CH(R^x)-(C$R^y R^z$)-; wherein X_1 is -NH– or S and R^x, R^y, and R^z are each hydrogen;

and

- X_1-(*R,R*-CH(R^x)CR^y(R^z))-; wherein X_1 is -NH–, R^x and R^z are methyl, and R^y is hydrogen;

v) m is 0;

w) R^a and R^d are independently hydrogen or C_{1-6}alkyl, wherein C_{1-6}alkyl is optionally substituted with one to three substituents independently selected from the group consisting of hydroxy, C_{1-4}alkoxy, fluoro, amino, C_{1-4}alkylamino, diC_{1-4}alkylamino, and C_{1-4}alkylcarbonyl; or R^a and R^c are taken together with the atoms to which they are attached to form a 5-8 membered monocyclic ring optionally substituted with oxo;

x) R^a and R^d are independently hydrogen or C_{1-3}alkyl, wherein C_{1-3}alkyl is optionally substituted with one to three substituents independently selected from the group consisting of hydroxy, C_{1-4}alkoxy, fluoro, amino, C_{1-4}alkylamino, diC_{1-4}alkylamino, and C_{1-4}alkylcarbonyl; or R^a and R^c are taken together with the atoms to which they are attached to form a 5-8 membered monocyclic ring optionally substituted with oxo;

y) R^a and R^d are independently hydrogen, methyl or ethyl; or R^a and R^c are taken together with the atoms to which they are attached to form a 5-8 membered monocyclic ring optionally substituted with oxo;

z) R^a and R^d are independently hydrogen, methyl or ethyl;

aa) R^b is hydrogen, C_{1-6}alkyl, C_{2-6}alkoxycarbonyl, or cyano; or, R^b and R^c are taken together with the atoms to which they are attached to form a 5-8 membered monocyclic ring, optionally substituted with oxo;

bb) R^b is hydrogen or C_{1-4}alkyl; or, R^b and R^c are taken together with the atoms to which they are attached to form a 5-8 membered monocyclic ring, optionally substituted with oxo;

cc) R^b is hydrogen

dd) R^c is hydrogen, C_{1-10}alkyl, C_{2-10}alkenyl, C_{3-7}cycloalkyl, adamantyl, amino, arylcarbonyl, aryl, heteroaryl, or heterocyclyl; wherein C_{1-10}alkyl is optionally substituted with one to two substituents independently selected from the group consisting of C_{1-4}alkoxy, trifluoromethyl, aryl, heteroaryl, and heterocyclyl; and wherein any aryl- or heteroaryl-containing substituents of R^c are optionally substituted with one to three substituents independently selected from the group consisting of C_{1-6}alkyl, C_{1-6}alkoxy, halogen, fluorinated C_{1-6}alkyl, fluorinated C_{1-6}alkoxy, C_{1-6}alkylcarbonyl, C_{1-6}alkoxycarbonyl, nitro, methylthio, hydroxy, and cyano; or, R^c and R^d are taken together with the atoms to which they are attached to form a 5-8 membered monocyclic ring that optionally includes 1 to 2 O or S heteroatoms within the ring, and said ring is optionally substituted with oxo;

ee) R^c is hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-7}cycloalkyl, adamantyl, heterocyclyl, arylcarbonyl, phenyl, or heteroaryl; wherein C_{1-6}alkyl is optionally substituted with one to two substituents independently selected from the group consisting of C_{1-3}alkoxy, trifluoromethyl, phenyl, heteroaryl, and heterocyclyl; and wherein any aryl-, phenyl-, or heteroaryl-containing substituents of R^c are optionally substituted with one to three substituents independently selected from the group consisting of C_{1-6}alkyl, C_{1-6}alkoxy, halogen, fluorinated C_{1-6}alkyl, fluorinated C_{1-6}alkoxy, C_{1-6}alkylcarbonyl, C_{1-6}alkoxycarbonyl, nitro, methylthio, hydroxy, and cyano; or, R^c and R^d are taken together with the atoms to which they are attached to form a 5-8 membered monocyclic ring and said ring is optionally substituted with oxo;

ff) R^c is hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-7}cycloalkyl, heterocyclyl, phenylcarbonyl, phenyl, or heteroaryl; wherein C_{1-6}alkyl is optionally substituted with one to two substituents independently selected from the group consisting of C_{1-3}alkoxy, phenyl, pyridinyl, furanyl, and tetrahydrofuranyl; and wherein any phenyl- or heteroaryl-containing substituents of R^c are optionally substituted with one to two substituents independently selected from the group consisting of C_{1-6}alkyl, C_{1-6}alkoxy, chloro, fluoro, bromo, fluorinated C_{1-3}alkoxy, nitro, methylthio, hydroxy, and cyano; or, R^c and R^d are taken together with the atoms to which they are attached to form a 5-8 membered monocyclic ring;

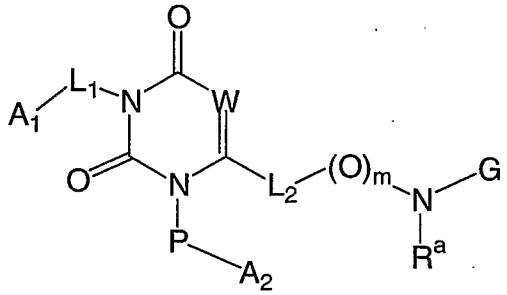
gg) R^c is hydrogen, C_{1-4}alkyl, C_{2-4}alkenyl, cyclohexyl, phenylcarbonyl, phenyl, pyrimidinyl, furanyl, benzo[1,3]dioxolyl, or pyridinyl; wherein C_{1-4}alkyl is optionally substituted with one to two substituents independently selected from the group consisting of C_{1-3}alkoxy, phenyl, pyridinyl, furanyl, and tetrahydrofuranyl; and wherein any phenyl- or heteroaryl-containing substituents of R^c are optionally substituted with one to two substituents independently selected from the group consisting of C_{1-6}alkyl, C_{1-6}alkoxy, chloro, fluoro, bromo, fluorinated C_{1-3}alkoxy, nitro, methylthio, hydroxy, and cyano; or, R^c and R^d are taken together with the atoms to which they are attached to form a 5-8 membered monocyclic ring;

hh) R^c is hydrogen, C_{1-4}alkyl, C_{2-4}alkenyl, cyclohexyl, phenylcarbonyl, phenyl, pyrimidinyl, furanyl, benzo[1,3]dioxolyl, or pyridinyl; wherein C_{1-4}alkyl is optionally substituted with one to two substituents independently selected from the group consisting of methoxy, phenyl, pyridinyl, furanyl, and tetrahydrofuranyl; and wherein any phenyl- or heteroaryl-containing substituents of R^c are optionally substituted with one to two substituents independently selected from the group consisting of C_{1-3}alkyl, C_{1-3}alkoxy, chloro, fluoro, bromo, trifluoromethoxy, nitro, hydroxy, and cyano; or, R^c and R^d are taken together with the atoms to which they are attached to form a 5-6 membered monocyclic ring;

with the proviso that in any instance, only one ring optionally exists between R^a and R^b, R^b and R^c, or R^c and R^d;

and combinations of a) through hh) above.

One aspect of the present invention is directed to compositions comprising a compound of Formula (Ia):



Formula (Ia)

wherein:

A_1 is hydrogen; aryl; heteroaryl; C_{5-8}cycloalkyl; or heterocyclyl provided that A_1 is other than piperidin-4-yl, *N*-t-butoxycarbonyl-piperidin-4-yl, or *N*-methyl-piperidin-3-yl; and wherein substituents of A_1 other than hydrogen are optionally substituted with one to three substituents independently selected from the group consisting of C_{1-6}alkyl, hydroxy(C_{1-6})alkyl, C_{1-6}alkoxy, halogen, nitro, halogenated C_{1-6}alkyl, halogenated C_{1-6}alkoxy, C_{1-6}alkylthio, C_{1-6}alkoxycarbonyl, amino,

cyano, hydroxy, aminocarbonyl, C_{1-6}alkylaminocarbonyl, di(C_{1-6}alkyl)aminocarbonyl, and C_{1-6}alkylcarbonyl;

L_1 is $-(CH_2)_r-$ optionally substituted with one to three substituents independently selected from the group consisting of C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, and halogen; provided that when A_1 is hydrogen, r is greater than or equal to 4;

r is an integer of 1 to 5;

P is $-(CH_2)_{4-6}-$ when A_2 is hydrogen; and P is $-(CH_2)_{1-2}-$ or $-CH_2CH=CH-$ when A_2 is other than hydrogen;

A_2 is hydrogen, heteroaryl other than unsubstituted pyridin-2-yl, C_{3-8}cycloalkyl, or phenyl optionally substituted at the meta and para positions with one to three substituents independently selected from the group consisting of C_{1-6}alkyl, C_{1-6}alkoxy, halogen, halogenated C_{1-6}alkyl, halogenated C_{1-6}alkoxy, aryl(C_{1-6})alkoxy, phenyl, C_{1-6}alkylthio, C_{1-6}alkoxycarbonyl, amino, cyano, hydroxy, nitro, aminocarbonyl, C_{1-6}alkylcarbonylamino, and a non fused C_{3-6}cycloalkyloxy; wherein heteroaryl other than unsubstituted pyridin-2-yl and C_{3-8}cycloalkyl are optionally substituted with one to three substituents independently selected from the group consisting of C_{1-6}alkyl, C_{1-6}alkoxy, halogen, halogenated C_{1-6}alkyl, halogenated C_{1-6}alkoxy, aryl(C_{1-6})alkoxy, phenyl, C_{1-6}alkylthio, C_{1-6}alkoxycarbonyl, amino, cyano, hydroxy, nitro, aminocarbonyl, C_{1-6}alkylcarbonylamino, and a non fused C_{3-6}cycloalkyloxy;

provided that no more than two substituents on A_2 are aryl(C_{1-6})alkoxy, phenyl, or a non fused C_{3-6}cycloalkyloxy;

provided that when A_1 is unsubstituted phenyl and L_2 is $-X_1-CH(R^x)-(CR^yR^z)-$ wherein X_1 is NH, and R^x, R^y, and R^z are each hydrogen, A_2 is other than unsubstituted phenyl; phenyl substituted with aryl(C_{1-6})alkoxy or phenyl; or phenyl substituted at the meta position with cyano;

and, further provided that when A_1 is unsubstituted phenyl and L_2 is $-X_1-CH(R^x)-(CR^yR^z)_2-$, wherein X_1 is NH and R^x, R^y, and R^z are each hydrogen, A_2 is other than phenyl substituted with methoxy;

and, provided that when A_1 is 3,4-dichloro-phenyl and P is $-CH_2-$, A_2 is other than phenyl substituted in the meta position with trifluoromethyl or trifluoromethoxy

and, further provided that when A_1 is 3,4-dichloro-phenyl and P is $-(CH_2)_2-$, A_2 is other than 4-methoxy-phenyl;

W is N or CH;

L_2 is a bivalent radical selected from the group consisting of

$-NH-C_{5-7}$cycloalkyl$-(CH_2)_{0-2}-$; provided that when C_{5-7}cycloalkyl is cyclohexyl, Q is attached at either the 2- or cis-4-position relative to the position of –NH-;

$-X_2-(CH_2)_{0-4}-$;

$-X_1-(CH_2)_{2-3}-X_3-(CH_2)_{2-3}-$;

$-NH(CH_2)_{1-4}C(=O)-$ provided that at least one of R^b, R^c, or R^d is not hydrogen and m is 0;

$-NHC(=O)-(CH_2)_{1-4}-$;

$-C(=O)NH(CR^yR^z)_{2-5}-$;

and

$-X_1-CH(R^x)-(CR^yR^z)_{1-5}-$; such that when X_1 is a direct bond and W is $C(R_w)$, then R^x of $CH(R^x)$ is hydrogen;

wherein X_1 is –NH-, O, S, or a direct bond; such that X_1 is other than O when W is N;

X_2 is –CH=CH-;

X_3 is O, S, NH, or C=O;

R^x, R^y, and R^z are independently H or C_{1-4}alkyl;

and provided that L_2 in any instance does not exceed 7 atoms in length;

and further provided that when L_2 is $-X_2-(CH_2)_{0-4}-$ or $-C(=O)NH(CR^yR^z)_{2-5}-$, then R_W is hydrogen;

m is 0 or 1;

G is $-C(=NR^b)NR^cR^d$;

R^a and R^d are independently hydrogen or C_{1-6}alkyl, wherein C_{1-6}alkyl is optionally substituted with one to three substituents independently selected from the group

consisting of hydroxy, C_{1-4}alkoxy, fluoro, amino, C_{1-4}alkylamino, diC_{1-4}alkylamino, and C_{1-4}alkylcarbonyl; or R^a and R^c are taken together with the atoms to which they are attached to form a 5-8 membered monocyclic ring optionally substituted with oxo;

R^b is hydrogen, C_{1-6}alkyl, C_{2-6}alkoxycarbonyl, or cyano; or, R^b and R^c are taken together with the atoms to which they are attached to form a 5-8 membered monocyclic ring optionally substituted with oxo;

R^c is hydrogen, C_{1-10}alkyl, C_{2-10}alkenyl, C_{3-7}cycloalkyl, adamantyl, amino, arylcarbonyl, aryl, heteroaryl, or heterocyclyl; wherein C_{1-10}alkyl is optionally substituted with one to two substituents independently selected from the group consisting of C_{1-4}alkoxy, trifluoromethyl, aryl, heteroaryl, and heterocyclyl; and wherein any aryl- or heteroaryl-containing substituents of R^c are optionally substituted with one to three substituents independently selected from the group consisting of C_{1-6}alkyl, C_{1-6}alkoxy, halogen, fluorinated C_{1-6}alkyl, fluorinated C_{1-6}alkoxy, C_{1-6}alkylcarbonyl, C_{1-6}alkoxycarbonyl, nitro, methylthio, hydroxy, and cyano; or, R^c and R^d are taken together with the atoms to which they are attached to form a 5-8 membered monocyclic ring that optionally includes 1 to 2 O or S heteroatoms within the ring, and said ring is optionally substituted with oxo;

with the proviso that in any instance, only one ring optionally exists between R^a and R^b, R^b and R^c, or R^c and R^d;

and enantiomers, diastereomers, tautomers, solvates, and pharmaceutically acceptable salts thereof.

A further aspect of the present invention is directed to a compound of Formula Ia wherein:

A_1 is hydrogen; aryl; heteroaryl; C_{5-8}cycloalkyl; or heterocyclyl other than piperidinyl; wherein substituents of A_1 other than hydrogen are optionally substituted with one to three substituents independently selected from the group consisting of C_{1-6}alkyl, hydroxy(C_{1-6})alkyl, C_{1-6}alkoxy, halogen, nitro, halogenated C_{1-6}alkyl, halogenated C_{1-6}alkoxy, C_{1-6}alkylthio, C_{1-6}alkoxycarbonyl, amino, cyano, hydroxy, aminocarbonyl, C_{1-6}alkylaminocarbonyl, di(C_{1-6}alkyl)aminocarbonyl, and C_{1-6}alkylcarbonyl;

L_1 is $-(CH_2)_r-$ optionally substituted with a substituent selected from the group consisting of C_{1-4}alkyl, C_{2-4}alkenyl, and C_{2-4}alkynyl; provided that r is 1 to 3 when A_1 is other than hydrogen; or r is 4 or 5 when A_1 is hydrogen;

P is $-CH_2-$;

A_2 is furanyl, pyridin-3-yl, pyridin-4-yl, or phenyl optionally substituted at the meta and para positions with one to three substituents independently selected from the group consisting of C_{1-4}alkyl, C_{1-4}alkoxy, halogen, halogenated C_{1-3}alkoxy, C_{1-3}alkylthio, hydroxy, amino, aminocarbonyl, C_{1-3}alkylcarbonylamino, and a non fused C_{3-6}cycloalkyloxy; and wherein furanyl, pyridin-3-yl, and pyridin-4-yl are optionally substituted with one to three substituents independently selected from the group consisting of C_{1-4}alkyl, C_{1-4}alkoxy, halogen, halogenated C_{1-3}alkoxy, C_{1-3}alkylthio, hydroxy, amino, aminocarbonyl, C_{1-3}alkylcarbonylamino, and a non fused C_{3-6}cycloalkyloxy;

provided that no more than two substituents on A_2 are non fused C_{3-6}cycloalkyloxy;

provided that when A_1 is unsubstituted phenyl and L_2 is $-X_1-CH(R^x)-(CR^yR^z)-$ wherein X_1 is NH, and R^x, R^y, and R^z are each hydrogen, A_2 is other than unsubstituted phenyl;

and, further provided that when A_1 is unsubstituted phenyl and L_2 is $-X_1-CH(R^x)-(CR^yR^z)_2-$ wherein X_1 is NH and R^x, R^y, and R^z are each hydrogen, A_2 is other than phenyl substituted with methoxy;

and, provided that when A_1 is 3,4-dichloro-phenyl, A_2 is other than phenyl substituted in the meta position with trifluoromethoxy;

W is N or CH;

L_2 is a bivalent radical selected from the group consisting of

-NH-C_{5-6}cycloalkyl–$(CH_2)_{0-2}$-; provided that when C_{5-6}cycloalkyl is cyclohexyl, Q is attached at either the 2- or cis-4-position relative to the position of –NH-;

-X_1-$CH(R^x)$-$(CR^yR^z)_{1-5}$-, wherein X_1 is -NH–, O, or S; and R^x, R^y, and R^z are each hydrogen; such that X_1 is other than O when W is N;

-C(=O)$NH(CH_2)_2$-;

and

-X_1-(*R,R*-$CH(R^x)CR^y(R^z)$)-; wherein X_1 is -NH–, and R^x and R^z are methyl, and R^y is hydrogen;

provided that when L_2 is -C(=O)$NH(CH_2)_2$-, then R_W is hydrogen;

m is 0 or 1;

G is $–C(=NR^b)NR^cR^d$;

R^a and R^d are independently hydrogen or C_{1-3}alkyl, wherein C_{1-3}alkyl is optionally substituted with one to three substituents independently selected from the group consisting of hydroxy, C_{1-4}alkoxy, fluoro, amino, C_{1-4}alkylamino, diC_{1-4}alkylamino, and C_{1-4}alkylcarbonyl; or R^a and R^c are taken together with the atoms to which they are attached to form a 5-8 membered monocyclic ring optionally substituted with oxo;

R^b is hydrogen or C_{1-4}alkyl; or, R^b and R^c are taken together with the atoms to which they are attached to form a 5-8 membered monocyclic ring, optionally substituted with oxo;

R^c is hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-7}cycloalkyl, adamantyl, heterocyclyl, arylcarbonyl, phenyl, or heteroaryl; wherein C_{1-6}alkyl is optionally substituted with one to two substituents independently selected from the group consisting of C_{1-3}alkoxy, trifluoromethyl, phenyl, heteroaryl, and heterocyclyl; and wherein any aryl-, phenyl-, or heteroaryl-containing substituents of R^c are optionally substituted with one to three substituents independently selected from the group consisting of C_{1-6}alkyl, C_{1-6}alkoxy, halogen, fluorinated C_{1-6}alkyl, fluorinated C_{1-}

$_6$alkoxy, C_{1-6}alkylcarbonyl, C_{1-6}alkoxycarbonyl, nitro, methylthio, hydroxy, and cyano; or, R^c and R^d are taken together with the atoms to which they are attached to form a 5-8 membered monocyclic ring and said ring is optionally substituted with oxo;

with the proviso that in any instance, only one ring optionally exists between R^a and R^b, R^b and R^c, or R^c and R^d;

and enantiomers, diastereomers, tautomers, solvates, and pharmaceutically acceptable salts thereof.

A further aspect of the present invention is directed to a compound of Formula Ia wherein:

A_1 is substituted phenyl, benzofuranyl, thiazolyl, or thiophenyl; wherein phenyl is substituted with, and benzofuranyl, thiazolyl, and thiophenyl are optionally substituted with, one to two substituents independently selected from the group consisting of C_{1-4}alkyl, C_{1-4}alkoxy, halogen, nitro, halogenated C_{1-4}alkyl, halogenated C_{1-4}alkoxy, methylthio, amino, cyano, and C_{1-4}alkylcarbonyl;

L_1 is $-(CH_2)_r-$ optionally substituted with a substituent selected from the group consisting of methyl and allyl, and r is 1 to 3;

P is $-CH_2-$;

A_2 is pyridin-3-yl, pyridin-4-yl, or phenyl optionally substituted at the meta and para positions with one to two substituents independently selected from the group consisting of methyl, ethyl, methoxy, ethoxy, isopropyloxy, trifluoromethoxy, difluoromethoxy, hydroxy, aminocarbonyl, and methylcarbonylamino; wherein pyridin-3-yl and pyridin-4-yl are optionally substituted with one to two substituents independently selected from the group consisting of methyl, ethyl, methoxy, ethoxy, isopropyloxy, trifluoromethoxy, difluoromethoxy, hydroxy, aminocarbonyl, and methylcarbonylamino; provided that when A_1 is 3,4-dichloro-phenyl, A_2 is other than phenyl substituted in the meta position with trifluoromethoxy;

W is N or CH;

L_2 is a bivalent radical selected from the group consisting of

-NH-cyclohexyl–$(CH_2)_{0-2}$– and Q is attached at either the 2- or cis-4-position relative to the position of –NH-;

-X_1-$CH(R^x)$-$(CR^yR^z)_{1-5}$-; wherein X_1 is –NH- or S; and R^x, R^y, and R^z are each hydrogen;

and

- X_1-(*R,R*-$CH(R^x)CR^y(R^z)$)-; wherein X_1 is -NH–, and R^x and R^z are methyl, and R^y is hydrogen;

m is 0;

G is $-C(=NR^b)NR^cR^d$;

R^a and R^d are independently hydrogen, methyl or ethyl; or R^a and R^c are taken together with the atoms to which they are attached to form a 5-8 membered monocyclic ring optionally substituted with oxo;

R^b is hydrogen;

R^c is hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-7}cycloalkyl, heterocyclyl, phenylcarbonyl, phenyl, or heteroaryl; wherein C_{1-6}alkyl is optionally substituted with one to two substituents independently selected from the group consisting of C_{1-3}alkoxy, phenyl, pyridinyl, furanyl, and tetrahydrofuranyl; and wherein any phenyl- or heteroaryl-containing substituents of R^c are optionally substituted with one to two substituents independently selected from the group consisting of C_{1-6}alkyl, C_{1-6}alkoxy, chloro, fluoro, bromo, fluorinated C_{1-3}alkoxy, nitro, methylthio, hydroxy, and cyano; or, R^c and R^d are taken together with the atoms to which they are attached to form a 5-8 membered monocyclic ring;

with the proviso that in any instance, only one ring optionally exists between R^a and R^b, R^b and R^c, or R^c and R^d;

and enantiomers, diastereomers, tautomers, solvates, and pharmaceutically acceptable salts thereof.

Another aspect of the present invention is directed to a compound of Formula Ia wherein:

A_1 is phenyl or benzofuranyl; wherein phenyl is substituted at either the 4-position or 3 and 4-positions with one to two substituents independently selected from the group consisting of ethyl, methoxy, fluoro, chloro, nitro, difluoromethoxy, and methylthio;

L_1 is $-CH_2-$ optionally substituted with methyl or allyl;P is $-CH_2-$;

A_2 is phenyl substituted at the para position with a substituent selected from the group consisting of methoxy, ethoxy, isopropyloxy, difluoromethoxy, hydroxy, and aminocarbonyl; or A_2 is pyridin-3-yl or pyridin-4-yl substituted with methoxy;

W is N or CH;

L_2 is a bivalent radical selected from the group consisting of

-NH-cyclohexyl–$(CH_2)_{0-2}$– and Q is attached at either the 2- or cis-4-position relative to the position of –NH-;

$-X_1-CH(R^x)-(CR^yR^z)-$; wherein X_1 is -NH– or S and R^x, R^y, and R^z are each hydrogen;

and

$-X_1-(R,R\text{-}CH(R^x)CR^y(R^z))-$; wherein X_1 is -NH–, R^x and R^z are methyl, and R^y is hydrogen;

m is 0;

G is $-C(=NR^b)NR^cR^d$;

R^a and R^d are independently hydrogen, methyl or ethyl;

R^b is hydrogen;

R^c is hydrogen, C_{1-4}alkyl, C_{2-4}alkenyl, cyclohexyl, phenylcarbonyl, phenyl, pyrimidinyl, furanyl, benzo[1,3]dioxolyl, or pyridinyl; wherein C_{1-4}alkyl is optionally substituted with one to two substituents independently selected from the group consisting of C_{1-3}alkoxy, phenyl, pyridinyl, furanyl, and tetrahydrofuranyl; and wherein any phenyl- or heteroaryl-containing substituents of R^c are optionally

substituted with one to two substituents independently selected from the group consisting of C_{1-6}alkyl, C_{1-6}alkoxy, chloro, fluoro, bromo, fluorinated C_{1-3}alkoxy, nitro, methylthio, hydroxy, and cyano; or, R^c and R^d are taken together with the atoms to which they are attached to form a 5-8 membered monocyclic ring;

and enantiomers, diastereomers, tautomers, solvates, and pharmaceutically acceptable salts thereof.

Another aspect of the present invention is directed to compounds of Formula (I) in Table 1 wherein A_1, L_1, D, W, L_2, and Q are as defined in the present invention.

Table 1

Cpd #	A_1	L_1	D	W	L_2	Q
1	phenyl	$-CH_2-$	$-CH_2$-(4-fluoro-phenyl)	N	$-NH(CH_2)_2-$	$-NHC(=NH)NH_2$
2	phenyl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	N	$-NH(CH_2)_2-$	$-NHC(=NH)NH_2$
3	phenyl	$-CH_2-$	$-CH_2$-(4-methylcarboxy-phenyl)	N	$-NH(CH_2)_2-$	$-NHC(=NH)NH_2$
4	phenyl	$-(CH_2)_2-$	$-CH_2$-(4-methoxy-phenyl)	N	$-NH(CH_2)_2-$	$-NHC(=NH)NH_2$
5	H	$-(CH_2)_4-$	$-CH_2$-(4-methoxy-phenyl)	N	$-NH(CH_2)_2-$	$-NHC(=NH)NH_2$
6	furan-2-yl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	N	$-NH(CH_2)_2-$	$-NHC(=NH)NH_2$

Cpd #	A_1	L_1	D	W	L_2	Q
7	phenyl	$-CH_2-$	$-CH_2$-(3-trifluoromethyl-phenyl)	N	$-NH(CH_2)_2-$	$-NHC(=NH)NH_2$
8	phenyl	$-CH_2-$	$-CH_2$-(4-t-butyl-phenyl)	N	$-NH(CH_2)_2-$	$-NHC(=NH)NH_2$
9	phenyl	$-CH_2-$	$-CH_2$-(4-nitro-phenyl)	N	$-NH(CH_2)_2-$	$-NHC(=NH)NH_2$
10	phenyl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	N	$-NH(CH_2)_2-$	$-ONHC(=NH)NH_2$
11	phenyl	$-CH_2-$	$-CH_2$-pyridin-4-yl	N	$-NH(CH_2)_2-$	$-NHC(=NH)NH_2$
12	phenyl	$-CH_2-$	$-CH_2$-(4-ethoxy-phenyl)	N	$-NH(CH_2)_2-$	$-NHC(=NH)NH_2$
13	phenyl	$-CH_2-$	$-CH_2$-(4-difluoromethoxy-phenyl)	N	$-NH(CH_2)_2-$	$-NHC(=NH)NH_2$
14	phenyl	$-CH_2-$	$-CH_2$-(4-n-butyl-phenyl)	N	$-NH(CH_2)_2-$	$-NHC(=NH)NH_2$
15	phenyl	$-CH_2-$	$-CH_2$-(4-trifluoromethyl-phenyl)	N	$-NH(CH_2)_2-$	$-NHC(=NH)NH_2$
16	2-fluoro-phenyl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	N	$-NH(CH_2)_2-$	$-NHC(=NH)NH_2$
17	4-fluoro-phenyl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	N	$-NH(CH_2)_2-$	$-NHC(=NH)NH_2$
18	3,4-dichloro-phenyl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	N	$-NH(CH_2)_2-$	$-NHC(=NH)NH_2$
19	phenyl	$-CH_2-$	$-CH_2$-(4-trifluoromethoxy-phenyl)	N	$-NH(CH_2)_2-$	$-NHC(=NH)NH_2$

Cpd #	A_1	L_1	D	W	L_2	Q
20	3-methoxy-phenyl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	N	$-NH(CH_2)_2-$	$-NHC(=NH)NH_2$
21	2-methoxy-phenyl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	N	$-NH(CH_2)_2-$	$-NHC(=NH)NH_2$
22	phenyl	$-CH_2-$	$-CH_2$-(4-aminocarbonyl-phenyl)	N	$-NH(CH_2)_2-$	$-NHC(=NH)NH_2$
23	phenyl	$-CH_2-$	$-CH_2$-(4-methylcarboxyl amino-phenyl)	N	$-NH(CH_2)_2-$	$-NHC(=NH)NH_2$
24	4-fluoro-phenyl	$-CH_2-$	$-CH_2$-(4-ethoxy-phenyl)	N	$-NH(CH_2)_2-$	$-NHC(=NH)NH_2$
25	phenyl	-(*R,R*–$CH(CH_3)$ $CH(CH_3)$)-	$-CH_2$-(4-methoxy-phenyl)	N	$-NH(CH_2)_2-$	$-NHC(=NH)NH_2$
26	phenyl	-(*R,R*–$CH(CH_3)CH(CH_3)$)-	$-CH_2$-(4-methoxy-phenyl)	N	$-NH(CH_2)_2-$	$-NHC(=NH)NH_2$
27	3,4-dichloro-phenyl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	N	$-NH(CH_2)_2-$	$-ONHC(=NH)NH_2$
28	3,4-dichloro-phenyl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	N	$-NH(CH_2)_2-$	$-NHC(=N-CN)NH_2$
29	3,4-dichloro-phenyl	$-CH_2-$	$-CH_2$-(4-ethoxy-phenyl)	N	$-NH(CH_2)_2-$	$-NHC(=NH)NH_2$
30	4-chloro-phenyl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	N	$-NH(CH_2)_2-$	$-NHC(=NH)NH_2$
31	4-methoxy-phenyl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	N	$-NH(CH_2)_2-$	$-NHC(=NH)NH_2$
32	3,4-dichloro-phenyl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	N	$-NH(CH_2)_4-$	$-NHC(=NH)NH_2$

Cpd #	A_1	L_1	D	W	L_2	Q
33	4-fluoro-phenyl	$-CH_2-$	$-(CH_2)_2$-(4-methoxy-phenyl)	N	$-NH(CH_2)_2-$	$-NHC(=NH)NH_2$
34	3,4-dichloro-phenyl	$-CH_2-$	$-CH_2$-(4-n-propyl-phenyl)	N	$-NH(CH_2)_2-$	$-NHC(=NH)NH_2$
35	3,4-dichloro-phenyl	$-CH_2-$	$-CH_2$-(4-*i*-propyl-phenyl)	N	$-NH(CH_2)_2-$	$-NHC(=NH)NH_2$
36	3,4-dichloro-phenyl	$-CH_2-$	$-CH_2$-(4-cyclopentyloxy-phenyl)	N	$-NH(CH_2)_2-$	$-NHC(=NH)NH_2$
37	3,4-dichloro-phenyl	$-CH_2-$	$-CH_2$-(4-methylthio-phenyl)	N	$-NH(CH_2)_2-$	$-NHC(=NH)NH_2$
38	3,4-dichloro-phenyl	$-CH_2-$	$-CH_2$-(4-ethyl-phenyl)	N	$-NH(CH_2)_2-$	$-NHC(=NH)NH_2$
39	3-chloro-phenyl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	N	$-NH(CH_2)_2-$	$-NHC(=NH)NH_2$
40	3,4-dichloro-phenyl	$-CH_2-$	$-CH_2$-(4-trifluoromethoxy-phenyl)	N	$-NH(CH_2)_2-$	$-NHC(=NH)NH_2$
41	3,4-dichloro-phenyl	$-CH_2-$	$-CH_2$-(4-difluoromethoxy-phenyl)	N	$-NH(CH_2)_2-$	$-NHC(=NH)NH_2$
42	3,4-dichloro-phenyl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	N	cis-racemic-1,2-cyclohexyl	$-NHC(=NH)NH_2$
43	3,4-dichloro-phenyl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	N	trans (1S, 2S)-cyclohexyl-	$-NHC(=NH)NH_2$
44	3,4-dichloro-phenyl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	N	$-NH(CH_2)_2-$	$-NHC(=NH)NH_2$
45	4-methylthio-phenyl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	N	$-NH(CH_2)_2-$	$-NHC(=NH)NH_2$

Cpd #	A_1	L_1	D	W	L_2	Q
46	4-ethyl-phenyl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	N	$-NH(CH_2)_2-$	$-NHC(=NH)NH_2$
47	3,4-dichloro-phenyl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	N	trans(1R, 2R)-cyclohexyl-	$-NHC(=NH)NH_2$
48	3,4-dichloro-phenyl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	N	$-NH(CH_2)_2-$	-NH(3,5-dihydro-imidazol-4-on-2-yl)
49	3,4-dichloro-phenyl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	N	$-NH(CH_2)_2-$	-NH(4,5-dihydro-1H-imidazol-2-yl)
50	3,4-dichloro-phenyl	$-CH_2-$	$-CH_2$-(4-methylcarbonyl amino-phenyl)	N	$-NH(CH_2)_2-$	$-NHC(=NH)NH_2$
51	3,4-dichloro-phenyl	$-CH_2-$	$-CH_2$-(4-aminocarbonyl-phenyl)	N	$-NH(CH_2)_2-$	$-NHC(=NH)NH_2$
52	3,4-dichloro-phenyl	$-CH_2-$	$-CH_2$-(3-ethoxy-phenyl)	N	$-NH(CH_2)_2-$	$-NHC(=NH)NH_2$
53	3,4-dichloro-phenyl	$-CH_2-$	$-CH_2$-(4-ethoxy-phenyl)	N	$-NH(CH_2)_2-$	-NHC(=NH)NH-ethyl
54	3,4-dichloro-phenyl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	N	$-NH(CH_2)_2-$	-NHC(=NH)NH-propyl
55	3,4-dichloro-phenyl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	N	pyrrolindin-1-yl	3-$NHC(=NH)NH_2$
56	4-chloro-phenyl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	N	-trans (1R, 2R)-cyclohexyl-	$-NHC(=NH)NH_2$
57	3,4-dichloro-phenyl	$-CH_2-$	$-CH_2$-(3-difluoromethoxy-phenyl)	N	$-NH(CH_2)_2-$	$-NHC(=NH)NH_2$
58	3,4-dichloro-phenyl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	N	$-NH(CH_2)_2-$	-NHC(=NH)NH (*i*-propyl)

Cpd #	A_1	L_1	D	W	L_2	Q
59	3,4-dichloro-phenyl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	N	$-NH(CH_2)_2-$	-N(ethyl) C(=NH)NH_2
60	3,4-dichloro-phenyl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	N	$-NH(CH_2)_2-$	2-imino-imidazolid-1-yl
61	3,4-dichloro-phenyl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	N	$-NH(CH_2)_2-$	-NHC(=NH)NH (n-butyl)
62	3,4-dichloro-phenyl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	N	$-NH(CH_2)_2-$	-NHC(=NH)NH (cyclohexyl)
63	3,4-dichloro-phenyl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	N	$-NH(CH_2)_2-$	-NHC(=NH)NH (benzyl)
64	3,4-dichloro-phenyl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	N	$-NH(CH_2)_2-$	-NHC(=NH)NH (tetrahydrofuran-2-ylmethyl)
65	3,4-dichloro-phenyl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	N	$-NH(CH_2)_2-$	-NHC(=NH)NH (phenylethyl)
66	3,4-dichloro-phenyl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	N	$-NH(CH_2)_2-$	-NHC(=NH)NH (furan-2-ylmethyl)
67	3,4-dichloro-phenyl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	N	$-NH(CH_2)_2-$	-NHC(=NH)NH (2-methoxy-ethyl)
68	3,4-dichloro-phenyl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	N	$-NH(CH_2)_3-$	-NHC(=NH)NH_2
69	3,4-dichloro-phenyl	$-CH_2-$	$-(CH_2)_6$-H	N	$-NH(CH_2)_3-$	-NHC(=NH)NH_2
70	3,4-dichloro-phenyl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	N	$-NH(CH_2)_2-$	-NHC(=NH)NH (allyl)
71	3,4-dichloro-phenyl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	N	$-NH(CH_2)_2-$	-NHC(=NH)NH (phenyl)

Cpd #	A_1	L_1	D	W	L_2	Q
72	3,4-dichloro-phenyl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	N	$-NH(CH_2)_2-$	-NHC(=NH)NH(4-methoxy-phenyl)
73	3,4-dichloro-phenyl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	N	$-NH(CH_2)_2-$	-NHC(=NH)NH(4-chloro-phenyl)
74	3,4-dichloro-phenyl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	N	$-NH(CH_2)_2-$	-NHC(=NH)NH(4-trifluoromethyl-phenyl)
75	3,4-dichloro-phenyl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	N	$-NH(CH_2)_2-$	-NHC(=NH)NH (pyridin-3-yl)
76	3,4-dichloro-phenyl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	N	$-NH(CH_2)_2-$	-NHC(=NH)NH(4-methylcarbonyl-phenyl)
77	furan-3-yl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	N	$-NH(CH_2)_2-$	$-NHC(=NH)NH_2$
78	thiophen-2-yl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	N	$-NH(CH_2)_2-$	$-NHC(=NH)NH_2$
79	4-methoxy-phenyl	R,S-mixture $-CH(CH_3)-$	$-CH_2$-(4-methoxy-phenyl)	N	$-NH(CH_2)_2-$	$-NHC(=NH)NH_2$
80	4-difluoromethoxy-phenyl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	N	$-NH(CH_2)_2-$	$-NHC(=NH)NH_2$
81	phenyl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	CH	$-NH(CH_2)_2-$	$-NHC(=NH)NH_2$
82	4-methoxy-phenyl	R,S-mixture -CH(allyl)-	$-CH_2$-(4-methoxy-phenyl)	N	$-NH(CH_2)_2-$	$-NHC(=NH)NH_2$
83	4-chloro-phenyl	R,S-mixture -CH(allyl)-	$-CH_2$-(4-methoxy-phenyl)	N	$-NH(CH_2)_2-$	$-NHC(=NH)NH_2$
84	4-methoxy-phenyl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	CH	$-NH(CH_2)_2-$	$-NHC(=NH)NH_2$

Cpd #	A_1	L_1	D	W	L_2	Q
85	4-methoxy-phenyl	$-CH_2-$	$-CH_2$-(6-methoxy-pyridin-3-yl)	N	$-NH(CH_2)_2-$	$-NHC(=NH)NH_2$
86	4-methoxy-phenyl	$-CH_2-$	$-CH_2$-(4-methoxy-cyclohexyl)	N	$-NH(CH_2)_2-$	$-NHC(=NH)NH_2$
87	4-fluoro-phenyl	$-CH_2-$	$-CH_2$-(4-nitro-phenyl)	N	$-NH(CH_2)_2-$	$-NHC(=NH)NH_2$
88	4-fluoro-phenyl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	N	$-NH(CH_2)_2-$	-NHC(=NH)NH(2-(morpholin-4-yl)-eth-1-yl)
89	4-fluoro-phenyl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	N	$-NH(CH_2)_2-$	-NHC(=NH)NH(3-(morpholin-4-yl)-prop-1-yl)
90	4-fluoro-phenyl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	N	$-NH(CH_2)_2-$	-NHC(=NH)NH(4-cyano-phenyl)
91	4-fluoro-phenyl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	N	$-NH(CH_2)_2-$	-NHC(=NH)NH(4-nitro-phenyl)
92	4-fluoro-phenyl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	N	$-NH(CH_2)_2-$	-NHC(=NH)NH (1,3-benzo dioxol-5-yl)
93	4-fluoro-phenyl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	N	$-NH(CH_2)_2-$	$-NHC(=NH)NHNH_2$
94	3-nitro-phenyl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	N	$-NH(CH_2)_2-$	$-NHC(=NH)NH_2$
95	4-nitro-phenyl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	N	$-NH(CH_2)_2-$	$-NHC(=NH)NH_2$
96	3-amino-phenyl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	N	$-NH(CH_2)_2-$	$-NHC(=NH)NH_2$

Cpd #	A_1	L_1	D	W	L_2	Q
97	4-cyano-phenyl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	N	$-NH(CH_2)_2-$	$-NHC(=NH)NH_2$
98	3-cyano-phenyl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	N	$-NH(CH_2)_2-$	$-NHC(=NH)NH_2$
99	4-methoxy carbonyl-phenyl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	N	$-NH(CH_2)_2-$	$-NHC(=NH)NH_2$
100	3-methoxy carbonyl-phenyl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	N	$-NH(CH_2)_2-$	$-NHC(=NH)NH_2$
101	4-carboxy-phenyl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	N	$-NH(CH_2)_2-$	$-NHC(=NH)NH_2$
102	3,4-dichloro-phenyl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	N	$-NH(CH_2)C(Me)_2-$	$-NHC(=NH)NH_2$
103	4-fluoro-phenyl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	N	$-NH(CH_2)_2-$	-NHC(=NH)NH(4-bromo-phenyl)
104	4-fluoro-phenyl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	N	$-NH(CH_2)_2-$	-NHC(=NH)NH (pyridin-2-yl)
105	4-fluoro-phenyl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	N	$-NH(CH_2)_2-$	-NHC(=NH)NH (pyridin-2-yl-ethyl)
106	4-fluoro-phenyl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	N	$-NH(CH_2)_2-$	-NHC(=NH)NH(4-ethoxycarbonyl-phenyl)
107	4-fluoro-phenyl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	N	$-NH(CH_2)_2-$	-NHC(=NH)NH (2,4-difluoro-phenyl)
108	4-fluoro-phenyl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	N	$-NH(CH_2)_2-$	-NHC(=NH)NH(*n*-decanyl)
109	4-t-butoxy-phenyl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	N	$-NH(CH_2)_2-$	$-NHC(=NH)NH_2$

Cpd #	A_1	L_1	D	W	L_2	Q
110	4-hydroxy-phenyl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	N	$-NH(CH_2)_2-$	$-NHC(=NH)NH_2$
111	2-chloro-thiazol-4-yl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	N	$-NH(CH_2)_2-$	$-NHC(=NH)NH_2$
112	benzo furan-2-yl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	N	$-NH(CH_2)_2-$	$-NHC(=NH)NH_2$
113	3,4-dichloro-phenyl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	N	$-NH(CH_2)_2-$	-N(Me) $C(=NH)NH_2$
114	4-fluoro-phenyl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	N	$-NH(CH_2)_2-$	-NHC(=NH)NH (CH_2CF_3)
115	4-fluoro-phenyl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	N	$-NH(CH_2)_2-$	-NHC(=NH)NH(3-methoxypropyl)
116	4-fluoro-phenyl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	N	$-NH(CH_2)_2-$	-NHC(=NH) piperidin-1-yl
117	4-fluoro-phenyl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	N	$-NH(CH_2)_2-$	-NHC(=NH)N(Me) phenyl
118	4-fluoro-phenyl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	N	$-NH(CH_2)_2-$	-NHC(=NH)NH(2-fluoro-phenyl)
119	4-fluoro-phenyl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	N	$-NH(CH_2)_2-$	-NHC(=NH)NH(4-fluoro-phenyl)
120	4-fluoro-phenyl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	N	$-NH(CH_2)_2-$	-NHC(=NH)NH(4-methyl-phenyl)
121	4-fluoro-phenyl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	N	$-NH(CH_2)_2-$	-NHC(=NH)NH(t-butyl)
122	4-chloro-phenyl	$-CH_2-$	$-CH_2$-(4-amino-phenyl)	N	$-NH(CH_2)_2-$	$-NHC(=NH)NH_2$

Cpd #	A_1	L_1	D	W	L_2	Q
123	t-butyl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	N	$-NH(CH_2)_2-$	$-NHC(=NH)NH_2$
124	cyclopentyl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	N	$-NH(CH_2)_2-$	$-NHC(=NH)NH_2$
125	4-amino-phenyl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	N	$-NH(CH_2)_2-$	$-NHC(=NH)NH_2$
126	4-fluoro-phenyl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	N	$-NH(CH_2)_2-$	-NHC(=NH)NH (adamantan-2-yl)
127	4-fluoro-phenyl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	N	$-NH(CH_2)_2-$	-NHC(=NH)NH(4-trifluoromethoxy-phenyl)
128	4-fluoro-phenyl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	N	$-NH(CH_2)_2-$	-NHC(=NH)NH(4-hydroxy-phenyl)
129	4-chloro-phenyl	$-CH_2-$	$-CH_2$-phenyl	N	$-NH(CH_2)_2-$	$-NHC(=NH)NH_2$
130	4-chloro-phenyl	$-CH_2-$	$-CH_2$-furan-3-yl	N	$-NH(CH_2)_2-$	$-NHC(=NH)NH_2$
131	4-fluoro-phenyl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	N	1,4-cyclohexyl	$-NHC(=NH)NH_2$
132	4-fluoro-phenyl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	N	$-NHCH_2C(=O)-$	-NHC(=NC(=O)O-t-butyl)NH_2
133	4-fluoro-phenyl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	N	$-NH(CH_2)_2-$	-NHC(=NH)NH(2-methylthio-phenyl)
134	4-fluoro-phenyl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	N	$-NH(CH_2)_2-$	-NHC(=NH)NH (C(=O)phenyl)
135	4-fluoro-phenyl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	N	$-NH(CH_2)_2-$	-NHC(=NH)NH (pyrimidin-2-yl)

Cpd #	A_1	L_1	D	W	L_2	Q
136	4-fluoro-phenyl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	N	$-NH((S)-CHMe)_2-$	$-NHC(=NH)NH_2$
137	4-fluoro-phenyl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	N	$-NH((R)-CHMe)_2-$	$-NHC(=NH)NH_2$, -NH(=NH)NH(4-trifluoromethyl-5,6,7,8-tetrahydro-quinazolin-2-yl)
138	4-fluoro-phenyl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	N	$-NH(CH_2)_2-$	
139	4-fluoro-phenyl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	N	$-NH(CH_2)_2-$	-NHC(=NH)NH(5-methyl-pyridin-2-yl)
140	4-fluoro-phenyl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	N	$-NH(CH_2)_2-$	-NHC(=NH) morpholin-4-yl
141	4-chloro-phenyl	$-CH_2-$	$-CH_2$-furan-2-yl	N	$-NH(CH_2)_2-$	$-NHC(=NH)NH_2$
142	4-chloro-phenyl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	N	$-NH(CH_2)_5-$	$-NHC(=NH)NH_2$
143	4-methoxy-phenyl	$-CH_2-$	$-CH_2$-(4-hydroxy-phenyl)	N	$-NH(CH_2)_2-$	$-NHC(=NH)NH_2$
144	4-chloro-phenyl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	N	$-NH(CH_2)_6-$	$-NHC(=NH)NH_2$
145	4-methoxy-phenyl	$-(CH_2)_2-$	$-CH_2$-(4-methoxy-phenyl)	N	$-NH(CH_2)_2-$	$-NHC(=NH)NH_2$
146	4-methoxy-phenyl	$-(CH_2)_3-$	$-CH_2$-(4-methoxy-phenyl)	N	$-NH(CH_2)_2-$	$-NHC(=NH)NH_2$
147	3,4-dichloro-phenyl	$-CH_2-$	$-CH_2$-(4-methoxycarbonyl-phenyl)	N	$-NH(CH_2)_2-$	$-NHC(=NH)NH_2$
148	phenyl	$-CH_2-$	$-CH_2$-(4-*n*-butyloxy-phenyl)	N	$-NH(CH_2)_2-$	$-NHC(=NH)NH_2$

Cpd #	A_1	L_1	D	W	L_2	Q
149	4-chloro-phenyl	$-CH_2-$	$-CH_2$-phenyl	N	$-NH(CH_2)_2-$	$-NHC(=NH)NH_2$
150	4-chloro-phenyl	$-CH_2-$	$-CH_2$-furan-3-yl	N	$-NH(CH_2)_2-$	$-NHC(=NH)NH_2$
151	4-fluoro-phenyl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	N	$-NH(CH_2)_2-$	-NHC(=NH) NHC(=O)methyl
152	4-fluoro-phenyl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	N	$-NH(CH_2)_2-$	-NHC(=NH) NH(allyl)
153	4-fluoro-phenyl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	N	$-NH(CH_2)_2-$	-NHC(=NH) NH(*i*-propyl)
154	4-fluoro-phenyl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	N	$-NH(CH_2)_2-$	-NHC(=NH) NH(*n*-propyl)
155	4-fluoro-phenyl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	N	$-NH(CH_2)_2-$	-NHC(=NH) NH(ethyl)
156	4-fluoro-phenyl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	N	$-NH(CH_2)_2-$	-NHC(=NH) NH(methyl)
157	4-methoxy-phenyl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	CH	$-C(=O)NH(CH_2)_2-$	$-NHC(=NH)NH_2$
158	4-methoxy-phenyl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	CH	$-O(CH_2)_2-$	$-NHC(=NH)NH_2$
159	4-methoxy-phenyl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	CH	$-S(CH_2)_2-$	$-NHC(=NH)NH_2$
160	4-methoxy-phenyl	$-CH_2-$	$-CH_2$-(4-methoxy-phenyl)	CH	$-(CH_2)_3-$	$-NHC(=NH)NH_2$

The compounds of the present invention may also be present in the form of pharmaceutically acceptable salts. For use in medicine, the salts of the compounds of this invention refer to non-toxic "pharmaceutically acceptable salts" (Ref. International J. Pharm., 1986, 33, 201-217; J. Pharm.Sci., 1997 (Jan), 66, 1, 1). Other salts well known to those in the art may, however, be useful in the preparation of compounds according to this invention or of their pharmaceutically acceptable salts. Representative organic or inorganic acids include, but are not limited to, hydrochloric, hydrobromic, hydroiodic, perchloric, sulfuric, nitric, phosphoric, acetic, propionic, glycolic, lactic, succinic, maleic, fumaric, malic, tartaric, citric, benzoic, mandelic, methanesulfonic, hydroxyethanesulfonic, benzenesulfonic, oxalic, pamoic, 2-naphthalenesulfonic, p-toluenesulfonic, cyclohexanesulfamic, salicylic, saccharinic or trifluoroacetic acid. Representative organic or inorganic bases include, but are not limited to, basic or cationic salts such as benzathine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine, procaine, aluminum, calcium, lithium, magnesium, potassium, sodium and zinc.

The present invention includes within its scope prodrugs of the compounds of this invention. In general, such prodrugs will be functional derivatives of the compounds that are readily convertible in vivo into the required compound. Thus, in the methods of treatment of the present invention, the term "administering" shall encompass the treatment of the various disorders described with the compound specifically disclosed or with a compound which may not be specifically disclosed, but which converts to the specified compound in vivo after administration to the patient. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

Where the compounds according to this invention have at least one chiral center, they may accordingly exist as enantiomers. Where the compounds possess

two or more chiral centers, they may additionally exist as diastereomers. It is to be understood that all such isomers and mixtures thereof are encompassed within the scope of the present invention. Furthermore, some of the crystalline forms for the compounds may exist as polymorphs and as such are intended to be included in the present invention. In addition, some of the compounds may form solvates with water (i.e., hydrates) or common organic solvents, and such solvates are intended to be encompassed within the scope of this invention.

Where the processes for the preparation of the compounds according to the invention give rise to mixture of stereoisomers, these isomers may be separated by conventional techniques such as preparative chromatography. The compounds may be prepared in racemic form, or individual enantiomers may be prepared either by enantiospecific synthesis or by resolution. The compounds may, for example, be resolved into their component enantiomers by standard techniques, such as the formation of diastereomeric pairs by salt formation with an optically active acid, such as (-)-di-p-toluoyl-d-tartaric acid and/or (+)-di-p-toluoyl-l-tartaric acid followed by fractional crystallization and regeneration of the free base. The compounds may also be resolved by formation of diastereomeric esters or amides, followed by chromatographic separation and removal of the chiral auxiliary. Alternatively, the compounds may be resolved using a chiral HPLC column.

During any of the processes for preparation of the compounds of the present invention, it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in Protective Groups in Organic Chemistry, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene & P.G.M. Wuts, Protective Groups in Organic Synthesis, John Wiley & Sons, 1991. The protecting groups may be removed at a convenient subsequent stage using methods known from the art.

Even though the compounds of the present invention (including their pharmaceutically acceptable salts and pharmaceutically acceptable solvates) can be administered alone, they will generally be administered in admixture with a pharmaceutical carrier, excipient, or diluent selected with regard to the intended route of administration and standard pharmaceutical or veterinary practice. Thus, the present invention is directed to pharmaceutical and veterinary compositions comprising compounds of Formula (I) and one or more pharmaceutically acceptable carriers, excipients or diluents.

By way of example, in the pharmaceutical and veterinary compositions of the present invention, the compounds of the present invention may be admixed with any suitable binder(s), lubricant(s), suspending agent(s), coating agent(s), and/or solubilising agent(s).

Tablets or capsules of the compounds may be administered singly or two or more at a time, as appropriate. It is also possible to administer the compounds in sustained release formulations.

Alternatively, the compounds of the general Formula (I) can be administered by inhalation or in the form of a suppository or pessary, or they may be applied topically in the form of a lotion, solution, cream, ointment or dusting powder. An alternative means of transdermal administration is by use of a skin patch. For example, they can be incorporated into a cream consisting of an aqueous emulsion of polyethylene glycols or liquid paraffin. They can also be incorporated, at a concentration of between 1 and 10% by weight, into an ointment consisting of a white wax or white soft paraffin base together with such stabilisers and preservatives as may be required.

For some applications, preferably the compositions are administered orally in the form of tablets containing excipients such as starch or lactose, or in capsules or ovules either alone or in admixture with excipients, or in the form of elixirs, solutions or suspensions containing flavouring or coloring agents.

The compositions (as well as the compounds alone) can also be injected parenterally, for example intracavernosally, intravenously, intramuscularly or subcutaneously. In this case, the compositions will comprise a suitable carrier or diluent.

For parenteral administration, the compositions are best used in the form of a sterile aqueous solution which may contain other substances, for example enough salts or monosaccharides to make the solution isotonic with blood.

For buccal or sublingual administration the compositions may be administered in the form of tablets or lozenges which can be formulated in a conventional manner.

By way of further example, pharmaceutical and veterinary compositions containing one or more of the compounds of the invention described herein as the active ingredient can be prepared by intimately mixing the compound or compounds with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending upon the desired route of administration (e.g., oral, parenteral). Thus for liquid oral preparations such as suspensions, elixirs and solutions, suitable carriers and additives include water, glycols, oils, alcohols, flavoring agents, preservatives, stabilizers, coloring agents and the like; for solid oral preparations, such as powders, capsules and tablets, suitable carriers and additives include starches, sugars, diluents, granulating agents, lubricants, binders, disintegrating agents and the like. Solid oral preparations may also be coated with substances such as sugars or be

enteric-coated so as to modulate the major site of absorption. For parenteral administration, the carrier will usually consist of sterile water and other ingredients may be added to increase solubility or preservation. Injectable suspensions or solutions may also be prepared utilizing aqueous carriers along with appropriate additives.

Advantageously, compounds of the present invention may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three or four times daily. Furthermore, compounds for the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal skin patches well known to those skilled in that art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

A therapeutically effective amount for use of the instant compounds or a pharmaceutical composition thereof comprises a dose range of from about 0.001 mg to about 1,000 mg, in particular from about 0.1 mg to about 500 mg or, more particularly from about 1 mg to about 250 mg of active ingredient per day for an average (70 kg) human.

For oral administration, a pharmaceutical composition is preferably provided in the form of tablets containing, 0.01, 0.05, 0.1, 0.5, 1.0, 2.5, 5.0, 10.0, 15.0, 25.0, 50.0, 100, 150, 200, 250 and 500 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the subject to be treated.

It is also apparent to one skilled in the art that the therapeutically effective dose for active compounds of the invention or a pharmaceutical composition thereof will vary according to the desired effect. Therefore, optimal dosages to be

administered may be readily determined and will vary with the particular compound used, the mode of administration, the strength of the preparation, and the advancement of the disease condition. In addition, factors associated with the particular subject being treated, including subject age, weight, diet and time of administration, will result in the need to adjust the dose to an appropriate therapeutic level. The above dosages are thus exemplary of the average case. There can, of course, be individual instances where higher or lower dosage ranges are merited, and such are within the scope of this invention.

Compounds of this invention may be administered in any of the foregoing compositions and dosage regimens or by means of those compositions and dosage regimens established in the art whenever use of the compounds of the invention as prokineticin receptor antagonists is required for a subject in need thereof.

The invention also provides a pharmaceutical or veterinary pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical and veterinary compositions of the invention. Optionally associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration.

As antagonists of a Prokineticin 2 receptor, the compounds of Formula (I) are useful in methods for treating or preventing a disease or condition in a mammal which disease or condition is affected by the antagonism of one or more Prokineticin 2 receptors. Such methods comprise administering to a mammal in need of such treatment or prevention a therapeutically effective amount of a compound, salt or solvate of Formula (I). The compounds of Formula (I) are useful in methods for preventing or treating gastrointestinal (GI) diseases, cancers of the GI tract and

reproductive organs, and pain. Examples of GI diseases to be within the scope of the present invention include, but are not limited to: irritable bowel syndrome (IBS, including diarrhea-predominant, as well as alternating diarrhea/constipation forms of IBS), inflammatory bowel disease (IBD, including ulcerative colitis, and Crohn's disease), and GERD and secretory bowel disorders induced by pathogens. Examples of cancers within the scope of the present invention include, but are not limited to, testicular cancer, ovarian cancer, Leydig cell carcinoma, and cancers of the small or large bowel. An example of pain to be covered within the scope of the present invention, is, but is not restricted to, visceral hyperalgesia often associated with IBS and IBD.

While the present invention comprises compositions comprising one or more of the compounds of Formula (I) the present invention also comprises compositions comprising intermediates used in the manufacture of compounds of Formula (I).

Representative IUPAC names for the compounds of the present invention were derived using the ACD/LABS SOFTWARE™ Index Name Pro Version 4.5 nomenclature software program provided by Advanced Chemistry Development, Inc., Toronto, Ontario, Canada.

Abbreviations used in the instant specification, particularly the Schemes and Examples, are as follows:

Boc	=	tert-butoxycarbonyl
BuLi	=	n-butyllithium
Cpd or Cmpd	=	compound
d	=	day/ days
DCM	=	dichloromethane
DIAD	=	diisopropyl azodicarboxylate
DIPEA or DIEA	=	diisopropylethylamine

	DMEM	=	Dulbecco's Modified Eagle Medium
	DMF	=	*N,N*-dimethylformamide
	DMSO	=	dimethylsulfoxide
	EDCI	=	1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
5	EtOAc	=	ethyl acetate
	EtOH	=	ethanol
	h	=	hour/hours
	HBTU		O-Benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium hexafluorophosphate
10	LDA	=	lithium diisopropyamide
	M	=	molar
	MeCN	=	acetonitrile
	MeOH	=	methanol
	min	=	minutes
15	NaOMe	=	sodium methoxide
	PyBOP	=	benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate
	rt/RT	=	room temperature
	THF	=	tetrahydrofuran
20	TFA	=	trifluoroacetic acid

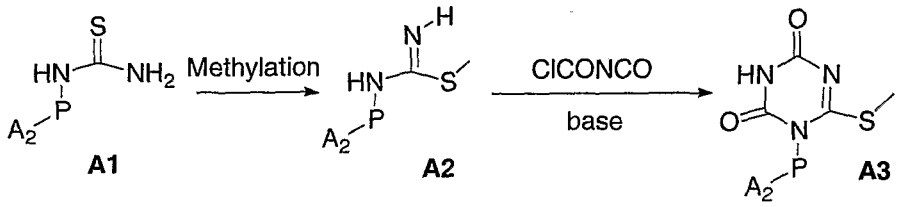
GENERAL SCHEMES

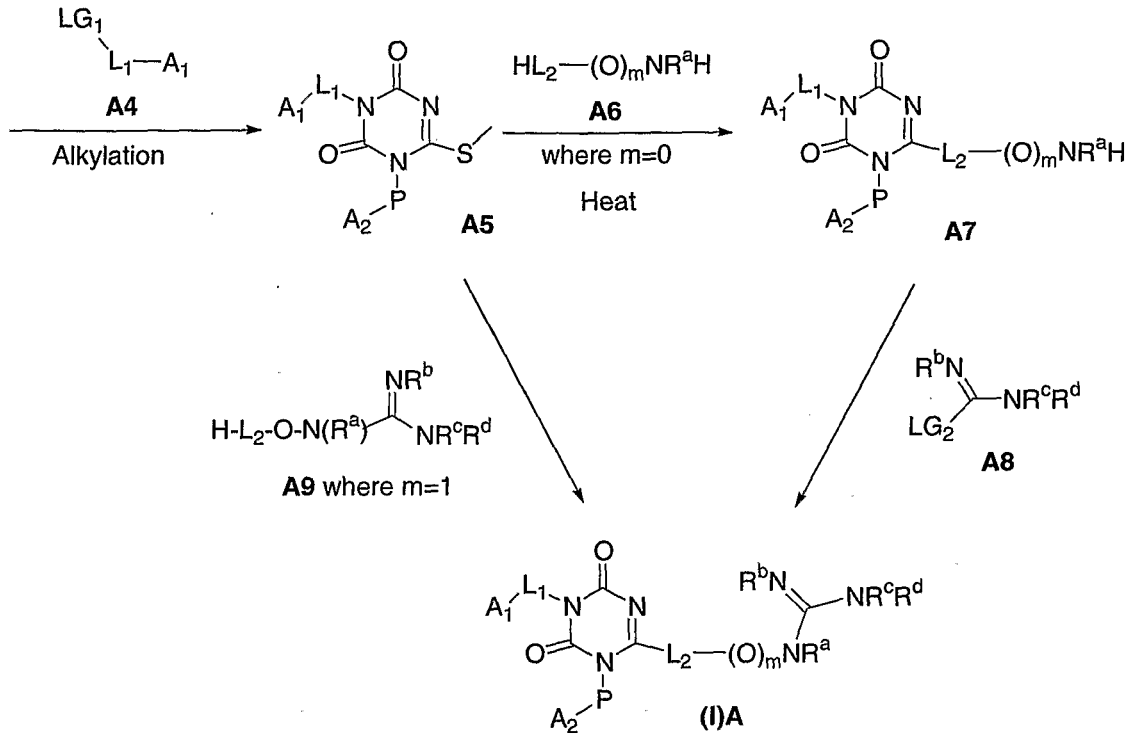
25 Representative compounds of the present invention can be synthesized in accordance with the general synthetic methods described below and are illustrated in the schemes that follows. The starting materials and reagents used in the schemes that follow are understood to be either commercially available or prepared by methods known to those skilled in the art. Since the schemes are an illustration,

the invention should not be construed as being limited by the chemical reactions and conditions expressed.

Scheme A illustrates the general synthesis of compounds of the present invention wherein L_2 is other than -NHC(=O)-$(CH_2)_{1-4}$-, -C(=O)NH$(CR^yR^z)_{2-5}$-, and -X_2-$(CH_2)_{0-4}$-. In Scheme A, X_1 of L_2 is NH. A compound of formula **A1** may be methylated with a methylating agent such as methyl iodide in a polar solvent such as methanol to give a compound of formula **A2**. A compound of formula **A2** may be condensed with an appropriately substituted isocyanate such as N-chlorocarbonyl isocyanate in the presence of excess tertiary amine such as diisopropylethylamine to give a triazine of formula **A3**.

Scheme A





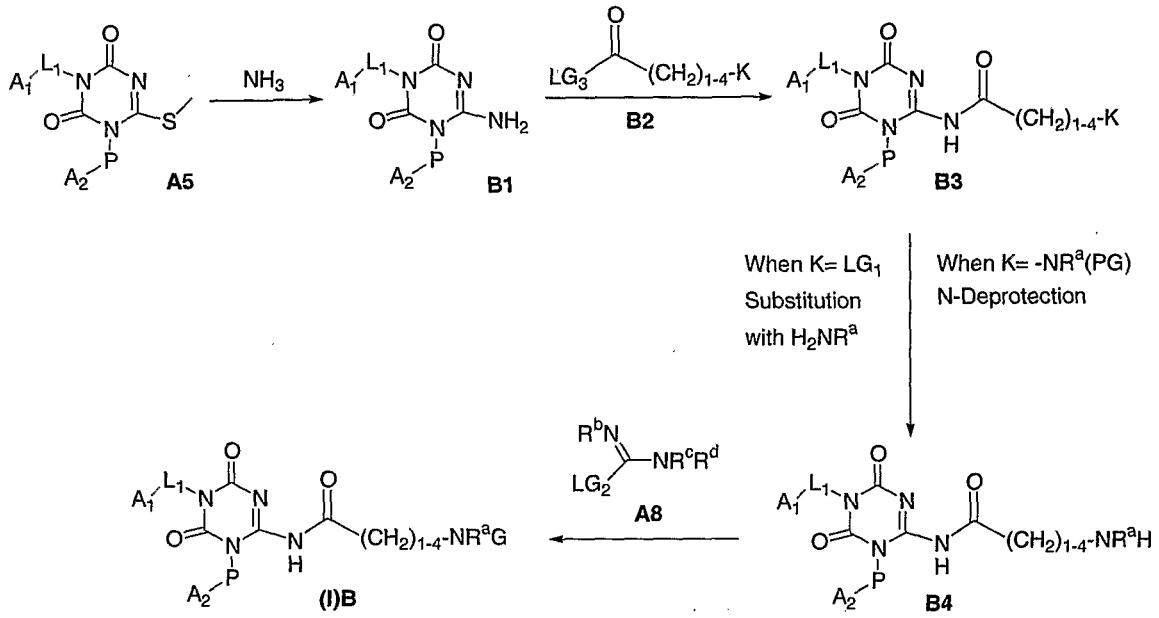
A compound of formula **A3** may be alkylated with a compound of formula **A4**, wherein LG_1 is a leaving group, using conventional chemistry known to one versed in the art. For instance, when LG_1 is a hydroxy group, compound **A4** may be coupled with compound **A3** with the aid of a coupling agent such as DIAD in the presence of triphenylphosphine in a non-alcoholic polar solvent such as THF or methylene chloride. Alternatively, LG_1 may be a halide, tosylate, or the like such that LG_1 is displaced by the amino portion of a compound of **A3** to give a compound of formula **A5**.

A compound of formula **A5** may be further elaborated by nucleophilic substitution with a compound of formula **A6** (wherein X_1 is NH and m is zero) to provide a compound of formula **A7**. One versed in the art will recognize that when L_2 is asymmetrical, a nitrogen-protecting group may be necessary to avoid

competing reactions. A G-substituent of Formula (I) may be installed by treatment of the terminal amine of a compound of formula **A7** with an activated amidine of formula **A8** wherein LG_2 is a leaving group such as a halide, an alkoxide, an imidazole or pyrazole, an activated alkoxide, or the like, to give compound **IA** of Formula (I) wherein m is zero. Alternatively, when m is equal to one, an oxy-guanidine substituent may be incorporated by treatment of a compound of formula **A7** with a compound of formula **A9** to form a compound **(I)A** of Formula (I) wherein m is one.

Scheme B illustrates the general synthesis of compounds of the present invention wherein L_2 is $-NHC(=O)-(CH_2)_{1-4}-$. A compound of formula **A5** may be converted to its corresponding amine by treatment with ammonia, or other source of ammonia such as ammonium hydroxide, to give a compound of formula **B1**. The amino group of a compound **B1** may be acylated using conventional chemistry with a compound of formula **B2**, wherein LG_3 is a leaving group such as a halide when **B2** is an acid chloride, a hydroxy group when **B2** is a carboxylic acid, an alkylcarboxylate when **B2** is an anhydride, or an imidazole when **B2** is an acylimidazole. Alternatively, **B2** may be an activated ester or the like. The K substituent of compounds of formula **B2** is either a leaving group LG_1 as defined herein, or K is an R^a-substituted amino group protected with an appropriate amino-protecting group (PG).

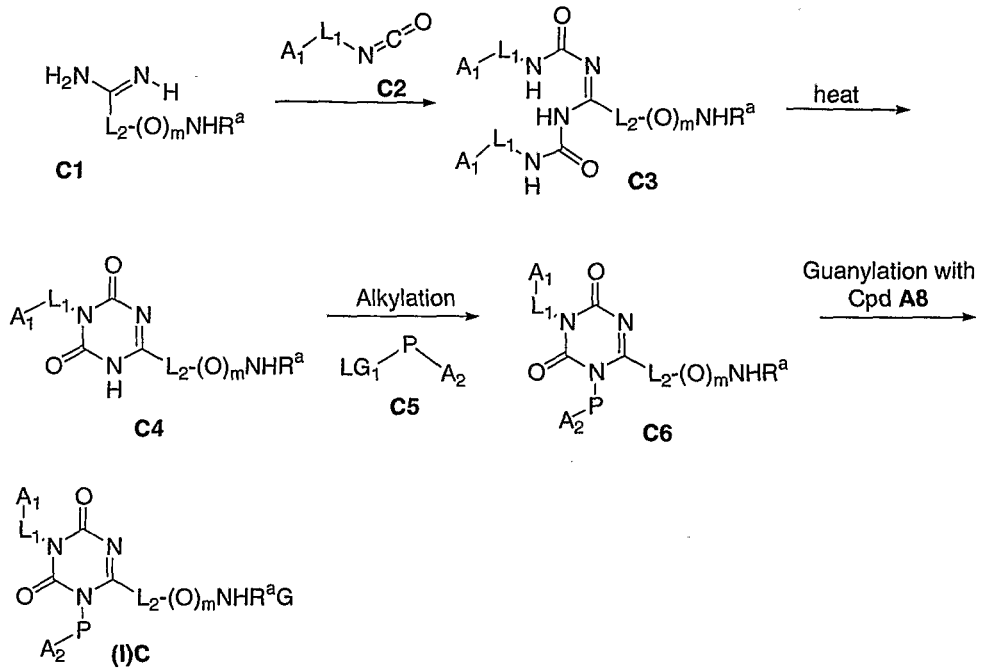
Scheme B



To prepare a compound of formula **B4**, a compound of formula **B3** may either be N-deprotected (when K is $-NR^a(PG)$) using reagents and methods known to one versed in the art, or may undergo a nucleophilic displacement with amine H_2NR^a (when K is a LG_1). The resulting amine of formula **B4** may then be treated with an activated amidine of formula **A8** to give a compound **(I)B** of Formula (I).

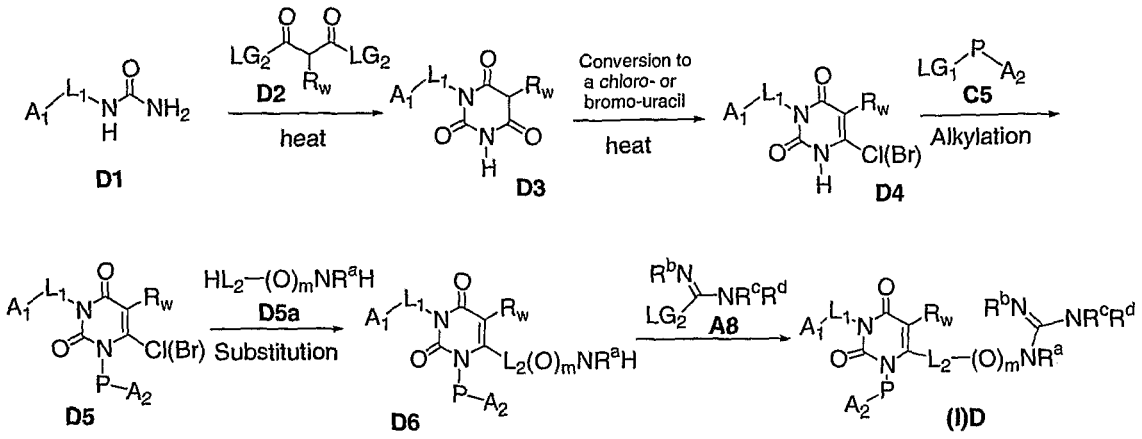
Scheme C describes the general synthesis of compounds of the present invention wherein X_1 of L_2 is a direct bond and L_2 is any of those which contains X_1. A compound of formula **C1** may be condensed with an isocyanate of formula **C2** to give a compound of formula **C3** which, upon heating, affords a triazine of formula **C4**. The amino group of a compound of formula **C4** may be appropriately substituted using an alkylating agent of formula **C5** to afford a compound of formula **C6**. A G-substituent may be introduced into a compound of formula **C6** using the methods described herein to provide a compound **(I)C** of Formula (I).

Scheme C



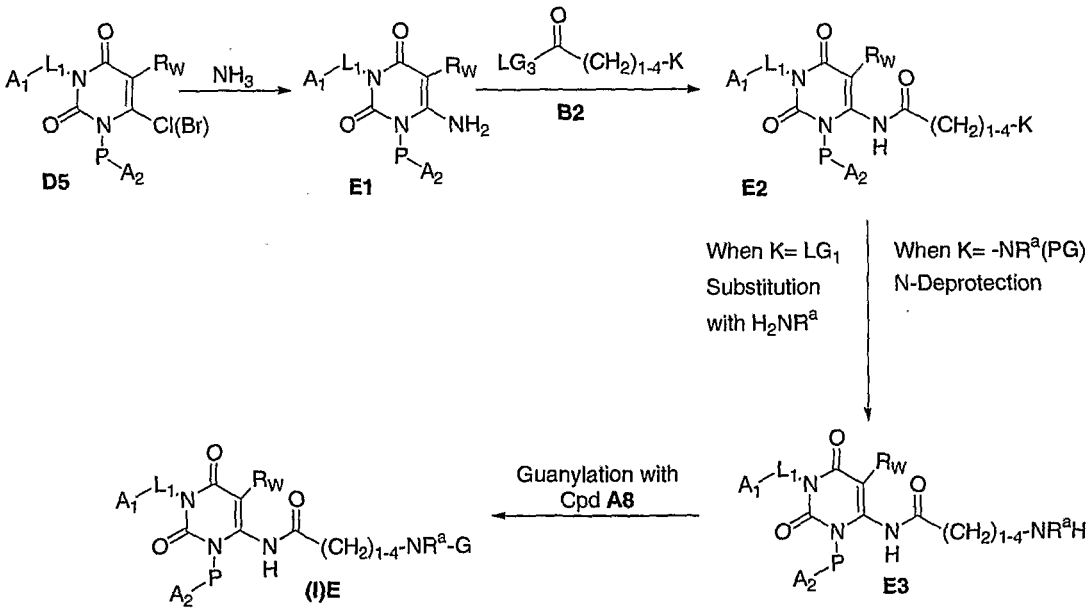
Scheme D illustrates the general synthesis of compounds of the present invention wherein W is $C(R_w)$, L_2 is other than $-NHC(=O)-(CH_2)_{1-4}-$ or $-C(=O)NH(CR^yR^z)_{2-5}-$, and X_1 of L_2 is NH, O, or S. A compound of formula **D1** may be condensed with a compound of formula **D2** with heating, (wherein LG_2 is C_{1-4}alkoxy, choro, or the like) to form a compound of formula **D3**. A compound of formula **D3** may then be treated with phosphorus oxychloride, PCl_5, or the like and heat to afford a compound of formula **D4**; alternatively, the bromo analog may be used in this synthetic sequence, which is prepared from **D3** using phosphorus oxybromide in place of phosphorus oxychloride. A compound of formula **C5** may be used to install $-P-A_2$ via conventional alkylation procedures. A compound of formula **D5** may be elaborated via a nucleophilic displacement of the chloride or bromide with a compound of Formula **D5a** (wherein X_1 is NH, O, or S) to afford a compound of formula **D6**. Further elaboration using the chemistry described herein may be employed to provide compound **(I)D** of Formula (I).

Scheme D



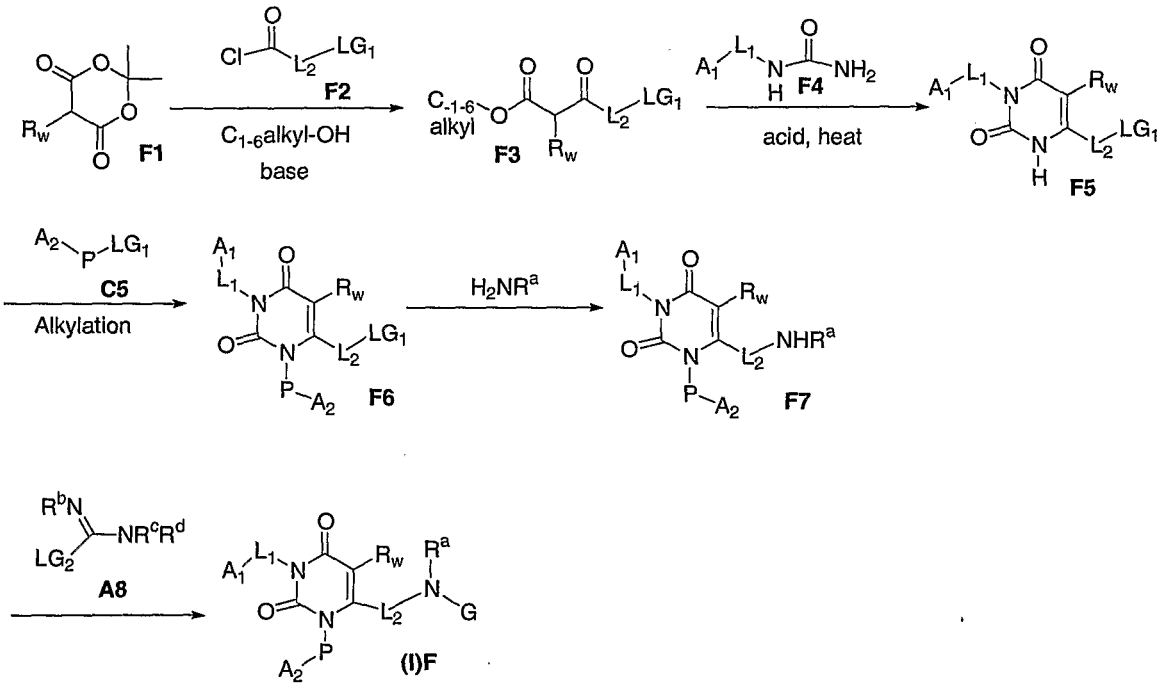
Scheme E illustrates the general synthesis of compounds of the present invention wherein W is $C(R_W)$ and L_2 is $-NHC(=O)-(CH_2)_{1-4}-$. A compound of formula **D5** may be treated with ammonia or other source of ammonia such as ammonium hydroxide to afford the corresponding amino compound of formula **E1**. The amino group may be acylated with a compound of formula **B2** and further elaborated to a compound **(I)E** of Formula (I) using the methods described herein.

Scheme E



Scheme F illustrates the general synthesis of compounds of the present invention wherein W is $C(R_w)$, X_1 of L_2 is a direct bond and L_2 is any one of those which includes X_1. A compound of formula **F1** may be condensed with a compound of formula **F2** under basic conditions in the presence of a lower alkyl alcohol to form a compound of formula **F3**. A compound of formula **F3** may be condensed with a urea of formula **F4** to form a cyclic compound of formula **F5**.

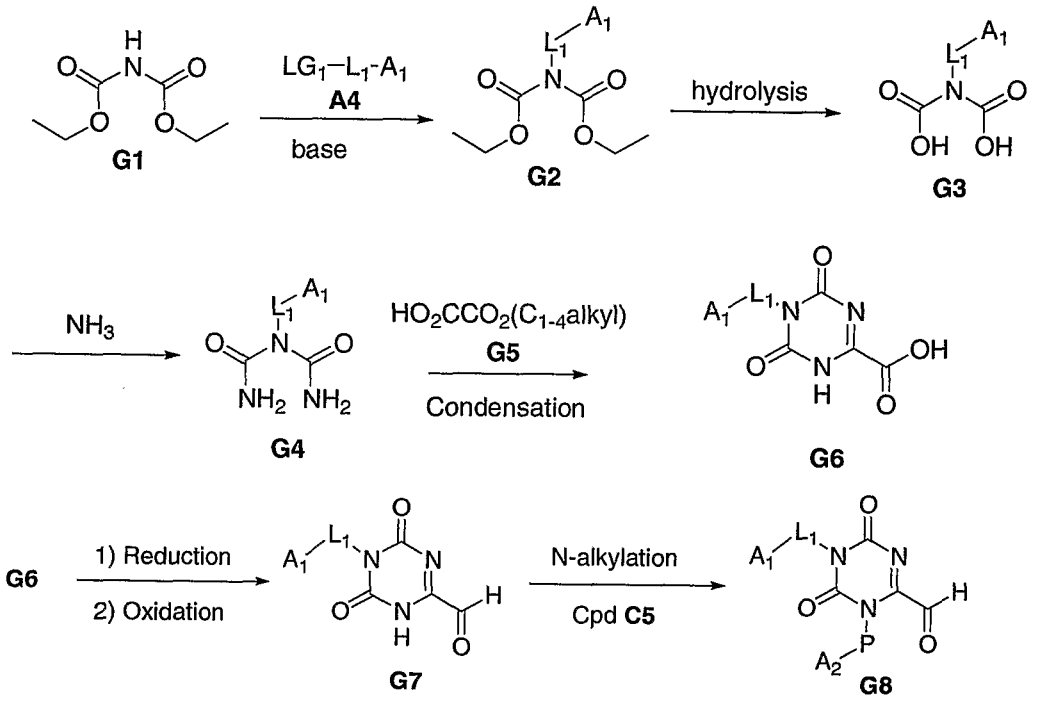
Scheme F

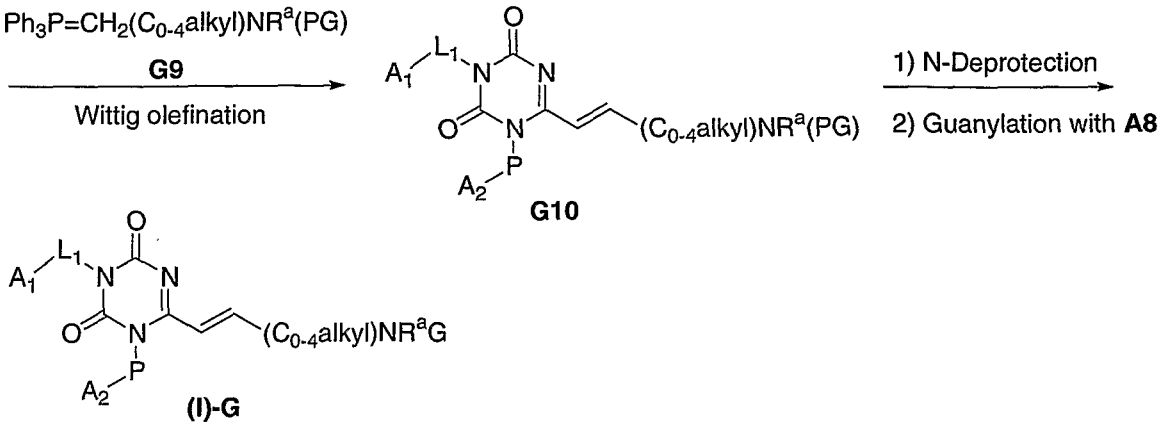


A compound of formula **F5** may be alkylated with an alkylating agent **C5** using conventional chemistry known to one versed in the art to prepare a compound of formula **F6**. A nucleophilic displacement of LG_1 with amine H_2NR^a affords a compound of formula **F7**, which may be further elaborated to include a G-substitutent using the methods described herein to give a compound **(I)F** of Formula (I).

Scheme G illustrates the general synthesis of compounds of the present invention wherein W is N and L_2 is $-X_2-(CH_2)_{0-4}-$. A compound of formula **G1** (either commercially available or prepared by known methods described in the scientific literature) may be treated with a base followed by alkylation with a compound of formula **A4** to afford a compound of formula **G2**. Treatment of a compound of formula **G2** with an aqueous base such as sodium hydroxide gives a compound of formula **G3**, which upon treatment with ammonia or its equivalent provides a compound of formula **G4**. The compound of formula **G4** may then be condensed with a compound of formula **G5** to form a triazine compound of formula **G6**.

Scheme G



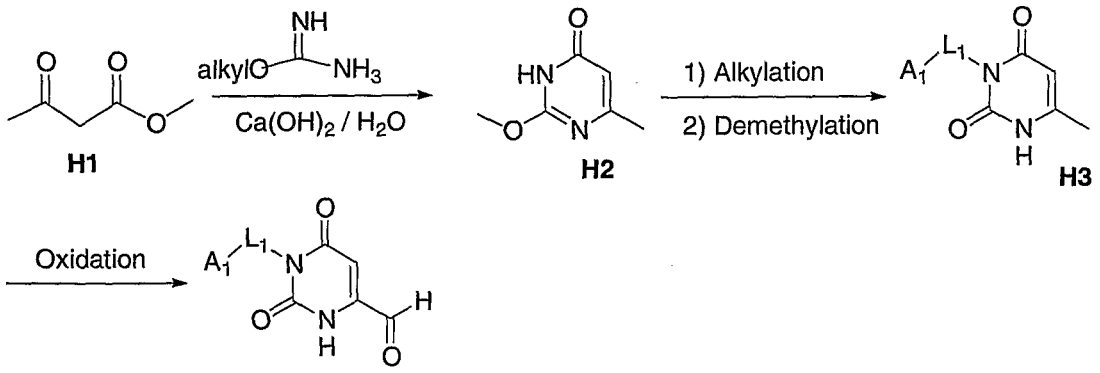


Using conventional reagents and methods known to one skilled in the art, the carboxy group of compounds of **G6** may be reduced to the corresponding alcohol, followed by oxidation to an aldehyde of formula **G7**. The secondary amino group may be substituted with a compound of formula **C5** using coupling chemistry or standard alkylation chemistry to afford a compound of formula **G8**. The aldehyde portion of the compound may participate in a Wittig olefination with a compound of formula **G9** (wherein PG is as previously defined) to provide a compound of formula **G10** wherein L_2 includes an alkenyl group, X_2. Subsequent removal of the amino-protecting group followed by guanylation gives a compound of Formula **(I)G**.

Scheme H illustrates the general synthesis of compounds of the present invention wherein W is CH and L_2 is $-X_2-(CH_2)_{0-4}-$. A compound of formula **H1** may be condensed with an O-alkylated isourea to afford a cyclic compound of formula **H2**. The amine may be deprotonated with an organometallic base and subsequently treated with a compound of formula **A4** to install the $-L_1A_1$ substituents of Formula (I). O-demethylation of the alkylated compounds of **H2** afford compounds of formula **H3**. Using conventional oxidation chemistry, the methyl substituent of **H3** may be converted to its corresponding aldehyde, affording a compound of formula **H4**. The aldehyde may be elaborated to a compound of Formula (I) wherein L_2 is $-X_2-(CH_2)_0$-

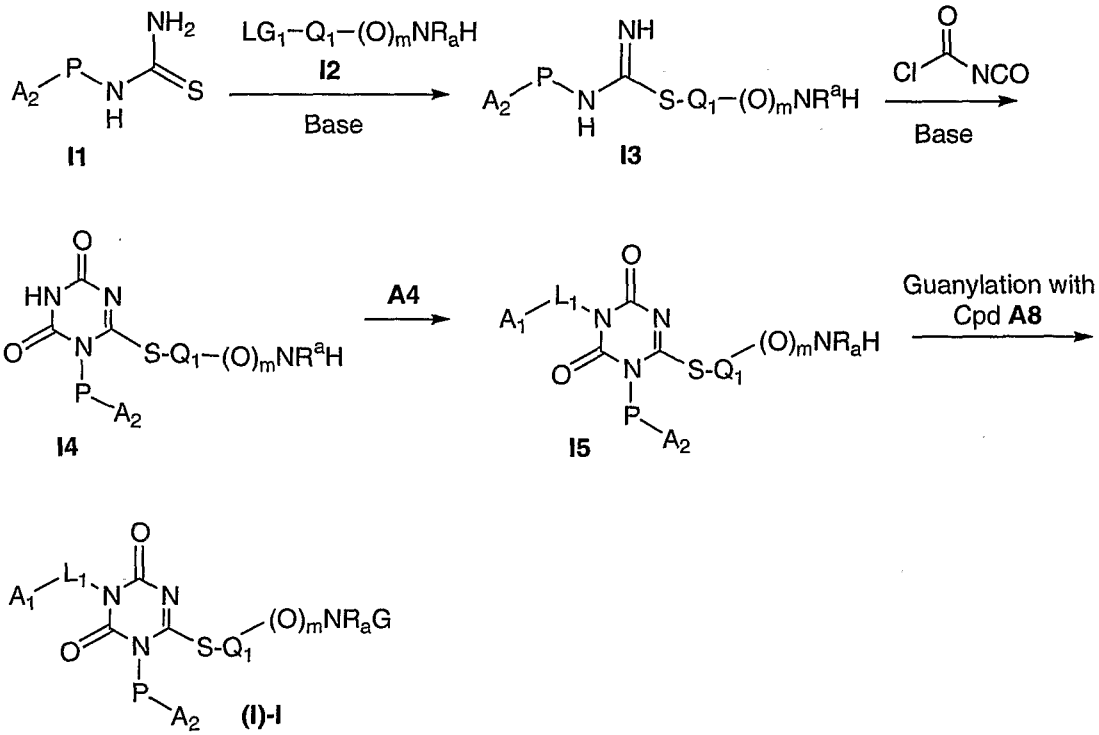
4- using the synthetic steps described in Scheme G for the conversion of a compound **G7** to compounds of formula **(I)G**.

Scheme H



Scheme I depicts the general synthesis of compounds of the present invention wherein L_2 of Formula (I) is one which contains an X_1 group, and W is N. In Scheme I, X_1 is S.

Scheme I

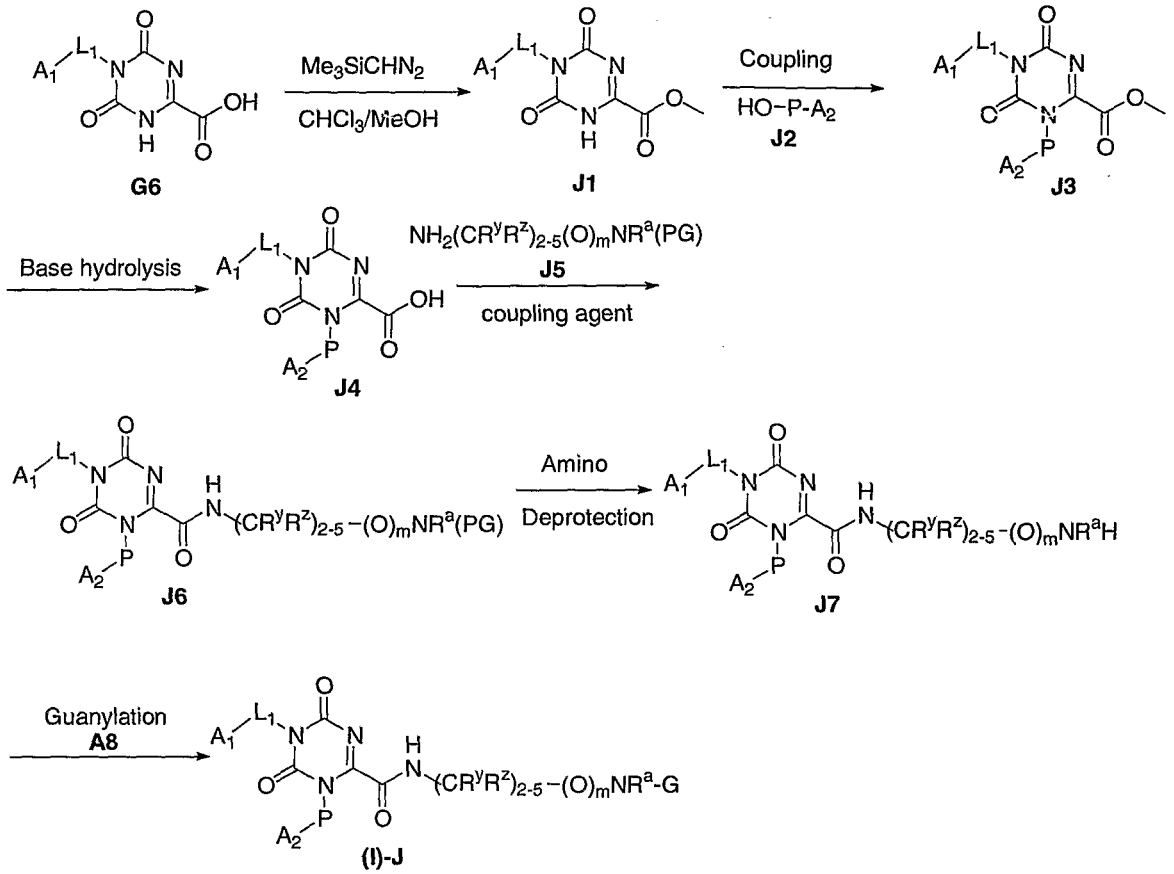


Q_1 = $-(CH_2)_u-X_2-(CH_2)_v-$, $-(CH_2)_{2-3}-X_3-(CH_2)_{2-3}-$, or $-CH(R^x)-(CR^yR^z)_{1-5}-$.

A compound of formula **I1** (either commercially available or prepared by known methods described in the scientific literature) may be alkylated under basic conditions with a compound of formula **I2** (wherein Q_1 is $-(CH_2)_u-X_2-(CH_2)_v-$, $-(CH_2)_{2-3}-X_3-(CH_2)_{2-3}-$, or $-CH(R^x)-(CR^yR^z)_{1-5}-$) to provide a compound of formula **I3**. A compound of formula **I3** may be condensed with an appropriately substituted isocyanate such as *N*-chlorocarbonyl isocyanate in the presence of excess tertiary amine such as diisopropylethylamine to give a triazine of formula **I4**. A compound of formula **I4** may be alkylated with a compound of formula **A4** to provide a compound of formula **I5**, which may then be guanylated according the methods described herein to provide a compound of formula (I)-I.

Scheme J illustrates the general synthesis of compounds of the present invention wherein L_2 is $-C(=O)NH(CR^yR^z)_{2-5}-$ and W is N.

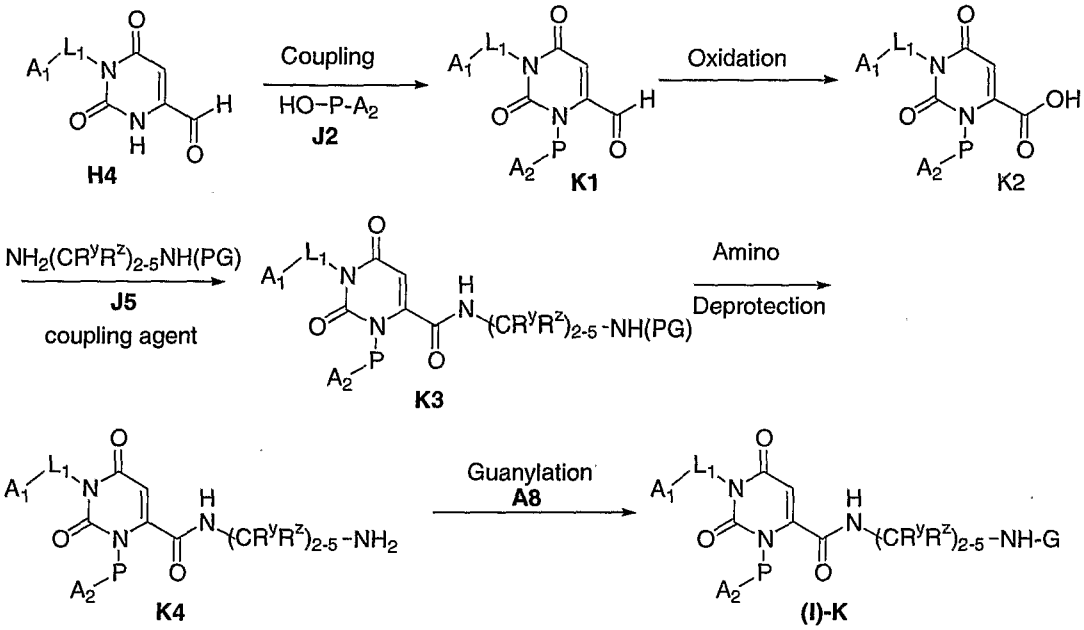
Scheme J



A compound of Formula **G6** may be treated with a methylating agent such as trimethylsilyl diazomethane to give the methyl ester of formula **J1**. Under Mitsunobu type coupling conditions (in the presence of a coupling agent, activating agent), an alcohol of formula **J2** may be coupled with the secondary amine of a compound of formula **J1** to afford a compound of formula **J3**. Standard base hydrolysis of the methyl ester gives a compound of formula **J4**, wherein the corresponding carboxylic acid may be coupled with an amine of formula **J5** (PG is an appropriate amino protecting group) to afford a compound of formula **J6**. Standard removal of the amino protecting group, PG, yields the primary amine of formula **J7**, which may be guanylated according to the methods described herein to yield a compound of formula (I)-J.

Scheme K illustrates the general synthesis of compounds of the present invention wherein L_2 is -C(=O)NH(CR^yR^z)$_{2-5}$- and W is CH.

Scheme K



A compound of formula **H4** may be treated under Mitsunobu-type coupling conditions (in the presence of a coupling agent and activating agent), with an alcohol of formula **J2** to afford a compound of formula **K1**. Oxidation of the aldehyde group using an appropriate oxidizing agent gives a compound of formula **K2**, wherein the corresponding carboxylic acid may be coupled with an amine of formula **J5** (PG is an appropriate amino protecting group) to afford a compound of formula **K3**. The conventional removal of the amino protecting group, PG, yields the primary amine of formula **K4**, which may be guanylated according to the methods described herein to yield a compound of formula (I)-K.

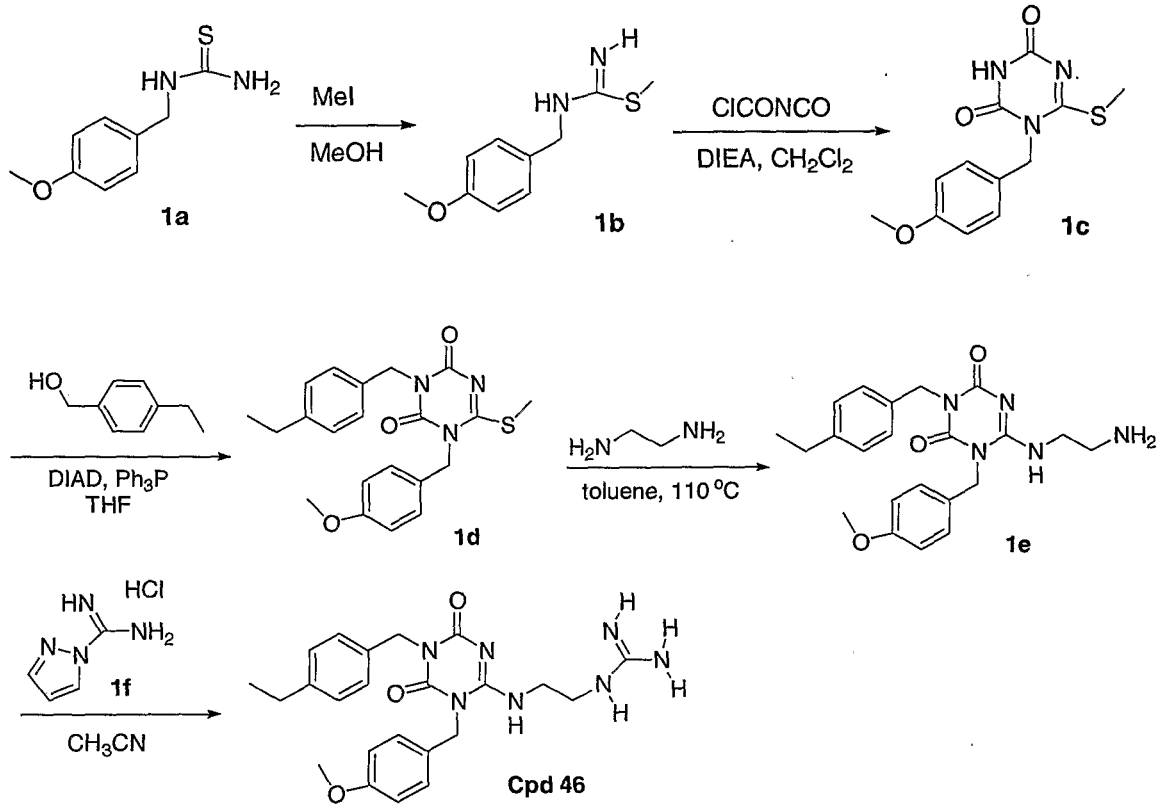
SPECIFIC EXAMPLES

Specific compounds which are representative of this invention were prepared as per the following examples and reaction sequences; the examples and the diagrams depicting the reaction sequences are offered by way of illustration, to aid in the understanding of the invention and should not be construed to limit in any way the invention set forth in the claims which follow thereafter. The instant compounds may also be used as intermediates in subsequent examples to produce additional compounds of the present invention. No attempt has been made to optimize the yields obtained in any of the reactions. One skilled in the art would know how to increase such yields through routine variations in reaction times, temperatures, solvents and/or reagents.

Reagents were purchased from commercial sources. Nuclear magnetic resonance (NMR) spectra for hydrogen atoms were measured in the indicated solvent with (TMS) as the internal standard on a Bruker–Biospin Inc. DRX 500 (500 MHz) or DPX 300 (300 MHz) spectrometer. The values are expressed in parts per million downfield from TMS. The mass spectra (MS) were determined on a Micromass Platform LC spectrometer, an Agilent LC spectrometer or a Micromass LCT spectrometer using electrospray techniques. Microwave accelerated reactions were performed using a CEM Discover microwave instrument, and were contained in a sealed pressure vessel unless otherwise noted. Stereoisomeric compounds may be characterized as racemic mixtures or as separate diastereomers and enantiomers thereof using X-ray crystallography and other methods known to one skilled in the art. Unless otherwise noted, the materials used in the examples were obtained from readily available commercial suppliers or synthesized by standard methods known to one skilled in the art of chemical synthesis. The substituent groups, which vary between examples, are hydrogen unless otherwise noted.

EXAMPLE 1

N-{2-[5-(4-Ethyl-benzyl)-1-(4-methoxy-benzyl)-4,6-dioxo-1,4,5,6-tetrahydro-[1,3,5]triazin-2-ylamino]-ethyl}-guanidine (Cpd 46)



A. **1-(4-Methoxy-benzyl)-6-methylsulfanyl-1*H*-[1,3,5]triazine-2,4-dione (Cpd_1c).** To (4-methoxy-benzyl) thiourea (2.00 g, 10.1 mmol) in MeOH (40 mL) was added methyl iodide (0.64 mL, 10.1 mmol). The reaction was stirred at room temperature for 24 h. The reaction mixture was concentrated to yield 2.00 g of crude compound (1b) that was used in the next step without further purification.

B. To Compound **1b** (3.6 g, 17.1 mmol) in methylene chloride (40 mL) was added excess diisopropylethylamine (6.61 g, 51.3 mmol). The reaction mixture was cooled to 0 C. A portion of *N*-chlorocarbonyl isocyanate (1.78 g, 17.1 mmol) was added dropwise. The reaction mixture was allowed to slowly warm to room

temperature. After 24 h, water was added and the reaction mixture was extracted with ethyl acetate. The phases were separated, and the organic layer was dried over sodium sulfate, filtered, and concentrated. Methanol was added to the crude product, and the solid was collected by vacuum filtration to give Compound **1c** (1.5 g). ^{1}H NMR (DMSO-d_6) δ 2.45 (3H, s), 3.73 (3H, s), 4.98 (2H, s), 6.89-6.92 (2H, d, J = 8.5 Hz), 7.22-7.25 (2H, d, J = 8.5 Hz), 11.58 (1H, s).

C. **3-(4-Ethyl-benzyl)-1-(4-methoxy-benzyl)-6-methylsulfanyl-1*H*-[1,3,5]triazine-2,4-dione (Cpd 1d).** To Cpd **1c** (0.1 g, 0.35 mmol) in tetrahydrofuran was added 4-ethylbenzyl alcohol (0.049 g, 0.35 mmol), triphenylphosphine (0.19 g 0.71 mmol) and diisopropyl azodicarboxylate (0.087 g, 0.43 mmol). The reaction stirred at room temperature for 64 h. The reaction mixture was taken up in ethyl acetate, washed with water, and the phases were separated. The organic layer was dried over sodium sulfate, filtered, and concentrated. The resulting material was purified by normal phase chromatography using an ISCO automated system to give Cpd **1d** (0.14 g) as a white solid.

D. **6-(2-Amino-ethylamino)-3-(4-ethyl-benzyl)-1-(4-methoxy-benzyl)-1*H*-[1,3,5]triazine-2,4-dione (Cpd 1e).** To 1-(4-methoxy-benzyl)-6-methylsulfanyl-1*H*-[1,3,5]triazine-2,4-dione (0.14 g, 0.33 mmol) in toluene was added excess ethylenediamine (0.10 g, 1.76 mmol). The reaction mixture was heated at 110 C for 18 h. The reaction mixture was cooled to room temperature, diluted with water and extracted with ethyl acetate. The phases were separated and the organic layer was dried over sodium sulfate, filtered and concentrated. The resultant Cpd **1e** (0.11 g) was used in the next step without further purification.

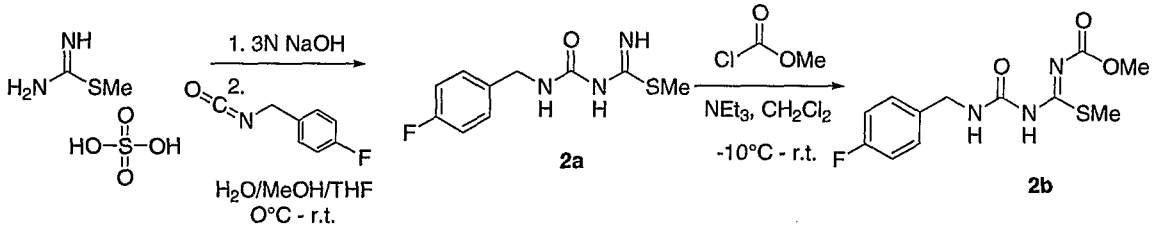
E. ***N*-{2-[5-(4-Ethyl-benzyl)-1-(4-methoxy-benzyl)-4,6-dioxo-1,4,5,6-tetrahydro-[1,3,5]triazin-2-ylamino]-ethyl}-guanidine (Cpd 46).** To a mixture of Cpd **1e** (0.11 g, 0.26 mmol) in acetonitrile (4 mL) was added excess

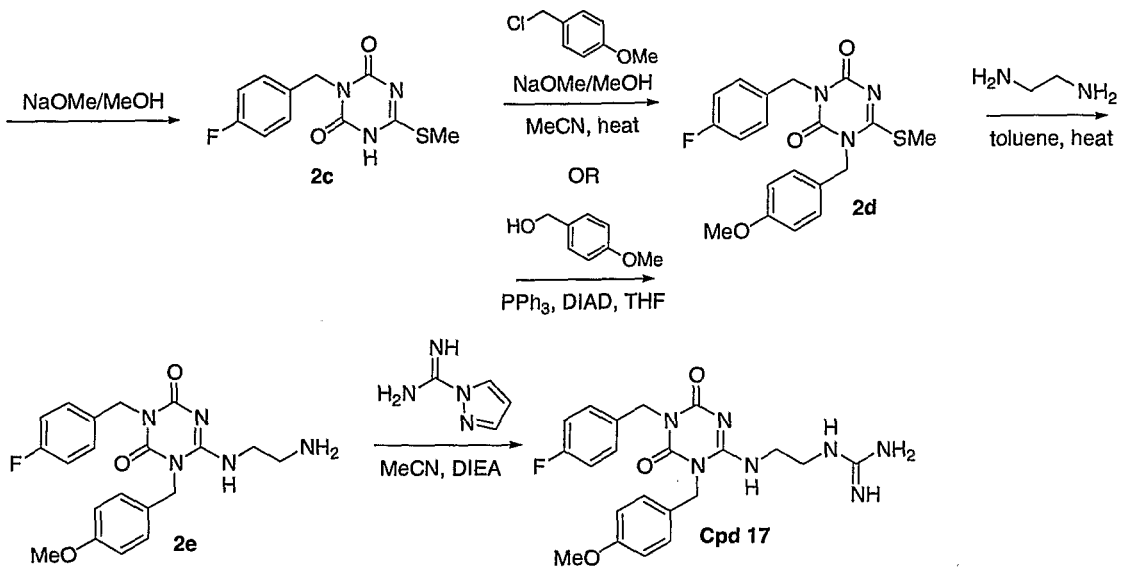
diisopropylamine (0.069 g, 0.53 mmol) and 1*H*-pyrazolo-1-carboxamidine hydrochloride, Cpd **1f**, (0.039 g, 0.26 mmol). The reaction mixture was stirred for 18 h at room temperature. A white solid precipitated from the reaction mixture and was collected by filtration to give the title compound **46** (98% pure by HPLC, 0.0119 g). ^{1}H NMR (DMSO-d_6) δ 1.01-1.04 (3H, t, J = 7.5Hz), 2.41-2.47 (2H, q, J = 7.4Hz), 3.26-3.16 (4H, m), 3.61 (3H, s), 4.75 (2H, s), 4.93 (2H, s), 6.77-6.79 (2H, d, J = 8.64 Hz), 7.00-7.12 (6H, m), 7.55 (1H, m), 8.06 (1H, m).

Using the procedures of Example 1 and the appropriate reagents, starting materials and purification methods known to those skilled in the art, the following compounds of the present invention were prepared: compounds 39, 45, 77, 78, 79, 80, 82, 83, 109, 111, 112, 123, 124, 131, 136, 137, 145, and 146.

EXAMPLE 2

N-{2-[5-(4-Fluoro-benzyl)-1-(4-methoxy-benzyl)-4,6-dioxo-1,4,5,6-tetrahydro-[1,3,5]triazin-2-ylamino]-ethyl}-guanidine (Cpd 17)





A. **((4-Fluorobenzyl)amino)carbonyl)carbamimidothioic acid methyl ester (Cpd 2a).** S-methylisothiouronium sulfate (10.0 g, 35.9 mmol) was dissolved in 8:2:1 MeOH/ H_2O/ THF and the mixture was treated with 3 N NaOH (12 mL, 35.9 mmol). The solution was then cooled to 0 C and 4-fluorobenzyl isocyanate (5.43 g, 35.9 mmol) was added dropwise over 30 min. The reaction was stirred overnight and gradually warmed to room temperature. The mixture was then washed with saturated aqueous NH_4Cl and extracted with dichloromethane. The combined organic phases were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resultant residue was purified on an Isco flash column (20% EtOAc – 100% EtOAc in heptanes), to give Compound **2a** (4.1 g) as a white powder.

B. **5-(Methylthio)-3,7-dioxo-1-(4-fluorobenzyl)-2-oxa-4,6,8-triazanon-4-en-9-oic acid methyl ester (Cpd 2b).** A solution of Compound **2a** (4.1 g, 17.0 mmol) in dichloromethane was treated with triethylamine (3.08 mL, 22.1 mmol) and the mixture was cooled to –10 C. Methyl chloroformate (2.62 mL, 34.0 mmol) was added dropwise via an addition funnel over 15 min and the reaction was allowed to

stir for 4 h while gradually warming to room temperature. The solution was then washed with saturated aqueous NH_4Cl and extracted with dichloromethane. The combined organic phases were dried over Na_2SO_4, filtered and concentrated. The resultant residue was purified on an Isco flash column (5% MeOH) to afford Compound **2b** (3.63 g) as a white solid.

C. **3-(4-Fluoro-benzyl)-6-methylsulfanyl-1*H*-[1,3,5]triazine-2,4-dione (Cpd 2c).** Compound **2b** (3.63 g, 12.1 mmol) was dissolved in MeOH (100 mL) and the solution was treated with NaOMe in MeOH (4.6 M, 2.90 mL, 13.3 mmol) and the reaction was allowed to stir at room temperature for 1 h. A white precipitate formed upon addition of the NaOMe. The reaction mixture was diluted with 1N HCl (50 mL) and the resultant precipitate was collected by filtration. The solid was dried under reduced pressure at 160 C over xylenes to afford Compound **2c** (3.6 g) as its HCl salt.

D. **3-(4-Fluoro-benzyl)-1-(4-methoxy-benzyl)-6-methylsulfanyl-1*H*-[1,3,5]triazine-2,4-dione (Cpd 2d).** Compound 2c (500 mg, 1.65 mmol) was dissolved in THF and was treated with 4-methoxybenzyl alcohol (227 mg, 1.65 mmol), triphenylphospine (866 mg, 3.30 mmol), and diisopropyl azodicarboxylate (334 mg, 1.65 mmol). The reaction was allowed to stir overnight at room temperature. After monitoring the reaction *via* HPLC, the solution was partitioned between water and ethyl acetate. Combined organic layers were dried over anhydrous sodium sulfate, filtered and reduced. The crude mixture was purified *via* Isco flash column (20% ethyl acetate – 100% ethyl acetate in heptanes, 40 min) to afford 390 mg of Cpd **2d** as a white solid. ^1H NMR (DMSO, d_6). δ 3.29 (s, 3H), 3.74 (s, 3H), 4.93 (s, 2H), 5.03 (s, 2H), 6.89 – 6.92 (d, 2H, J = 8.62), 7.12 – 7.36 (m, 4H), 7.38 – 7.41 (m, 2H).

E. **4-[3-(3,4-Dichloro-benzyl)-6-methylsulfanyl-2,4-dioxo-3,4-dihydro-2*H*-[1,3,5]triazin-1-ylmethyl]-benzamide (Cpd 2d).** Compound **2c** (dichorobenzyl) (200 mg, 0.56 mmol) was dissolved in MeCN and was treated with diisopropylethylamine (0.196 mL, 1.13 mmol) and 4-chloromethyl benzyl chloride (96 mg, 0.56 mmol). The reaction mixture was heated to 80 C and was allowed to stir overnight. The reaction mixture was washed with saturated aqueous NH_4Cl and extracted with ethyl acetate. The combined organic extracts were dried over Na_2SO_4, filtered and concentrated. The resultant crude mixture was purified by Isco flash column (20%– 100% EtOAc in heptanes, 40 min) to afford 70 mg of Cpd **2d** as a white powder.

F. **6-(2-Amino-ethylamino)-3-(4-fluoro-benzyl)-1-(4-methoxy-benzyl)-1H-[1,3,5]triazine-2,4-dione (Cpd 2e).** A solution of Compound 2d (390 mg, 1.01 mmol) in toluene (8 mL) and was treated with ethylenediamine (302 mg, 5.03 mmol). The reaction was heated to 90 C and was allowed to stir overnight. The mixture was then partitioned between water and ethyl acetate. The combined organic layers were dried over Na_2SO_4, filtered and reduced. Reduction provided 390 mg of Cpd **2e** as a crude mixture. The crude compound was used in further synthesis without additional purification.

G. ***N*-{2-[5-(4-Fluoro-benzyl)-1-(4-methoxy-benzyl)-4,6-dioxo-1,4,5,6-tetrahydro-[1,3,5]triazin-2-ylamino]-ethyl}-guanidine (Cpd 17).** A crude mixture of Cpd **2e** (390 mg, 0.98 mmol) was dissolved in acetonitrile (10 mL) and was treated with pyrazole-1-carboxamidine hydrochloride (143 mg, 0.98 mmol) and diisopropylethylamine (0.340 mL, 1.95 mmol). The reaction was allowed to proceed overnight at room temperature. Inspection of the reaction mixture showed that a white precipitate had formed and the precipitate was collected and dried by vacuum filtration . The solid collected afforded 307 mg of Cpd **17** as a white powder. M^+ (ES+) = 442.3. ^1H NMR (DMSO, d_6). δ 3.33 (m, 4H), 3.73 (s, 3H), 4.89 (s, 2H), 5.04

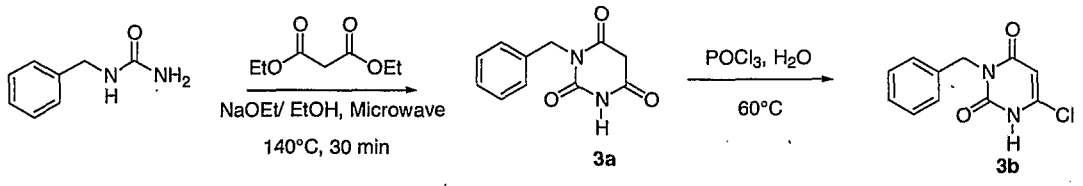
(s, 2H), 6.89 – 6.91 (d, 2H, *J* = 8.66 Hz), 7.10 – 7.16 (t, 2H, *J* = 8.91 Hz), 7.21 – 7.24 (d, 2H, *J* = 8.63 Hz), 7.32 – 7.36 (dd, 2H, *J* = 2.90, 5.57 Hz), 7.66 (s, 1H), 8.19 (s, 1H).

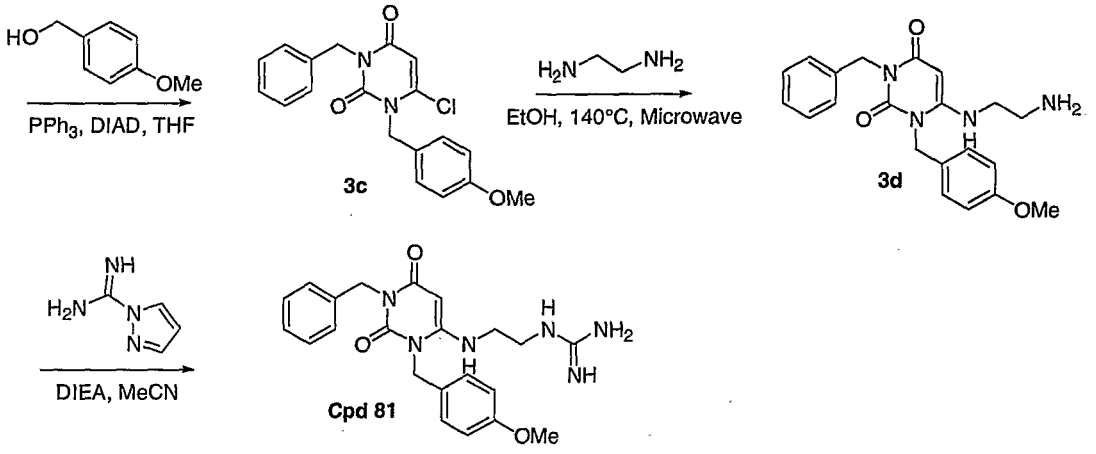
Using the procedures of Example 2 and the appropriate reagents, starting materials and purification methods known to those skilled in the art, the following compounds of the present invention were prepared: compounds 1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13, 14, 15, 16, 18, 19, 20, 21, 22, 23, 24, 25, 25, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 40, 41, 50, 51, 52, 57, 68, 69, 85, 86, 87, 129, 130, 142, 144, 147, 148, 149, and 150.

Cpd 51: **4-[3-(3,4-Dichlorobenzyl)-6-(2-guanidinoethylamino)-2,4-dioxo-3,4-dihydro-2*H*-[1,3,5]triazin-1-yl-methyl]-benzamide** δ (DMSO, d_6) 3.30 – 3.37 (m, 4H), 4.90 (s, 2H), 5.10 (s, 1H), 7.27 – 7.32 (m, 3H), 7.51 – 7.61 (m, 2H), 7.83 (d, 2H, *J* = 9.7 Hz), 7.94 (s, 1H), 8.08 (t, 1H, *J* = 3.7 Hz).

EXAMPLE 3

N-{2-[1-Benzyl-3-(4-methoxy-benzyl)-2,6-dioxo-1,2,3,6-tetrahydro-pyrimidin-4-ylamino]-ethyl}-guanidine (Cpd 81)





A. **1-Benzyl-pyrimidine-2,4,6-trione (Cpd 3a).** *N*-benzyl urea (500 mg, 3.33 mmol) was dissolved in ethanol (8 mL) and the mixture was treated with diethyl malonate (640 mg, 4.0 mmol) and NaOEt in EtOH (1.29 mL, 3.1M, 4.0 mmol). The reaction was then run under microwave conditions at 140 C for 30 min. The solution was reduced in vacuo and the residue was triturated with ethanol. The desired compound was collected by vacuum filtration to give Cpd **3a** (500 mg) as a white powder. ^{1}H NMR (DMSO, d_6). δ 3.69 (s, 2H), 4.87 (s, 2H), 7.21 – 7.31 (m, 5H) 11.41 (s, 1H).

B. **6-Chloro-3-benzyl uracil (Cpd 3b).** Cpd **3a** (500mg, 2.29 mmol) was dissolved in phosphorous oxychloride (3.5 mL, 22.9 mmol) and the reaction mixture was cautiously treated with water (0.103 mL, 5.7 mmol). The solution was heated to 60 C and was stirred overnight. The reaction mixture was then concentrated and the residue was poured over 2N NaOH (15 mL). The crude material was collected by vacuum filtration and purified by recrystallization from ethanol to afford Cpd **3b** (60 mg) as a white powder. A second crop of 300 mg of crude 3b was recovered from the recrystallization and used in subsequent reactions without further purification. ^{1}H NMR (MeOD, d_4). δ 5.04 (s, 2H), 5.87 (s, 1H), 7.25 – 7.38 (m, 5H).

C. **1-(4-Methoxylbenzyl)-6-chloro-3-benzyl uracil (Cpd 3c).** A stirred solution of Cpd **3b** (60 mg, 0.25 mmol) in THF was treated with 4-methoxylbenzyl alcohol (35mg, 0.25 mmol), triphenylphosphine (133 mg, 0.51 mmol) and diisopropyl azocarboxylate (51 mg, 0.25 mmol). The reaction was allowed to stir overnight at room temperature. The mixture was washed with water and extracted with ethyl acetate. Combined organic extracts were dried over Na_2SO_4, filtered and concentrated. The resultant residue was purified by Isco flash column chromatography (20% EtOAc – 100 EtOAc in heptanes, 40 min) to afford Cpd **3c** (60 mg) as a white powder. M^+ (ES+) = 356.9.

D. **6-(2-Amino-ethylamino)-3-benzyl-1-(4-methoxybenzyl)-uracil (Cpd 3d).** Cpd **3c** (60 mg, 0.17 mmol) was dissolved in ethanol (3 mL) and the reaction mixture was treated with ethylenediamine (51 mg, 0.84 mmol). The solution was run at 140 C for 20 min under power max conditions in a microwave reactor. The solution was washed with water and extracted with ethyl acetate. Combined organic phases were dried over Na_2SO_4, filtered and concentrated to give crude Cpd **3d** (35 mg) as a yellow oil. The crude mixture was used in subsequent reactions without further purification.

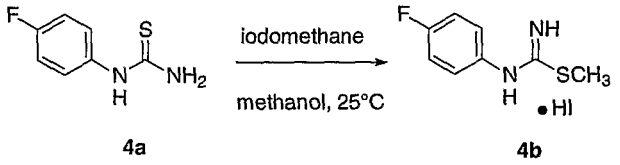
E. ***N*-{2-[1-Benzyl-3-(4-methoxy-benzyl)-2,6-dioxo-1,2,3,6-tetrahydro-pyrimidin-4-ylamino]-ethyl}-guanidine (Cpd 81).** The title compound was prepared as described in Example 2, Step G. The crude material was purified by reverse phase preparative HPLC to give the title compound as its TFA salt (8.2 mg). M+ (ES+) = 422.9. ^{1}H NMR (MeOD, d_4). δ 3.19 – 3.24 (m, 4H), 3.67 (s, 3H), 4.77 (s, 1H), 4.99 (s, 2H), 5.03 (s, 2H), 6.77 – 6.80 (d, 2H, J = 8.79 Hz), 7.01 – 7.04 (d, 2H, J = 8.75 Hz), 7.12 – 7.25 (m, 5H).

Using the procedures of Example 3 and the appropriate reagents, starting materials and purification methods known to those skilled in the art, the following compounds of the present invention were prepared: compound 84.

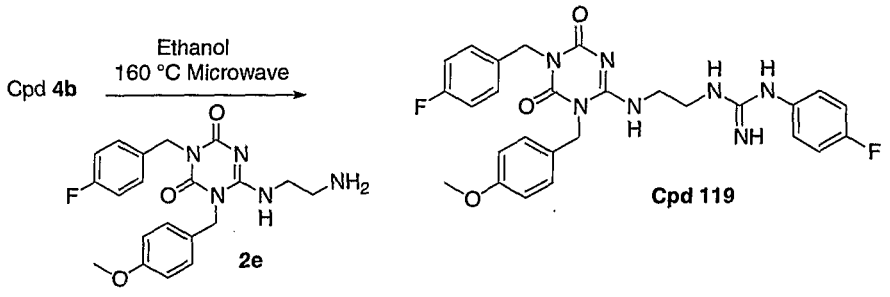
Cpd 84: N-{2-[1,3-Bis-(4-methoxy-benzyl)-2,6-dioxo-1,2,3,6-tetrahydro-pyrimidin-4-ylamino]-ethyl}-guanidine (DMSO, d_6) δ 3.25 – 3.27 (m, 2H), 3.35 – 3.37 (m, 2H), 3.74 (s, 3H), 3.75 (s, 3H), 4.83 (s, 1H), 4.90 (s, 2H), 5.15 (s, 2H), 6.81 – 6.89 (m, 4H), 7.14 – 7.24 (m, 4H), 7.70 (s, 1H).

EXAMPLE 4

N-{2-[5-(4-Fluoro-benzyl)-1-(4-methoxy-benzyl)-4,6-dioxo-1,4,5,6-tetrahydro-[1,3,5]triazin-2-ylamino]-ethyl}-N'-(4-fluoro-phenyl)-guanidine (Cpd 119)



4a 4b



A. **1-(4-Fluoro-phenyl)-2-methyl-isothiourea (Cpd. 4b).** To a solution of (4-Fluoro-phenyl)-thiourea (18.7 mg, 0.11 mmol) and methanol (0.25 mL) was added iodomethane (8 μL, 0.13 mmol). The mixture was stirred at 25°C for 16 h, then concentrated to a residue to provide crude compound **4b**.

C. ***N*-{2-[5-(4-Fluoro-benzyl)-1-(4-methoxy-benzyl)-4,6-dioxo-1,4,5,6-tetrahydro-[1,3,5]triazin-2-yiamino]-ethyl}-*N'*-(4-fluoro-phenyl)-guanidine (Cpd 127).** To a solution of Compound **4b** in ethanol (0.5 mL) was added Compound **2e** (40 mg, 0.10 mmol). The mixture was irradiated in a microwave reactor at 160 C for 15 min, then concentrated. The resulting residue was dissolved into dimethylsulfoxide and purified by reversed-phase chromatography to furnish the title compound **119** (18.3 mg, 0.024 mmol) as its TFA salt. ^{1}H NMR (methanol-d_4): δ 7.42 (m, 2H), 7.24-7.12 (m, 6H), 7.00 (m, 2H), 6.89 (m, 2H), 5.06 (s, 2H), 5.01 (s, 2H), 3.75 (s, 3H), 3.56 (m, 2H), 3.43 (m, 2H); HRMS *m/z* $(M + H)^+$ calcd 536.2222, found 536.2227.

Using the procedures of Example 4 and the appropriate reagents, starting materials and purification methods known to those skilled in the art, the following compounds of the present invention were prepared: compounds 44, 53, 54, 58, 61, 62, 63, 64, 65, 66, 67, 70, 71, 72, 73, 74, 75, 76, 88, 89, 90, 91, 92, 103, 104, 105, 106, 107, 108, 114, 115, 116, 117, 118, 120, 121, 126, 127, 128, 133, 134, 135, 138, 139, 140, 151, 152, 153, 154, 155, and 156.

Cpd 58: *N*-{2-[5-(3,4-Dichloro-benzyl)-1-(4-methoxy-benzyl)-4,6-dioxo-1,4,5,6-tetrahydro-[1,3,5]triazin-2-ylamino]-ethyl}-*N'*-isopropyl-guanidine. ^{1}H NMR (methanol-d_4): δ 7.56 (s, 1H), 7.45 (d, 1H, J = 8.3 Hz), 7.35 (d, 1H, J = 8.3 Hz), 7.22 (d, 2H, J = 8.3 Hz), 6.89 (d, 2H, J = 8.4 Hz), 5.12 (s, 2H), 5.01 (s, 2H), 3.77 (s, 3H), 3.68 (m, 1H), 3.57 (t, 2H, J = 6.3 Hz), 3.41 (t, 2H, J = 6.3 Hz), 1.17 (d, 6H, J = 6.5 Hz); HRMS *m/z* $(M + H)^+$ calcd 534.1787, found 534.1792.

Cpd 90: *N*-(4-Cyano-phenyl)-*N'*-{2-[5-(4-fluoro-benzyl)-1-(4-methoxy-benzyl)-4,6-dioxo-1,4,5,6-tetrahydro-[1,3,5]triazin-2-ylamino]-ethyl}-guanidine. ^{1}H NMR

(methanol-d_4): δ 7.74 (d, 2H, J = 8.7 Hz), 7.44 (m, 2H), 7.35 (d, 2H, J = 8.3 Hz), 7.21 (d, 2H, J = 8.6 Hz), 7.01 (t, 2H, J = 8.8 Hz), 6.88 (d, 2H, J = 8.8 Hz), 5.11 (s, 2H), 5.02 (s, 2H), 3.75 (s, 3H), 3.61 (t, 2H, J = 6.3 Hz), 3.51 (m, 2H); HRMS *m/z* $(M + H)^+$ calcd 543.2268, found 543.2273.

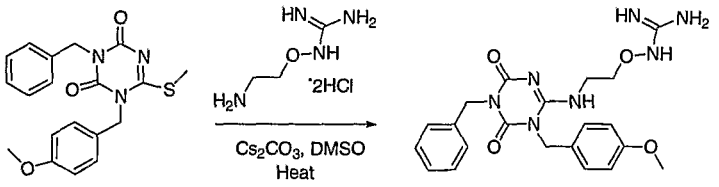
Cpd 104: ***N*-{2-[5-(4-Fluoro-benzyl)-1-(4-methoxy-benzyl)-4,6-dioxo-1,4,5,6-tetrahydro-[1,3,5]triazin-2-ylamino]-ethyl}-*N'*-pyridin-2-yl-guanidine.** ^{1}H NMR (DMSO-d_6): δ 10.90 (br, 1H), 9.78 (br, 1H), 8.65 (br, 2H), 8.17 (d, 1H, J = 5.4 Hz), 8.07 (m, 1H), 7.87 (t, 1H, J = 7.8 Hz), 7.33 (m, 2H), 7.13 (m, 4H), 7.05 (d, 1H, J = 8.2 Hz), 6.78 (d, 2H, J = 8.7 Hz), 4.98 (s, 2H), 4.86 (s, 2H), 3.67 (s, 3H), 3.54 (m, 2H), 3.36 (br, 2H); HRMS *m/z* $(M + H)^+$ calcd 519.2268, found 519.2253.

Cpd 118: ***N*-{2-[5-(4-Fluoro-benzyl)-1-(4-methoxy-benzyl)-4,6-dioxo-1,4,5,6-tetrahydro-[1,3,5]triazin-2-ylamino]-ethyl}-*N'*-(2-fluoro-phenyl)-guanidine.** ^{1}H NMR (methanol-d_4): δ 7.47-7.37 (m, 3H), 7.31 (t, 1H, J = 7.8 Hz), 7.23 (m, 2H), 7.18 (d, 2H, J = 8.6 Hz), 7.01 (t, 2H, J = 8.8 Hz), 6.89 (d, 2H, J = 8.8 Hz), 5.06 (s, 2H), 5.01 (s, 2H), 3.76 (s, 3H), 3.56 (t, 2H, J = 6.3 Hz), 3.45 (t, 2H, J = 6.3 Hz); HRMS *m/z* $(M + H)^+$ calcd 536.2222, found 536.2227.

Cpd 134: ***N*-Benzoyl-*N'*-{2-[5-(4-fluoro-benzyl)-1-(4-methoxy-benzyl)-4,6-dioxo-1,4,5,6-tetrahydro-[1,3,5]triazin-2-ylamino]-ethyl}-guanidine.** ^{1}H NMR (methanol-d_4): δ 7.93 (d, 2H, J = 8.2 Hz), 7.70 (t, 1H, J = 7.5 Hz), 7.57 (t, 2H, J = 7.5 Hz), 7.41 (m, 2H), 7.16 (d, 2H, J = 8.7 Hz), 6.97 (t, 2H, J = 8.7 Hz), 6.85 (d, 2H, J = 8.7 Hz), 5.08 (s, 2H), 4.99 (s, 2H), 3.70 (s, 3H), 3.66 (t, 2H, J = 6.2 Hz), 3.55 (t, 2H, J = 6.2 Hz); HRMS *m/z* $(M + H)^+$ calcd 546.2265, found 546.2259.

EXAMPLE 5

N-{2-[5-Benzyl-1-(4-methoxy-benzyl)-4,6-dioxo-1,4,5,6-tetrahydro-[1,3,5]triazin-2-ylamino]-ethyl}-oxyguanidine (Cpd 27)



5a Cpd 27

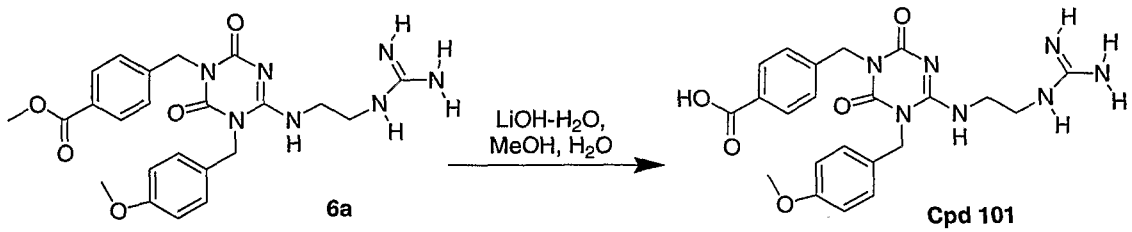
A. Compound **5a** was prepared by the method described in Example 1, Step C, substituting phenyl methanol for 4-ethylbenzyl alcohol.

B. To 3-benzyl-1-(4-methoxy-benzyl)-6-methylsulfanyl-1*H*-[1,3,5]triazine-2,4-dione **5a** (0.056 g, 0.15 mmol) in DMSO (1 mL) was added *N*-(2-amino-ethyl)-oxyguanidine dihydrochloride salt (0.058 g, 0.30 mmol) and Cs_2CO_3 (0.098 mg, 0.30 mmol). The reaction mixture was heated at 70 C for 5 h and cooled to rt. *N*-(2-Amino-ethyl)-oxyguanidine dihydrochloride salt (0.058 g, 0.30 mmol) and Cs_2CO_3 (0.098 mg, 0.30 mmol) were again added and the resulting slurry stirred at 40 C for 16 h. The reaction mixture was cooled to room temperature, loaded onto a 1g C-18 SPE cartridge, and eluted with CH_3CN. The eluant was concentrated and the resulting residue was purified by reverse-phase liquid chromatography using a gradient of 90:10 (acetonitrile: water, with 0.1% TFA) to 90:10 (acetonitrile: water, with 0.1% TFA) to give the title compound **27** (99% pure by HPLC, 0.0289 g). ^1H NMR (d^6-DMSO/$CDCl_3$) δ 3.65-3.73 (2H, m), 3.78 (3H, s), 3.96-4.04 (2H, m), 5.01 (2H, s), 5.10 (2H, s), 6.85 (2H, d, J = 8.7 Hz), 7.21-7.40 (7H. m), 7.74 (4H, bs); 7.89 (1H, m) 11.58 (1H, bs); HRMS calcd. for $C_{21}H_{26}N_7O_4$ m/z 440.2046 (M+H), found: 440.2030.

Using the procedures of Example 5 and the appropriate reagents, starting materials and purification methods known to those skilled in the art, the following compounds of the present invention were prepared: compound 10.

EXAMPLE 6

4-[4-(2-Guanidino-ethylamino)-3-(4-methoxy-benzyl)-2,6-dioxo-3,6-dihydro-2*H*-[1,3,5]triazin-1-ylmethyl]-benzoic acid (Cpd 101)



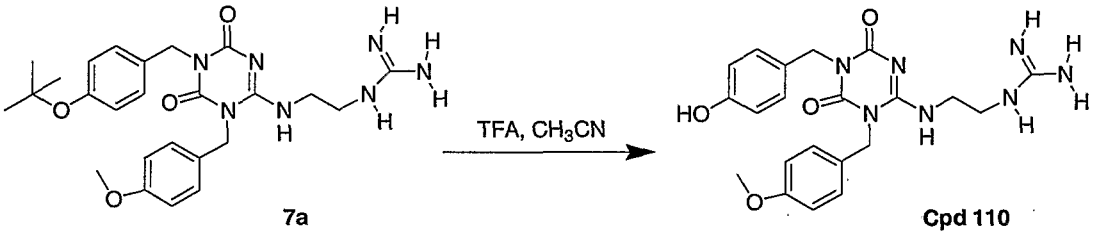
6a Cpd 101

A. Compound **6a** was prepared according to the methods described in Example 1, and substituting 4-hydroxymethyl-benzoic acid methyl ester for 4-ethylbenzyl alcohol.

B. **4-[4-(2-Guanidino-ethylamino)-3-(4-methoxy-benzyl)-2,6-dioxo-3,6-dihydro-2*H*-[1,3,5]triazin-1-ylmethyl]-benzoic acid (Cpd. 101).** A mixture of compound **6a** (20mg, 0.028mmol) and lithium hydroxide (6 mg, 0.014 mmol) in 5 mL of MeOH and 1 mL of H_2O was allowed to stir overnight at room temperature. At that time, an additional 6 mg of lithium hydroxide was added and the mixture stirred for and additional 18 h. The mixture was then concentrated and purified by HPLC. The title compound **101** was obtained as its TFA salt (10 mg, 0.014 mmol). ^{1}H NMR (DMSO-d_6) δ 3.26 (m, 2H), 3.40 (m, 2H), 3.68 (s, 3H), 4.97 (s, 2H), 5.02 (s, 2H), 6.79-6.82 (d, 2H, J = 8.7 Hz), 7.06-7.09 (d, 2H, J = 8.7 Hz), 7.35-7.38 (d, 2H, J = 8.2 Hz), 7.86-7.88 (d, 2H, J = 8.3 Hz).

EXAMPLE 7

N-{2-[5-(4-Hydroxy-benzyl)-1-(4-methoxy-benzyl)-4,6-dioxo-1,4,5,6-tetrahydro-[1,3,5]triazin-2-ylamino]-ethyl}-guanidine (Cpd 110)



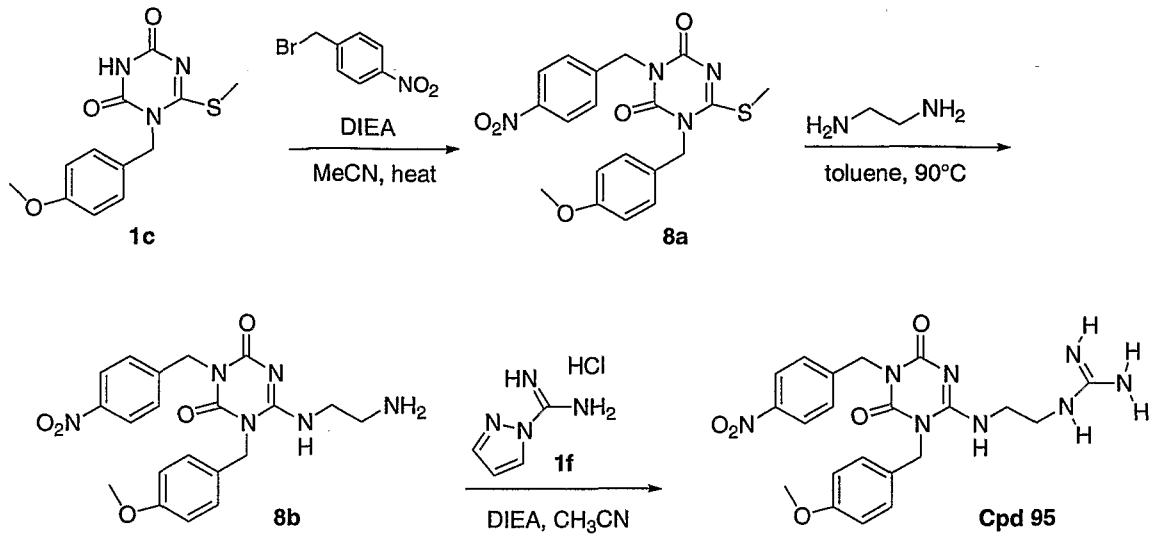
7a Cpd 110

A. Compound **7a** was prepared according to the methods described in Example 1, and substituting (4-tert-butoxy-phenyl)-methanol) for 4-ethylbenzyl alcohol.

B. ***N*-{2-[5-(4-Hydroxy-benzyl)-1-(4-methoxy-benzyl)-4,6-dioxo-1,4,5,6-tetrahydro-[1,3,5]triazin-2-ylamino]-ethyl}-guanidine (Cpd 110).** The crude Compound **7a** (assumed to be about 0.24 mmol) was dissolved in CH_3CN. To this mixture was added 3 mL of TFA. The resulting mixture was allowed to stir overnight at room temperature. The mixture was concentrated and purified by HPLC to give the title compound **110** as its TFA salt (31 mg, 0.046 mmol). ^1H NMR (DMSO-d_6) δ 1.25-1.28 (m, 1H), 3.28-2.31 (m, 2H), 3.31-3.36 (m, 2H), 3.73 (s, 3H), 4.78 (s, 2H), 4.98 (s, 2H), 6.65-6.68 (d, 2H, J = 8.4 Hz), 6.89-6.91 (d, 2H, J = 8.7 Hz), 7.11-7.14 (d, 2H, J = 8.6 Hz), 7.52-7.54 (d, 2H, J = 5.5 Hz), 7.99 (m, 1H).

EXAMPLE 8

N-{2-[1-(4-Methoxy-benzyl)-5-(4-nitro-benzyl)-4,6-dioxo-1,4,5,6-tetrahydro-[1,3,5]triazin-2-ylamino]-ethyl}-guanidine (Cpd 95)



A. **1-(4-Methoxy-benzyl)-6-methylsulfanyl-3-(4-nitro-benzyl)-1*H*-[1,3,5]triazine-2,4-dione (Cpd 9a).** Compound **1c** (200 mg, 0.73 mmol) was dissolved in CH_3CN and was treated with 4-nitrobenzyl bromide (168 mg, 0.86 mmol) and 80 μL (0.73 mmol) of diisopropylethylamine. The resulting mixture was heated to 87°C and allowed to stir overnight. The reaction mixture was cooled to room temperature, diluted with ethyl acetate, and washed with saturated sodium bicarbonate solution. The organic phase was dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography to give compound **8a** (44 g, 0.36 mmol).

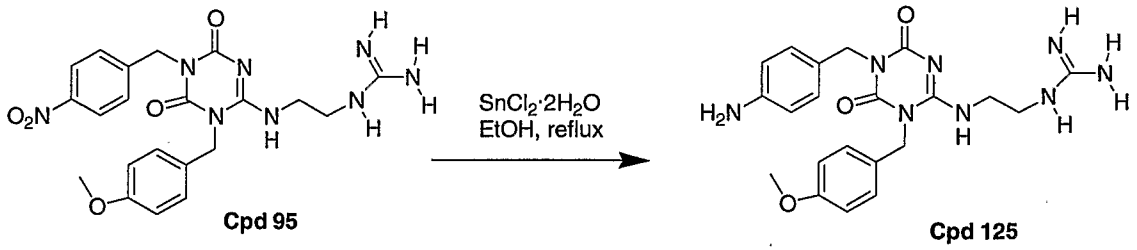
B. **6-(2-Amino-ethylamino)-1-(4-methoxy-benzyl)-3-(4-nitro-benzyl)-1*H*-[1,3,5]triazine-2,4-dione (Cpd. 9b).** To compound **8a** (80 mg, 0.19 mmol) in 10 mL of toluene was added an excess of ethylene diamine (64 μL, 0.95 mmol). The resulting mixture was heated to 90°C for 26 h. The mixture was taken up in ethyl acetate and washed with water. The organic layer was separated, dried over $MgSO_4$ and concentrated. The crude product **8b** (79mg, 0.18 mmol, 97% yield) was used in the next step without further purification.

C. ***N*-{2-[1-(4-Methoxy-benzyl)-5-(4-nitro-benzyl)-4,6-dioxo-1,4,5,6-tetrahydro-[1,3,5]triazin-2-ylamino]-ethyl}-guanidine (Cpd 95).** A mixture of compound **8b** (51 mg, 0.12 mmol), 1*H*-pyrazole-1-carboxamidine hydrochloride (18 mg, 0.12mmol), and diisopropylethylamine (26 μL, 0.36 mmol) in 10 mL of acetonitrile was allowed to stir at room temperature for several days. The resulting mixture was concentrated and purified by liquid chromatography. The title compound **95** was obtained as a white powder (17 mg, 0.036 mmol) and was submitted as a TFA salt. ^{1}H NMR (DMSO-d_6) δ 3.65-3.71 (m, 4H), 3.85 (s, 3H), 5.30 (bm, 4H), 6.99-7.02 (m, 2H), 7.26-7.30 (m, 2H), 7.54-7.60 (m, 2H), 8.02-8.20 (bs, 1H), 8.25 (m, 2H).

Using the procedures of Example 8 and the appropriate reagents, starting materials and purification methods known to those skilled in the art, the following compounds of the present invention were prepared: compounds 42, 43, 47, 55, 56, 59, 94, 97, 98, 99, 100, 102, and 113.

EXAMPLE 9

N-{2-[5-(4-Amino-benzyl)-1-(4-methoxy-benzyl)-4,6-dioxo-1,4,5,6-tetrahydro-[1,3,5]triazin-2-ylamino]-ethyl}-guanidine (Cpd 125)



Cpd 95 Cpd 125

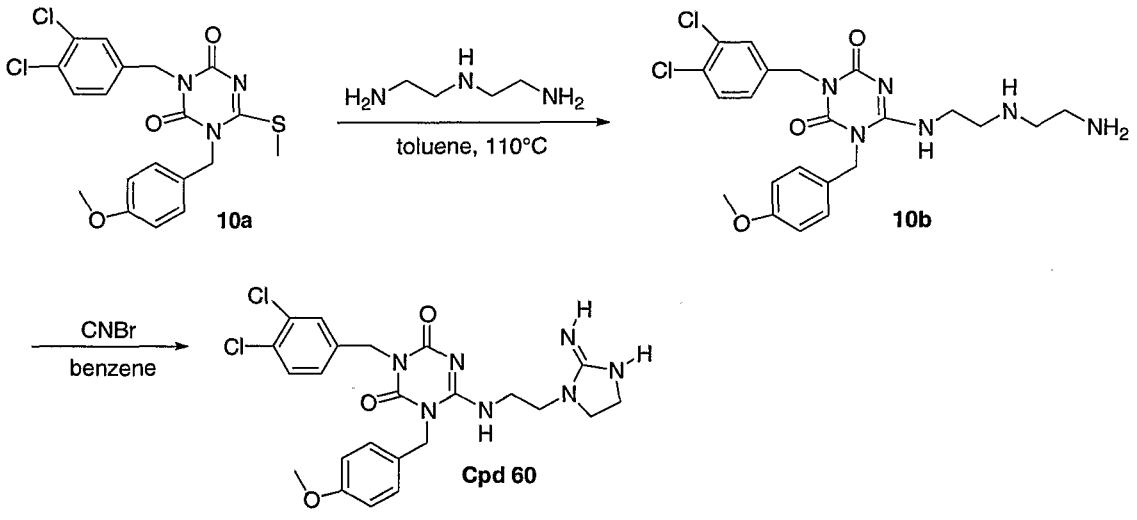
A mixture of the crude Compound **95** (39 mg, 0.083 mmol) and tin (II) chloride dihydrate (94 mg, 0.42 mmol) in 20 mL of EtOH was heated to reflux for 24 h. The

solution was concentrated and the residue was purified by HPLC to give the title compound **125** as its TFA salt (6.5 mg, 0.015 mmol). ^{1}H NMR (DMSO-d_6) δ 3.30 (m, 4H), 3.73 (s, 3H), 4.80 (s, 2H), 4.98 (s, 2H), 6.56-6.78 (m, 2H), 6.88-6.91 (d, 2H, J = 8.6 Hz), 7.13-7.20 (m, 4H), 7.43-7.47 (m, 1H), 7.92-7.99 (m, 1H).

Using the procedures of Example 9 and the appropriate reagents, starting materials and purification methods known to those skilled in the art, the following compounds of the present invention were prepared: compound 96.

EXAMPLE 10

3-(3,4-Dichloro-benzyl)-6-[2-(2-imino-imidazolidin-1-yl)-ethylamino]-1-(4-methoxy-benzyl)-1*H*-[1,3,5]triazine-2,4-dione (Cpd 60)



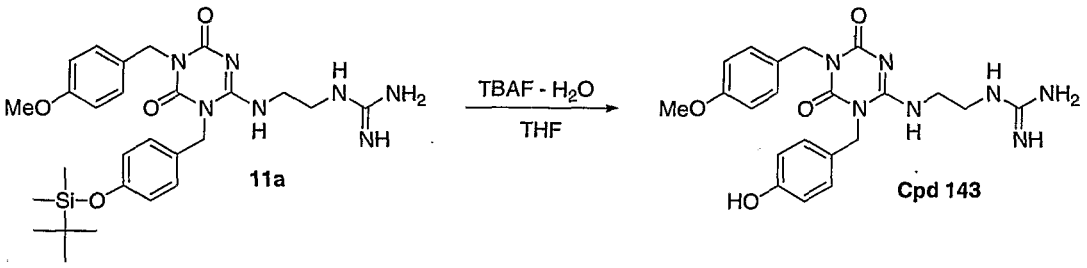
A. Compound **10a** was prepared according to the methods described in Example 1, Step C, and substituting (3,4-dichloro-phenyl)-methanol for 4-ethylbenzyl alcohol.

B. **6-[2-(2-Amino-ethylamino)-ethylamino]-3-(3,4-dichloro-benzyl)-1-(4-methoxy-benzyl)-1*H*-[1,3,5]triazine-2,4-dione (Cpd 10b).** To compound **10a** (0.400 g, 0.968 mmol) in toluene (6 mL) was added 2,2'-diaminodiethylamine (0.300 g, 2.9 mmoi) and the reaction mixture was heated at 110 C for 4 h. The reaction mixture was cooled to room temperature and then water was added. The mixture was extracted with ethyl acetate, dried over sodium sulfate, filtered, and concentrated to give compound **10b** (0.46 g) which was used in the subsequent reaction without further purification.

C. **3-(3,4-Dichloro-benzyl)-6-[2-(2-imino-imidazolidin-1-yl)-ethylamino]-1-(4-methoxy-benzyl)-1*H*-[1,3,5]triazine-2,4-dione.(Cpd 60).** To compound **10b** (0.100 g, 0.203 mmol) in benzene (2 mL) was added cyanogen bromide (0.022 g, 0.203 mmol). The reaction mixture was stirred for 2.5 h at room temperature. The reaction mixture was concentrated and then dissolved in a mixture of acetonitrile and methanol. The mixture was purified by reverse-phase chromatography to yield the title compound **60** (0.017 g). ^{1}H NMR (DMSO-d_6) δ 3.28-3.59 (8H, m), 3.66 (3H, s), 4.83 (2H, s), 4.92 (2H, s), 6.81-6.84 (2H, d, J = 8.7 Hz), 7.09-7.12 (2H, d, 8.7 Hz), 7.19-7.22 (1H, d, J = 8.3 Hz), 7.46 (1H,s), 7.51-7-54 (1H, d, J = 8.3 Hz), 7.86-7.95 (3H, m).

EXAMPLE 11

N-{2-[1-(4-Hydroxy-benzyl)-5-(4-methoxy-benzyl)-4,6-dioxo-1,4,5,6-tetrahydro-[1,3,5]triazin-2-ylamino]-ethyl}-guanidine (Cpd 143)

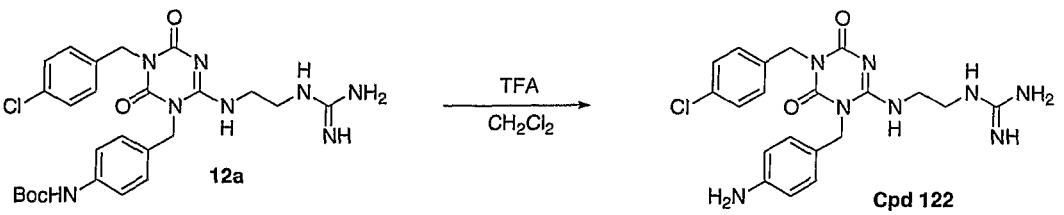


A. Compound **11a** (50 mg, 0.09 mmol) was prepared according to the methods described in Example 2, and substituting [4-(tert-butyl-dimethyl-silanyloxy)-phenyl]-methanol for 4-methoxybenzyl alcohol in Step D.

B. Compound **11a** was suspended in THF (2 mL) and the reaction mixture was treated with tetrabutylammonium fluoride monohydrate (24 mg, 0.09 mmol). The solution was stirred at room temperature overnight. The mixture was then concentrated under nitrogen and the residue was purified by reverse phase preparative HPLC to give the title compound **143** (3.8 mg) as a white solid. M+ (ES+) = 440.1; ^{1}H NMR (MeOD, d_4). δ 3.32 (m, 2H), 3.50 (t, 2H, J = 7.08 Hz), 3.78 (s, 3H), 4.99 (s, 2H), 5.03 (s, 2H), 6.77 (d, 2H, J = 8.58 Hz), 6.85 (d, 2H, J = 8.71 Hz), 7.07 (d, 2H, J = 8.62 Hz), 7.36 (d, 2H, J = 8.67 Hz).

EXAMPLE 12

N-{2-[1-(4-Amino-benzyl)-5-(4-chloro-benzyl)-4,6-dioxo-1,4,5,6-tetrahydro-[1,3,5]triazin-2-ylamino]-ethyl}-guanidine (Cpd 122)

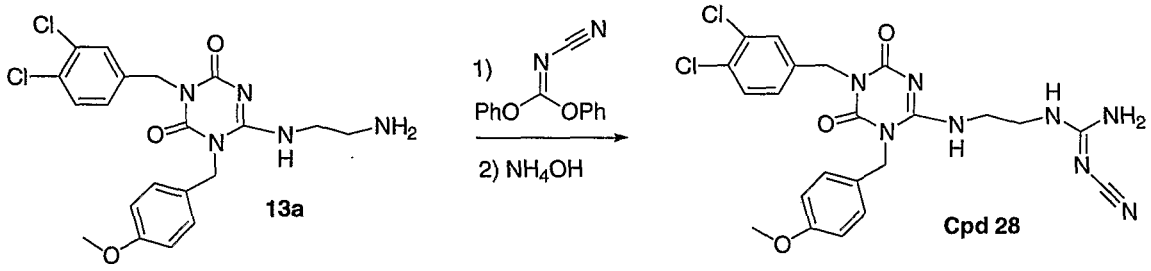


A. Compound **12a** (50 mg, 0.09 mmol) was prepared according to the methods described in Example 2, and substituting (4-hydroxymethyl-phenyl)-carbamic acid tert-butyl ester for 4-methoxybenzyl alcohol in Step D.

B. Compound **12a** (70 mg, 0.129 mmol) was suspended in dichloromethane (3 mL) and the solution was treated with trifluoroacetic acid (0.5 mL). The reaction was allowed to stir overnight at room temperature. The mixture was concentrated under nitrogen and the residue was purified by reverse phase preparative HPLC to give the title compound **122** (35.9 mg) as a white solid. M+ (ES+) = 443.1; ^{1}H NMR (DMSO, d_6). δ 3.18 – 3.25 (m, 2H), 3.28 – 3.31 (m, 2H), 4.76 (s, 2H), 4.82 (s, 2H), 4.88 (s, 2H), 6.75 (d, 2H, J = 8.25 Hz), 7.02 (d, 2H, J = 8.38 Hz), 7.22 – 7.32 (m, 4H), 7.53 (d, 2H, J = 4.02 Hz), 7.95 (m, 1H).

EXAMPLE 13

_N_-{2-[5-(3,4-Dichloro-benzyl)-1-(4-methoxy-benzyl)-4,6-dioxo-1,4,5,6-tetrahydro-[1,3,5]triazin-2-ylamino]-ethyl}-_N'_-cyano-guanidine (Cpd 28)



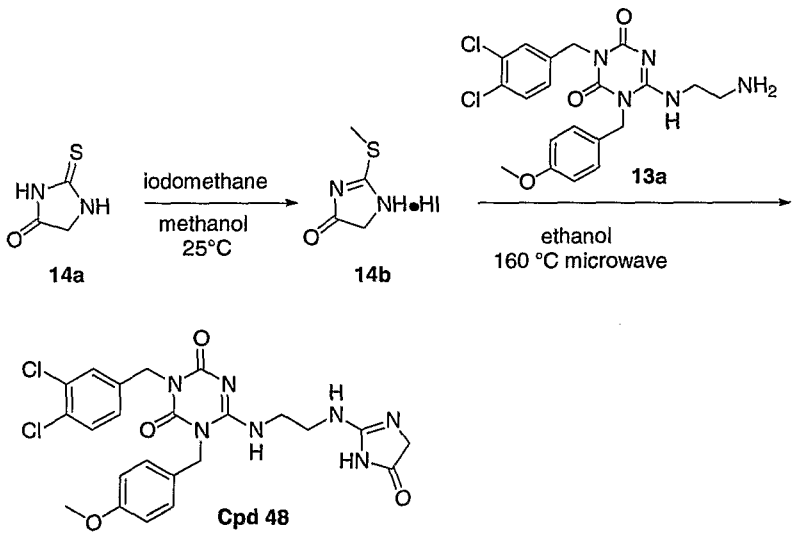
A. Compound **13a** was prepared according to Example 1, substituting 3,4-dichlorophenyl methanol for 4-ethylbenzyl alcohol in Step D.

B. To a mixture of Cpd **13a** (0.050 g, 0.11 mmol) in isopropyl alcohol (1 mL) was added triethylamine (0.017 mL, 0.12 mmol) and diphenyl _N_-cyanocarbonimidate

(0.029 g, 0.12 mmol). The reaction mixture was stirred for 2 h at room temperature then concentrated under vacuum. The resulting residue was suspended in EtOH (0.75 mL) and NH_4OH (0.25 mL, 14.8 N (aq)) was added. The reaction mixture was stirred for 16 h at 50°C, concentrated under vacuum, and the resulting residue was purified by reverse-phase liquid chromatography using a gradient of 90:10 (water:acetonitrile, with 0.1% TFA) to 90:10 (acetonitrile: water, with 0.1% TFA) to give the title compound **28** (99% pure by HPLC, 0.0017 g); HRMS calcd. for $C_{22}H_{23}Cl_2N_8O_3$ m/z 517.1270 (M+H), found: 517.1281.

Using the procedures of Example 13 and the appropriate reagents, starting materials and purification methods known to those skilled in the art, the following compounds of the present invention were prepared: compound 143.

EXAMPLE 14



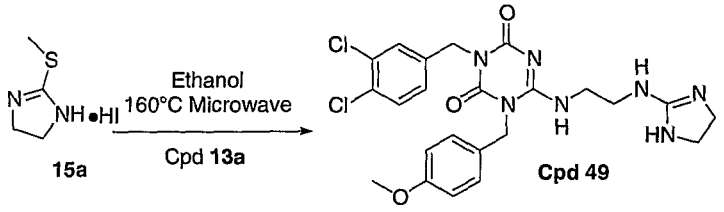
A. **1,5-Dihydro-2-(methylthio)-4*H*-imidazol-4-one monohydriodide (Cpd 15b).** To a solution of compound **14a** (420 mg, 3.6 mmol) in EtOH (5 mL) was added iodomethane (0.268 mL, 4.3 mmol). The mixture was stirred at 25°C for 16 h,

then concentrated to a residue to provide compound **14b**, which was used in the next reaction without further purification.

B. **3-(3,4-Dichloro-benzyl)-1-(4-methoxy-benzyl)-6-[2-(5-oxo-4,5-dihydro-1H-imidazol-2-ylamino)-ethylamino]-1*H*-[1,3,5]triazine-2,4-dione 4 (Cpd 52).** To a solution of compound **14b** (0.0373 mg, 0.14 mmol) in ethanol (0.75 mL) was added compound **13a** (50 mg, 0.13 mmol). The mixture was irradiated (μwave) at 160°C for 15 min, concentrated, and the resulting residue was purified by reverse-phase liquid chromatography using a gradient of 90:10 (water:acetonitrile, with 0.1% TFA) to 90:10 (acetonitrile: water, with 0.1% TFA) to give the title compound **48** (89% pure by HPLC, 0.0025 g). HRMS calcd. for $C_{23}H_{24}Cl_2N_7O_4$ m/z 532.1267 (M+H), found: 532.1257.

EXAMPLE 15

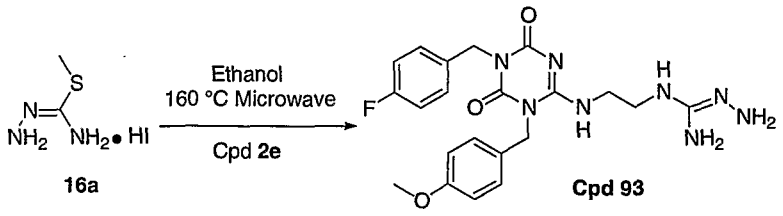
3-(3,4-Dichloro-benzyl)-6-[2-(4,5-dihydro-1*H*-imidazol-2-ylamino)-ethylamino]-1-(4-methoxy-benzyl)-1*H*-[1,3,5]triazine-2,4-dione (Cpd 49)



To a solution of compound **15a** (0.054 mg, 0.22 mmol) in ethanol (1 mL) was added compound **13a** (50 mg, 0.11 mmol). The mixture was irradiated in a microwave reactor at 160°C for 15 min, concentrated, and the resulting residue was purified by reverse-phase liquid chromatography using a gradient of 90:10 (water:acetonitrile, with 0.1% TFA) to 90:10 (acetonitrile: water, with 0.1% TFA) to give the title compound **49** (93% pure by HPLC, 0.0082 g). HRMS calcd. for $C_{23}H_{26}Cl_2N_7O_3$ m/z 518.1474 (M+H), found: 518.1479.

EXAMPLE 16

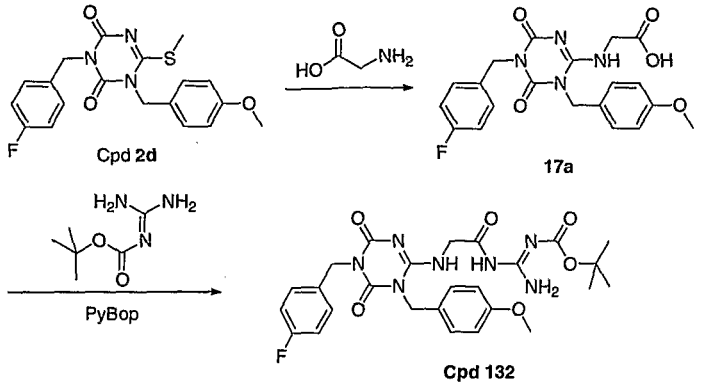
N-{2-[5-(4-Fluoro-benzyl)-1-(4-methoxy-benzyl)-4,6-dioxo-1,4,5,6-tetrahydro-[1,3,5]triazin-2-ylamino]-ethyl}-N'-amino-guanidine (Cpd 93)



To a solution of compound **16a** (0.061 mg, 0.22 mmol) in ethanol (1 mL) was added compound **2e** (50 mg, 0.13 mmol). The mixture was irradiated in a microwave reactor at 160°C for 15 min, concentrated, and the resulting residue was purified by reverse-phase liquid chromatography using a gradient of 90:10 (water:acetonitrile, with 0.1% TFA) to 90:10 (acetonitrile: water, with 0.1% TFA) to give the title compound **93** (99% pure by HPLC, 0.018 g). ^{1}H NMR ($CDCl_3$) δ 3.22-3.73 (2H, m), 3.38-3.55 (2H, m), 3.75 (2H, t, J = 5.8 Hz), 3.77 (3H, s), 5.01 (2H, s), 5.07 (2H, s), 5.44-4.86 (2H, bs), 6.83 (2H, d, J = 8.7Hz), 6.90-7.03 (2H, m), 7.16 (2H, d, J = 8.7Hz), 7.48-7.36 (2H, m).HRMS calcd. for $C_{21}H_{26}FN_8O_3$ m/z 457.2112 (M+H), found: 457.2101.

EXAMPLE 17

N-{2-[5-(4-fluoro-benzyl)-1-(4-methoxy-benzyl)-4,6-dioxo-1,4,5,6-tetrahydro-[1,3,5]triazin-2-ylamino]-acetyl}-N'-boc-guanidine (Cpd 132)



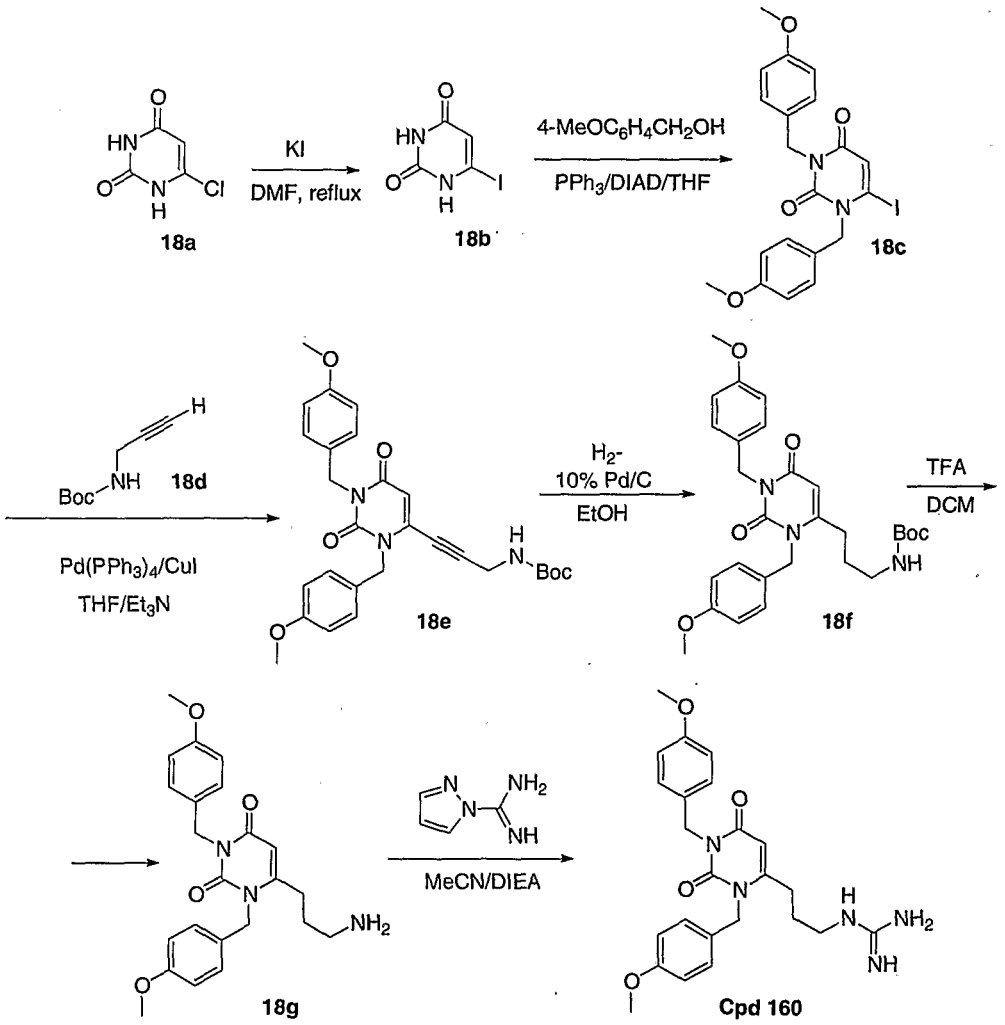
A. **[5-(4-Fluoro-benzyl)-1-(4-methoxy-benzyl)-4,6-dioxo-1,4,5,6-tetrahydro-[1,3,5]triazin-2-ylamino]-acetic acid (Cpd 17a).** To a solution of compound **2d** (0.10 g, 0.26 mmol) in ethanol (1 mL) was added glycine (0.056 g, 0.75 mmol) and DIEA (0.143 mL, 0.82 mmol). The mixture was irradiated in a microwave reactor at 150°C for 30 min then cooled to rt. Glycine (0.056 g, 0.75 mmol) and DIEA (0.143 mL, 0.82 mmol) were again added and the resulting mixture was irradiated (μwave) at 150°C for 30 min, cooled to rt, concentrated, and the resulting residue was purified by reverse-phase liquid chromatography using a gradient of 90:10 (water:acetonitrile, with 0.1% TFA) to 90:10 (acetonitrile:water, with 0.1% TFA) to give compound **17a** (99% pure by HPLC, 0.058 g). MS calcd. for $C_{20}H_{20}FN_4O_5$ m/z 415.1 (M+H), found: 415.1.

B. ***N*-{2-[5-(4-fluoro-benzyl)-1-(4-methoxy-benzyl)-4,6-dioxo-1,4,5,6-tetrahydro-[1,3,5]triazin-2-ylamino]-acetyl}-*N'*-boc-guanidine (Cpd 132).** To a solution of compound **17a** (0.025 g, 0.047 mmol), DIEA (0.032 mL, 0.18 mmol), and monobocguanidine (0.015 g, 0.091mmol) in DMF (0.40 mL) was added PyBop (0.047 g, 0.091 mmol). The mixture was stirred for 16 h at rt, quenched with water (3 mL), and the resulting solution was extracted 4 X 1 mL EtOAc. The combined organic layers were dried over Na_2SO_4, concentrated, and the resulting residue was purified by normal-phase flash chromatography on silica gel using a gradient of

50:50 (EtOAc:Heptane, with 0.1% Et_3N) to EtOAc (with 0.1% Et_3N) to give the title compound **132** (85% pure by HPLC, 0.0263 g). ^1H NMR ($CDCl_3$) δ 1.46 (9H, s), 3.79 (3H, s), 4.05 (2H, s), 5.07 (4H, s), 6.90 (2H, d, J = 8.7 Hz), 6.98 (2H, at, J = 6.7Hz), 7.30 (2H, d, J = 8.7Hz), 7.50 (2H, dd, J = 8.7 and 8.6Hz), 8.61 (1H, bs); MS calcd. for $C_{26}H_{31}FN_7O_6$ m/z 556.2320 (M+H), found: 556.2341.

EXAMPLE 18

N-{3-[1,3-Bis-(4-methoxy-benzyl)-2,6-dioxo-1,2,3,6- tetrahydro-pyrimidin-4-yl]-propyl}guanidine (Cpd 160)



A. **6-Iodo-1H-pyrimidine-2,4-dione (18b).** Compound **18a** (5 g, 34 mmol) and sodium iodide (20 g) were dissolved in anhydrous DMF (50 mL) and heated to reflux for 1.5 h (Ar atmosphere). The DMF was evaporated, and the solid residue dissolved in H_2O (200 mL). The solution was stirred at RT for 4 h, a solid material was collected by vacuum filtration, and the solid was washed with H_2O and dried. The solid was crystallized from EtOAc, providing compound **18b**. ^{1}H NMR (DMSO-d_6) δ 6.03 (s, 1H), 11.2 (s, 1H), 11.6 (s, 1H).

B. **6-Iodo-1,3-bis-(4-methoxy-benzyl)-1H-pyrimidine-2,4-dione (Cpd 18c).** Compound **18b** (1.00 g, 4.2 mmol), 4-methoxybenzyl alcohol (1.7 g, 3 eq), PPh_3 (4.00 g) were dissolved in dry THF (25 mL) under an atmosphere of N_2. DIAD was added dropwise at approximately 1 mL/ min until the yellow color remained (about 4 eq total). The reaction mixture was stirred for 4 h at RT and evaporated. The residue was subjected to normal phase column chromatography (silica gel, gradient mixture heptane-ethyl acetate), providing compound **18c**. ^{1}H NMR ($CDCl_3$) δ 3.78 (s, 3H), 3.79 (s, 3H), 5.04 (s, 2H), 5.27 (s, 2H), 6.54 (s, 1H), 6.82 (d, *J*= 7.3 Hz, 2H), 6.86 (d, *J*=8.7 Hz, 2H), 7.22 (d, *J*=7.3 Hz, 2H), 7.42 (d, *J*=8.7 Hz, 2H). MS *m/z* 479.1 (M+H).

C. **N-Boc-Propargylamine (Cpd 18d).** Propargylamine (5.50 g, 0.1 mol) and di-tert-butyl dicarbonate (4.36 g, 2 eq.) were suspended together in 100 mL of a 10% aqueous solution of $NaHCO_3$. Reaction mixture was stirred overnight and extracted by EtOAc (3x20 mL). The organic phases were combined together, washed with citric acid 10% aq., dried over $MgSO_4$, filtered and evaporated, providing compound **18d** as white solid (10.1 g, 65% yield). ^{1}H N MR ($CDCl_3$) δ 4.72 (bs, 1H), 3.91 (d, *J*= 3.0 Hz, 2H), 2.22 (t, *J*= 2.9 Hz, 1H), 1.51 (s, 9H).

D. **{3-[1,3-Bis-(4-methoxy-benzyl)-2,6-dioxo-1,2,3,6-tetrahydro-pyrimidin-4-yl]-prop-2-ynyl}-carbamic acid tert-butyl ester (Cpd 18e).** Compound **18c** (240

mg, 0.5 mmol) and compound **18d** (150 mg, 1 mmol) were dissolved in a mixture of dry THF (10 mL) and Et_3N (2 mL). $Pd(PPh_3)_4$ (40 mg) and copper (I) iodide (20 mg) were added simultaneously in one portion. The reaction mixture was stirred overnight at RT under a N_2 atmosphere and evaporated. The residue was subjected to normal phase column chromatography (silica gel column, heptane-EtOAc 8:2 to 0:10 gradient mixture), providing compound **18e** as yellow solid. ^1H NMR ($CDCl_3$) δ 7.42 (d, *J*= 8.7 Hz, 2H), 7.28 (d, *J*= 8.7 Hz, 2H), 6.84 (d, *J*= 9.1 Hz, 2H), 6.81 (d, *J*= 9.1 Hz, 2H), 5.93 (s, 1H), 5.08 (s, 2H), 5.03 (s, 2H), 3.78 (s, 3H), 3.76 (s, 3H), 1.44 (s, 9H).

E. **{3-[1,3-Bis-(4-methoxy-benzyl)-2,6-dioxo-1,2,3,6-tetrahydro-pyrimidin-4-yl]-propyl}-carbamic acid tert-butyl ester (Cpd 18f).** Compound **18e** (500 mg, 0.1 mmol) was dissolved in EtOH (10 mL) and suspended with 10% Pd on carbon (40 mg). The reaction mixture was hydrogenated for 24 h at RT under atmospheric pressure, filtered through a Celite™ plug, and evaporated, providing 501 mg of white solid **18f**. ^1H NMR ($CDCl_3$) δ 7.38 (d, *J*= 8.7 Hz, 2H), 7.00 (d, *J*= 8.7 Hz, 2H), 6.87-6.72 (m, 4H), 5.54 (s, 1H), 5.01 (s, 2H), 4.99 (s, 2H), 3.71 (s, 3H), 3.70 (s, 3H), 3.08-3.00 (m, 2H), 2.39-2.30 (m, 2H), 1.65-1.55 (m, 2H), 1.34 (s, 9H).

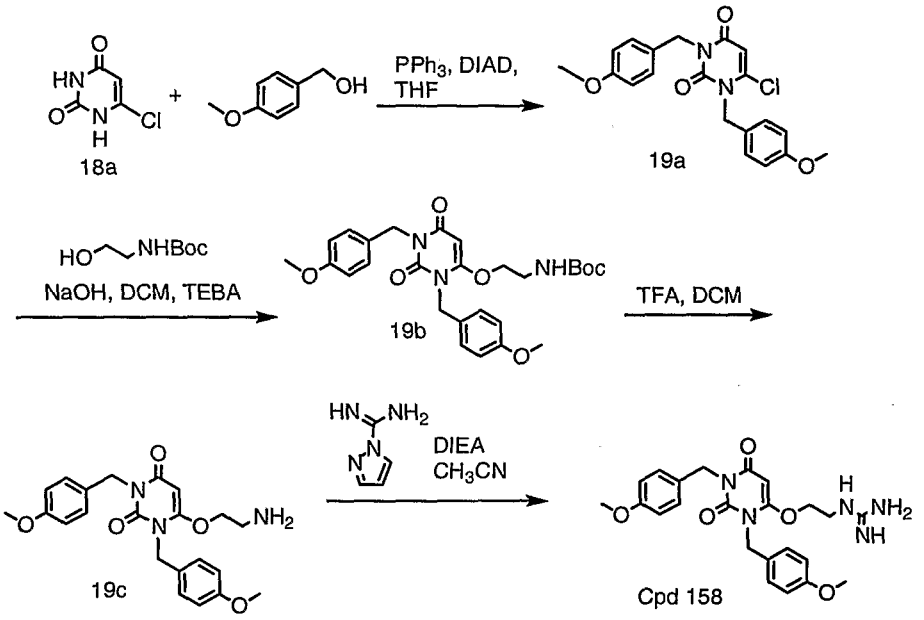
F. **6-(3-Amino-propyl)-1,3-bis-(4-methoxy-benzyl)-1H-pyrimidine-2,4-dione (Cpd 18g).** Compound **(18f)** (500 mg, 0.098 mmol) was dissolved in 10 ml DCM-TFA 9:1 mixture and stirred at RT. Reaction was monitored by HPLC. After 10 h all starting material disappeared, reaction mixture was filtered through Celite™ plug and evaporated, providing 350 mg of **18g** (TFA salt, white solid). MS *m/z* 410.0 (M+H).

G. **N-{3-[1,3-Bis-(4-methoxy-benzyl)-2,6-dioxo-1,2,3,6-tetrahydro-pyrimidin-4-yl]-propyl}-guanidine (Cpd 160).** Compound **18g** (260 mg TFA salt, 0.5 mmol) and 1*H*-pyrazole-1-carboxamidine hydrochloride (290 mg, 4 eq) were

suspended in 20 ml MeCN-DIEA 9:1 mixture, stirred at RT overnight and evaporated. The residue was dissolved in MeOH and subjected to HPLC, providing after lyophilization 128.5 mg of Compound **160** (30% yield, white powder, di-TFA salt). ^{1}H NMR (CD_3CN) δ 7.50 (m, 1H), 7.28 (d, *J*= 8.7 Hz, 2H), 7.08 (d, *J*= 8.7 Hz, 2H), 6.87 (d, *J*= 7.6 Hz, 2H), 6.83 (d, *J*= 7.7 Hz, 2H), 6.6 (bs, 3H), 5.61 (s, 1H), 5.01 (s, 2H), 4.99 (s, 2H), 3.75 (s, 6H), 3.14-3.07 (m, 2H), 2.55-2.45 (m, 2H), 1.79-1.69 (m, 2H). MS *m/z* 452.0 (M+H).

EXAMPLE 19

N-{2-[1,3-Bis-(4-methoxy-benzyl)-2,6-dioxo-1,2,3,6-tetrahydro-pyrimidin-4-yloxy]-ethyl}-guanidine (Cpd 158)



A. **6-Chloro-1,3-bis-(4-methoxy-benzyl)-1H-pyrimidine-2,4-dione (Cpd 19a)**. A solution of compound **18a** (500mg, 3.4 mmol), 4-methoxybenzyl alcohol (990 mg, 7.2 mmol), triphenylphosphine (2.9 g, 11.2 mmol), and diisopropylazodicarboxylate (1.6 mL, 8.2 mmol) in THF (100 mL) was allowed to stir at room temperature overnight. The solution was concentrated. The concentrate was taken up in ethyl acetate and washed sequentially with saturated sodium

bicarbonate and brine. The organic layer was dried over magnesium sulfate, filtered, and the filtrate was concentrated. The concentrate was purified by reverse phase chromatography to give the title compound **19a** (552 mg). M+ (ES+) = 386.9. ^{1}H NMR (methanol-d_4). δ 3.75 (s, 3H), 3.76 (s, 3H), 5.01 (s, 2H), 5.21 (s, 2H), 5.99 (s, 1H), 6.83 (d, 4H, J = 8.9Hz), 6.87 (d, 2H, J = 8.9Hz), 7.23 (d, 2H, 8.5Hz), 7.32 (d, 2H, J = 8.9Hz).

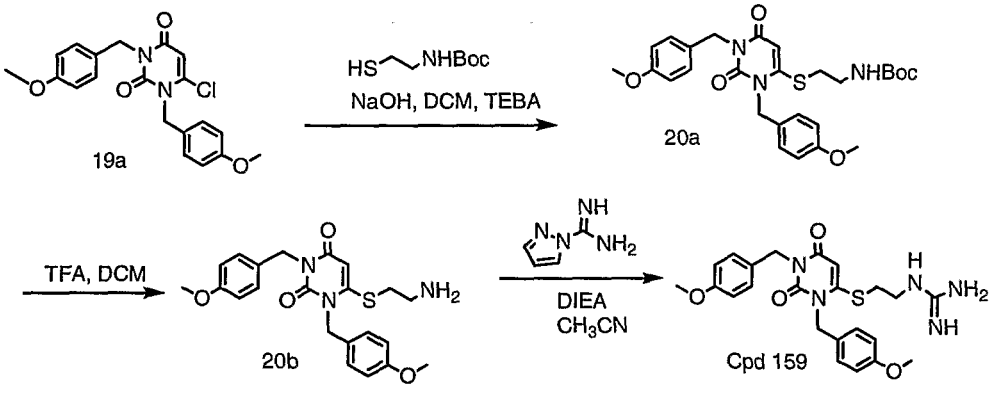
B. **{2-[1,3-Bis-(4-methoxy-benzyl)-2,6-dioxo-1,2,3,6-tetrahydro-pyrimidin-4-yloxy]-ethyl}-carbamic acid tert-butyl ester (Cpd 19b).** To a solution of t-butyl-N-(2-hydroxyethyl)carbamate (40 μL, 0.26 mmol), benzyltriethyammonium chloride (3 mg, 0.013 mmol) and 3M NaOH solution (870 μL, 2.6 mmol) was added a solution of compound **19a** (50 mg, 0.13 mmol) in dichloromethane (3 mL). After stirring overnight, the mixture was separated. The aqueous layer was extracted two times with dichloromethane. The combined organic extracts were dried over magnesium sulfate, filtered, and the filtrate was concentrated. The concentrate was purified by reverse phase chromatography after dissolving in DMSO to afford the title compound **19b** as white powder. M+ (ES+) = 512.0. ^{1}H NMR (DMSO, d_6). δ 1.36 (s, 9H), 3.33 (m, 2H), 3.72 (m, 2H), 4.88 (s, 2H), 4.94 (s, 2H), 6.85 (m, 4H), 7.20 (m, 4H).

C. **6-(2-Amino-ethoxy)-1,3-bis-(4-methoxy-benzyl)-1H-pyrimidine-2,4-dione (Cpd 19c).** To a solution of compound **19b** (assume 0.12 mmol) in dichloromethane (2 mL) was added trifluoroacetic acid (50 μL). Additional TFA (100 μL) was added. Additional TFA (150 μL) was added and the reaction was allowed to stir for an additional 16 hrs. The mixture was concentrated and purified by reverse phase chromatography to obtain the title compound **19c** (24 mg) as a white solid. M+ (ES+) = 411.9. ^{1}H NMR (methanol-d_4). δ 3.36 (t, 2H, J = 4.9, 5.0Hz), 3.75 (s, H), 3.76 (s, 3H), 5.01 (s, 2H), 5.10 (s, 2H), 5.28 (s, 1H), 6.84 (m, 4H), 7.22 (d, 2H, J = 8.6Hz), 7.30 (d, 2H, J = 5.6Hz).

D. **N-{2-[1,3-Bis-(4-methoxy-benzyl)-2,6-dioxo-1,2,3,6-tetrahydro-pyrimidin-4-yloxy]-ethyl}-guanidine (Cpd 158).** A mixture of compound **19c** (20 mg, 0.05mmol), 1H-pyrazole-1-carboxamidine HCl (8.7 mg, 0.06 mmol), and DIEA (16.5 μL, 0.15 mmol) in acetonitrile (5mL) was allowed to stir at rt overnight. The mixture was concentrated and purified by reverse phase chromatorgraphy to obtain the title compound **158** as a white solid. M+ (ES+) = 453.9. ^{1}H NMR (DMSO, d_6). δ 3.57 (t, 2H, J = 4.7, 5.2Hz), 3.71 (s, 3H), 3.72 (s, 3H), 4.20 (t, 2H, J = 4.9, 4.6Hz), 4.89 (s, 2H), 4.94 (s, 2H), 5.31 (s, 1H), 6.87 (m, 4H), 7.22 (m, 4H), 7.78 (t, 1H, J = 5.6, 5.6Hz).

EXAMPLE 20

N-{2-[1,3-Bis-(4-methoxy-benzyl)-2,6-dioxo-1,2,3,6-tetrahydro-pyrimidin-4-ylsulfanyl]-ethyl}-guanidine (Cpd 159)



A. **{2-[1,3-Bis-(4-methoxy-benzyl)-2,6-dioxo-1,2,3,6-tetrahydro-pyrimidin-4-ylsulfanyl]-ethyl}-carbamic acid tert-butyl ester (Cpd 20a).** To a solution of 2-(boc-amino)ethanethiol (87 μL, 0.52 mmol), 3M NaOH (1.7 mL, 5.2 mmol), and benzyltriethyammonium chloride (5 mL) was added a mixture of compound **19a** (100 mg, 0.26 mmol) in dichloromethane (5 mL). The mixture was allowed to stir overnight at rt. The mixture was separated, and the aqueous layer was washed with dichloromethane. The combined organic extracts were dried over magnesium

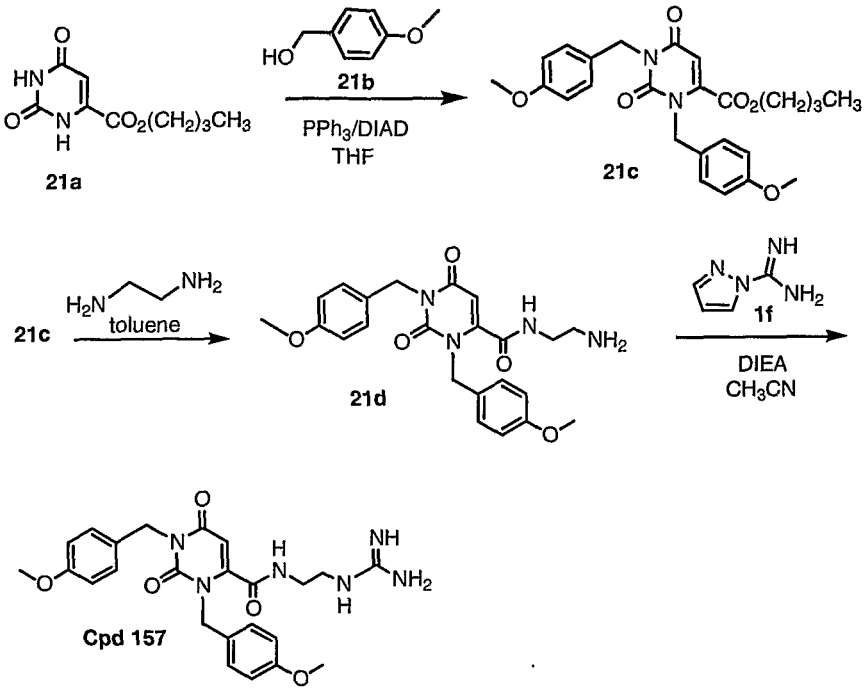
sulfate, filtered, and the filtrate was concentrated. The concentrate was triturated in MeOH and collected to obtain the title compound **20a** as a white solid. M+ (ES+) = 527.8.

B. **6-(2-Amino-ethylsulfanyl)-1,3-bis-(4-methoxy-benzyl)-1H-pyrimidine-2,4-dione (Cpd 20b).** To a mixture of compound **20a** (78 mg, 0.15 mmol) in dichloromethane (3 mL) was added TFA (0.5 mL), and the reaction was stirred for 2 h. The mixture was concentrated and the residue was purified by reverse phase chromatography to obtain the title compound **20b** as a white powder. M+ (ES+) = 427.8. ^{1}H NMR (methanol-d_4). δ 3.37 (s, 6H), 4.84 (m, 4H), 5.05 (s, 2H), 5.20 (s, 2H), 6.85 (m, 4H), 7.18 (d, 2H, J = 8.7 Hz), 7.34 (d, 2H, J = 6.6 Hz).

C. **N-{2-[1,3-Bis-(4-methoxy-benzyl)-2,6-dioxo-1,2,3,6-tetrahydro-pyrimidin-4-ylsulfanyl]-ethyl}-guanidine (Cpd 159).** A solution of compound **20b** (assumed 0.09 mmol), 1-H-pyrazole-1-carboxamidine HCl (16 mg, 0.108 mmol), and DIEA (5 µL, 0.45 mmol) in acetonitrile (3 mL) was allowed to stir at rt overnight. The mixture was concentrated and purified by reverse phase chromatography to obtain the title compound **159** as a white powder. M+ (ES+) = 469.8. ^{1}H NMR (DMSO, d_6). δ 3.19 (t, 2H, J = 6.2, 6.6Hz), 3.42 (m, 2H), 3.72 (s, 6H), 4.93 (s, 2H), 5.08 (s, 2H), 5.84 (s, 1H), 6.86 (d, 2H, J = 8.7Hz), 6.90 (s, 2H, J = 8.7Hz), 7.16 (d, 2H, J = 8.7Hz), 7.25 (d, 2H, J = 8.6Hz), 7.60 (m, 1H).

EXAMPLE 21

1,3-Bis-(4-methoxy-benzyl)-2,6-dioxo-1,2,3,6-tetrahydro-pyrimidine-4-carboxylic acid (2-guanidino-ethyl)-amide (Cpd 157)



A. **1,3-Bis-(4-methoxy-benzyl)-2,6-dioxo-1,2,3,6-tetrahydro-pyrimidine-4-carboxylic acid butyl ester (Cpd 21c).** A mixture Compound **21a** (1.00 g, 4.7 mmol), 4-methoxybenzyl alcohol (Cpd **21b**, 2.00 g, 14.1 mmol) and PPh_3 (5.00 g, 19 mmol) were dissolved in 50 mL of dry THF at 20 C. DIAD (3.8 g, 18 mmol) was added dropwise, and the reaction mixture was allowed to stir overnight at room temperature. The reaction mixture was washed with water, and extracted with EtOAc. The combined organic fractions were dried over $MgSO_4$, filtered and evaporated, providing compound **21c** as white solid. M+ (ES+) = 453.3. ^{1}H NMR ($CDCl_3$). δ 7.43 (d, 2H, J = 8.7 Hz), 7.07 (d, 2H, J = 8.7 Hz), 6.88-6.78 (m, 4H), 6.08 (s, 1H), 5.27 (s, 2H), 5.09 (s, 2H), 4.13 (t, 3H, J = 6.6 Hz), 3.79 (s, 3H), 3.77 (s, 3H), 1.60-1.48 (m, 2H), 1.35-1.20 (m, 2H), 0.90 (t, 3H, J = 7.2 Hz).

B.**1,3-Bis-(4-methoxy-benzyl)-2,6-dioxo-1,2,3,6-tetrahydro-pyrimidine-4-carboxylic acid (2-amino-ethyl)-amide (Cpd 21d).** Compound **21c** (390 mg, 0.86 mmol) and ethylene diamine (400 µl, 6 mmol) in 10 mL of toluene were refluxed for 4

hrs, cooled to rt, and concentrated under reduced pressure. The resultant residue was subjected to HPLC to give the di-TFA salt of **21d**.

C. **1,3-Bis-(4-methoxy-benzyl)-2,6-dioxo-1,2,3,6-tetrahydro-pyrimidine-4-carboxylic acid (2-guanidino-ethyl)-amide (Cpd 157).** The di-TFA salt of **21d** (280 mg, 0.42 mmol) was dissolved in a mixture of 5 mL of MeCN and 1 mL of DIEA. Compound **1f** (200 mg, 1.8 mmol) was added as one portion, the reaction mixture was allowed to stir overnight at room temperature, and then concentrated under reduced pressure. The resultant residue was subjected to HPLC, providing 59.4 mg of the di-TFA salt of **Cpd 157**. M+ (ES+) = 481.2. ^{1}H NMR (DMSO, d_6). δ 7.21 (d, 2H, J = 8.6 Hz), 7.16 (d, 2H, J = 8.6 Hz), 6.85 (d, 4H, J = 8.7 Hz), 6.69 (s, 1H), 5.99 (s, 1H), 4.87 (s, 2H), 4.92 (s, 2H), 3.72 (s, 6H), 3.65-3.50 (m, 2H), 3.24 (broad s, 4H), 3.05-3.15 (m, 2H).

Biological Examples

Example 1

Expression, isolation, and purification of Prokineticin-1

Recombinant N-terminal FLAG-tagged human prokineticin-1 (sequence-MRGATRVSIMLLLVTVSDCDYKDDDDKAVITGACERDVQCGAGTCCAISLWLRGL RMCTPLGREGEECHPGSHKVPFFRKRKHHTCPCLPNLLCSRFPDGRYRCSMDLK NINF) was expressed in stably transfected HEK 293 cells.

HEK 293 cells were grown to 100% confluence in DMEM selective high-glucose media (Invitrogen, Carlsbad, California) containing 10% FBS, 20mM HEPES, sodium pyruvate, penicillin and streptomycin (50 µg/ ml each), and G418 (400 mg/ L). The DMEM media used to culture the HEK 293 cells was replenished every other day with fresh media over a two-week period of time. Culture media containing the PK-1 peptide was collected, and filtered in 500 mL 0.2 µm pore size

filters (Corning Incorporated, Corning, NY). The filtrate was stored in a filtrate bottle at 4 C. The PK-1 peptide containing media was purified by gravity flow passage of media over M2 agarose columns (Sigma Chemical, St. Louis, MO) at 4 C. Following media passage, the agarose columns were washed with sterile 1X PBS (pH 7.4) until protein could no longer be detected by OD 280 nm. Columns were then eluted with a 0.1 M glycine-HCl solution at pH 2.8. The eluted material was immediately neutralized, by collecting into tubes containing 1M Tris pH8. Peak fractions were identified by OD 280 and pooled. The pooled fractions were subjected to Enterokinase cleavage of Flag epitope 4units/ mL overnight at room temperature. Enterokinase was removed, and sample aliquot was stored at –80 C

Results of Mass Spectral analysis of Prokineticin 1 ligand from above purification.

The samples were analyzed using Maldi TOF-MS and LC- Electrospray-Mass Spectral Analysis.

Desired Protein Sequence:

AVITGACERDVQCGAGTCCAISLWLRGLRMCTPLGREGEECHPGSHKVPF
FRKRKHHTCPCLPNLLCSRFPDGRYRCSMDLKNINF

Calculated Avg. Molecular Mass = 9667.4.

MALDI-TOF ANALYSIS

Sample preparation

The protein sample solution (10 µL) was desalted using a C4 Zip Tip according to the User Guide for Reversed-Phase ZipTip, 2002 Millipore Corporation.

Mass Spectrometry

A Micromass TOF Spec E mass spectrometer was used to determine molecular mass. MassLynx software 3.4 was used for the system control and data acquisition. MALDI positive ion mass spectra were acquired over a mass range of

0-80,000 Da. The raw MS data were baseline subtracted and smoothed using Masslynx software and compared to the masses obtained from a reference standard.

Masses of eluting components were calculated using the Agilent deconvolution software.

Results

The mass spectral data shows the presence of the desired protein (molecular mass = 9667) and an additional related component with a measured molecular mass of 9172 in about the same abundance based on mass spectral response. This mass agrees, within measurement error, with a possible truncation product missing the last four C-terminal residues indicated below.

Proposed Additional Protein Component Sequence

AVITGACERDVQCGAGTCCAISLWLRGLRMCTPLGREGEECHPGSHKVPF FRKRKHHTCPCLPNLLCSRFPDGRYRCSMDLK

Calculated Avg. Molecular Mass= 9178.8.

No other related protenaceous components were detected. The mass accuracy for all measurements is approximately 0.1%.

Example 2

Functional Assay

Screening procedure for PK1 Antagonists on the Fluorometric Imaging Plate Reader (FLIPR)

At a time of 24 h prior to running the assay, in cell culture media (DMEM containing high Glucose and L-glutamine, 10% FBS, 1% Pen/Streptomycin, 1% Sodium Pyruvate, 20mM HEPES, Zeocin 200mg/L), 100 µL of $1.3*10^6$/ml HEK 293

GPR73 (prokineticin 1 receptor) expressing cells were plated in a 96 well poly-d-lysine coated plate (Costar), and incubated at 37 C and 5% CO_2. On the day in which the assay was run, the media was removed and 200 µL of 5X Calcium Plus Dye (Molecular Devices) which was previously resuspended with 200 mL of assay buffer [HBSS w/ Ca^{2+} and Mg^{2+} w/o phenol red, 20 mM HEPES, 0.1% BSA, 10 mL probenecid (710 mg probenecid in 5 mL of 1N NaOH, to which was then added 5 mL HBSS containing 20 mM HEPES)] was added to each well of the 96-well plate. The plate was incubated at 37 C and 5% CO_2 for 30 min in dark. The plate was removed and allowed to reach RT for 15 min in the dark. The assay was then run on the FLIPR. In Brief: base line read for 1 min, compound added (25 µL) and incubated for 4 min, 15 seconds, PK1 ligand preparation added (25 µL) for a final concentration of a previously determined EC_{50} and fluorescence was counted for 1 min, 45 seconds. Baseline is described as the amount of relative fluorescence read when buffer alone is added to cells. Baseline was subtracted from all wells. Percent of control was calculated as follows:
(Baseline subtracted well value is divided by baseline subtracted max value)*100.
Percent inhibition is 100 minus the percent of control value.

The IC_{50} is defined as the amount of a given compound required to inhibit 50% of the maximum signal that is generated by the concentration of PK1 preparation used in our assay. IC_{50} values were calculated using GraphPad Prism.

Table 2 includes data generated from the PK1 functional assay described in Example 2.

Biological and Mass Spectral Data

Table 2

Cpd	Ca^{2+} Mobilization IC50 (μM)	Ca^{2+} Mobilization %Inh @10 μM	MS obs	MS calc
1	>10	30	411.9	412.19
2	0.125, 0.363, 0.336, 0.927*	92, 85, 74, 87*	424.3	424.21
3	4.96	52	452.0	452.20
4	2.5	71	438.0	438.23
5	2.18	67	390.1	390.23
6	2.59	59	414.0	414.19
7	>10	52	462.0	462.19
8	3.85	64	450.1	450.26
9	>10	35	438.9	439.18
10	>10	33	440.2	440.20
11	>10	32	395.2	395.19
12	0.034, 0.082, 0.247*	97, 96, 94, 90*	438.3	438.23
13	0.104, 0.256	92, 91	460.2	460.19
14	>10	41	465.9	466.26
15	6.11	55	461.9	462.19
16	0.836	77	442.0	442.20
17	0.014, 0.033, 0.087*	100, 99, 97*	442.0	442.20
18	0.007, 0.028, 0.041, 0.022, 0.054*	98, 100, 101, 99*	492.0	492.13
19	0.862	81	477.8	478.18
20	3.69	61	454.0	454.22
21	>10	43	454.0	454.22
22	0.947	80	436.9	437.21
23	1.25	74	450.9	451.22

Cpd	Ca^{2+} Mobilization IC50 (μM)	Ca^{2+} Mobilization %Inh @10 μM	MS obs	MS calc
24	0.041	99	456.0	456.22
25	0.137	94	437.9	438.23
26	0.354	88	437.9	438.23
27	1.97	55	508.2	508.13
28	0.71	101	517.1	517.13
29	0.042, 0.047	101, 102	505.8	506.15
30	0.009, 0.019	101, 103	457.8	458.17
31	0.009, 0.021	101, 102	453.9	454.22
32	0.601, 0.781	88, 86	519.7	520.16
33	2.86	66	455.9	456.22
34	0.515	89	519.7	520.16
35	0.061, 0.097, 0.113*	100, 101, 101*	519.7	520.16
36	1.32	77	545.8	546.18
37	0.038, 0.201, 0.326*	98, 100, 98, 99*	507.7	508.11
38	0.055, 0.178, 0.194*	98, 94, 98	489.7	490.15
39	0.909	81	457.8	458.17
40	0.248	98	545.7	546.10
41	0.027, 0.047, 0.064*	101, 100, 99*	527.7	528.11
42	0.281	92	545.8	546.18
43	>10	31	547.8	546.18
44	0.011, 0.046	100, 98	506.1	506.15
45	0.018	103	469.8	470.20
46	0.058	101	452.0	452.24
47	0.057	101	547.7	546.18

Cpd	Ca^{2+} Mobilization IC50 (μM)	Ca^{2+} Mobilization %Inh @10 μM	MS obs	MS calc
48	0.798	94	532.1	532.13
49	2	75	518.1	518.15
50	0.248	96	518.7	519.14
51	0.047	100	504.8	505.13
52	6.52	58	505.8	506.15
53	0.014, 0.025	99, 101	520.1	520.16
54	0.014, 0.006	98, 101	534.1	534.18
55	6.73	58	517.7	518.15
56	0.061	98	511.8	512.22
57	8.21	51	527.7	528.11
58	0.007, 0.016, 0.016*	102, 99, 98*	534.2	534.18
59	0.05, 0.035	99, 100	519.7	520.16
60	0.054	100	517.7	518.15
61	0.045	102	548.2	548.19
62	0.059	98	574.2	574.21
63	0.12	101	582.1	582.18
64	0.072	100	576.1	576.19
65	0.485	88	596.1	596.19
66	0.023	99	572.1	572.16
67	0.018	99	550.1	550.17
68	1.21	84	505.8	506.15
69	6.51	60	455.9	456.17
70	0.009, 0.007	101, 101	532.2	532.16
71	0.012, 0.007	100, 99	568.2	568.16
72	0.064	100	598.1	598.17

Cpd	Ca^{2+} Mobilization IC50 (μM)	Ca^{2+} Mobilization %Inh @10 μM	MS obs	MS calc
73	0.039	100	602.1	602.12
74	0.138	100	636.1	636.15
75	0.036	101	569.2	569.16
76	0.23	93	610.1	610.17
77	0.789	81	413.9	414.19
78	0.3	89	429.8	430.17
79	0.071	101	467.9	468.24
80	0.071	100	489.7	490.20
81	0.452	84	422.9	423.21
82	0.498	84	493.8	494.25
83	0.988	80	497.7	498.20
84	0.042	99	452.9	453.23
85	0.051	96	455.2	455.22
86	3.26	61	459.9	460.27
87	>10	38	456.9	457.17
88	4.74	59	555.2	555.28
89	9.07	46	569.3	569.30
90	0.031, 0.043, 0.043*	100, 100, 101*	543.2	543.23
91	0.054	101	563.2	563.22
92	0.04	97	562.2	562.22
93	0.227	92	457.2	457.21
94	4.8	60	468.7	469.19
95	0.084	96	468.7	469.19
96	>10	43	438.9	439.22
97	0.318	86	448.8	449.21

Cpd	Ca^{2+} Mobilization IC50 (μM)	Ca^{2+} Mobilization %Inh @10 μM	MS obs	MS calc
98	>10	34	448.8	449.21
99	0.794	73	481.8	482.22
100	8.82	48	481.8	482.22
101	>10	33	468.9	468.20
102	3.49	68	519.7	520.16
103	0.023	99	596.1	596.14
104	0.011, 0.011	99, 102	519.2	519.23
105	0.089	100	547.2	547.26
106	0.508	89	590.3	590.25
107	0.012	101	554.2	554.21
108	0.369	89	582.3	582.36
109	0.129	99	495.9	496.27
110	1.16	81	440.9	440.20
111	0.154	100	464.7	465.12
112	0.026	101	463.8	464.20
113	0.011, 0.024, 0.046, 0.076*	101, 100, 102*	505.8	506.15
114	0.041	99	524.2	524.20
115	0.047	99	514.2	514.26
116	0.057	99	510.2	510.26
117	0.084	79	532.2	532.25
118	0.006, 0.006	98, 102	536.2	536.22
119	0.006, 0.012	102, 99	536.2	536.22
120	0.009, 0.015	100, 102	532.2	532.25
121	0.020, 0.033	101, 98	498.2	498.26
122	1.08	78	443.1	443.17

Cpd	Ca^{2+} Mobilization IC50 (μM)	Ca^{2+} Mobilization %Inh @10 μM	MS obs	MS calc
123	>10	34	404.0	404.24
124	1.56	74	416.0	416.24
125	0.487	83	438.9	439.22
126	0.115	95	576.3	576.31
127	0.058	100	602.1	602.21
128	0.04	100	534.2	534.23
129	4.78	64	427.8	428.16
130	1.87	71	417.9	418.14
131	>10	32	496.3	495.9
132	8.5	54	556.2	556.2
133	0.2	93	564.2	564.22
134	0.019, 0.028	97, 97	546.2	546.23
135	0.013, 0.024	100, 94	520.2	520.22
136	>10	50	470.2	470.23
137	0.015, 0.031	101, 98	470.2	470.23
138	1.34	70	642.2	642.26
139	0.018	95	533.2	533.24
140	0.455	89	512.2	512.24
141	1.84.	73	417.9	417.85
142	0.323	90	500.1	500.22
143	0.006, 0.027	100, 101	440.1	440.20
144	1.33	77	514.2	514.23
145	0.461	86	467.9	468.24
146	0.67	87	482.0	482.25
147	808	82	520.3	520.1

Cpd	Ca^{2+} Mobilization IC50 (μM)	Ca^{2+} Mobilization %Inh @10 μM	MS obs	MS calc
148	>10	41	465.9	465.56
149	4.78	64	427.8	427.89
150	1.87	71	417.9	417.85
151	0.003	99	484.2	484.21
152	0.009	97	482.2	482.23
153	0.013	99	484.2	484.24
154	0.003, 0.006	99, 98	484.2	484.24
155	0.016	99	470.2	470.23
156	0.004, 0.007	102, 99	456.2	456.21
157	0.197	92	481.2	480.21
158	0.254	93	453.9	453.49
159	0.013	98	469.8	469.56
160	0.616	89	452.0	451.22

* Where multiple values are displayed for a single compound. These values are representative of values determined upon multiple testing.

Example 3

Expression, isolation, and purification of Prokineticin-2

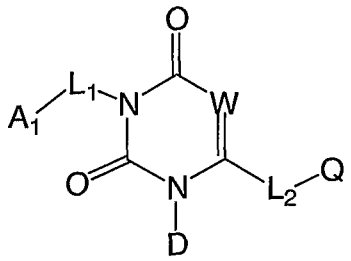
Recombinant N-terminal FLAG-tagged human prokineticin-2 (sequence-MRSLCCAPLL LLLLLPPLLLTPRAGDADYKDDDDKAVI TGACDKDSQC GGGMCCAVSI WVKSIRICTPMGKLGDSCHP LTRKVPFFGRRMHHTCP CLPGLACLRTSFNRFICLAQK) is expressed in stably transfected HEK 293 cells. The PK2 ligand preparation production and purification may be achieved using the methods provided in Example 1 for the production and purification PK1 ligand.

The PK 2 functional activity of compounds of the present invention may be determined in a manner analogous to Example 2. (Martucci, C. et al. *Brit. J. Pharmacol.* (2005), 1-10).

While the foregoing specification teaches the principles of the present invention, with examples provided for the purpose of illustration, it will be understood that the practice of the invention encompasses all of the usual variations, adaptations and/or modifications as come within the scope of the following claims and their equivalents.

Claims:

1. A compound of Formula (I):



Formula (I)

wherein:

A_1 is hydrogen; aryl; heteroaryl; C_{5-8}cycloalkyl; or heterocyclyl; provided that A_1 is other than piperidin-4-yl, *N*-t-butoxycarbonyl-piperidin-4-yl, or *N*-methyl-piperidin-3-yl; and wherein substituents of A_1 other than hydrogen are optionally substituted with one to three substituents independently selected from the group consisting of C_{1-6}alkyl, hydroxy(C_{1-6})alkyl, C_{1-6}alkoxy, halogen, nitro, halogenated C_{1-6}alkyl, halogenated C_{1-6}alkoxy, C_{1-6}alkylthio, C_{1-6}alkoxycarbonyl, amino, C_{1-6}alkylamino, di(C_{1-6}alkyl)amino, cyano, hydroxy, aminocarbonyl, C_{1-6}alkylaminocarbonyl, di(C_{1-6}alkyl)aminocarbonyl, C_{1-6}alkoxycarbonylamino, C_{1-6}alkylcarbonyl, C_{1-6}alkylthiocarbonyl, formyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, aminosulfonyl, C_{1-6}alkylaminosulfonyl, and di(C_{1-6}alkyl)aminosulfonyl;

L_1 is $-(CH_2)_r-$ or $-CH_2CH_2X(CH_2)_s-$, optionally substituted with one to three subsitutuents independently selected from the group consisting of C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, and halogen; provided that when A_1 is hydrogen, r is greater than or equal to 4;

r is an integer of 1 to 5;

s is an integer of 1 to 3;

X is O or S;

D is –P-A_2; wherein when A_2 is hydrogen, P is –$(CH_2)_{4-6}$– , and when A_2 is other than hydrogen, P is –$(CH_2)_{1-2}$– or –$CH_2CH=CH$–;

A_2 is hydrogen; benzodioxalyl; heteroaryl other than unsubstituted pyridin-2-yl; C_{3-8}cycloalkyl; or phenyl optionally substituted at the meta and para positions with one to three substituents independently selected from the group consisting of C_{1-6}alkyl, C_{1-6}alkoxy, halogen, halogenated C_{1-6}alkyl, halogenated C_{1-6}alkoxy, aryl(C_{1-6})alkoxy, phenyl, C_{1-6}alkylthio, C_{1-6}alkoxycarbonyl, amino, C_{1-6}alkylamino, di(C_{1-6}alkyl)amino, cyano, hydroxy, nitro, C_{1-6}alkylcarbonyl, C_{1-6}alkylthiocarbonyl, aminocarbonyl, C_{1-6}alkylaminocarbonyl, di(C_{1-6}alkyl)aminocarbonyl, C_{1-6}alkylcarbonylamino, and a non fused C_{3-6}cycloalkyloxy; wherein benzodioxalyl, heteroaryl, and C_{3-8}cycloalkyl are optionally substituted with one to three substituents independently selected from the group consisting of C_{1-6}alkyl, C_{1-6}alkoxy, halogen, halogenated C_{1-6}alkyl, halogenated C_{1-6}alkoxy, aryl(C_{1-6})alkoxy, phenyl, C_{1-6}alkylthio, C_{1-6}alkoxycarbonyl, amino, C_{1-6}alkylamino, di(C_{1-6}alkyl)amino, cyano, hydroxy, nitro, C_{1-6}alkylcarbonyl, C_{1-6}alkylthiocarbonyl, aminocarbonyl, C_{1-6}alkylaminocarbonyl, di(C_{1-6}alkyl)aminocarbonyl, C_{1-6}alkylcarbonylamino, and a non fused C_{3-6}cycloalkyloxy;

provided that no more than two substituents on A_2 are aryl(C_{1-6})alkoxy, phenyl, or a non fused C_{3-6}cycloalkyloxy;

provided that when A_1 is unsubstituted phenyl and L_2 is -X_1-$CH(R^x)$-(CR^yR^z)- wherein X_1 is NH, and R^x, R^y, and R^z are each hydrogen, A_2 is other than unsubstituted phenyl; phenyl substituted with aryl(C_{1-6})alkoxy or phenyl; or phenyl substituted at the meta position with cyano;

and, further provided that when A_1 is unsubstituted phenyl and L_2 is -X_1-$CH(R^x)$-$(CR^yR^z)_2$- wherein X_1 is NH and R^x, R^y, and R^z are each hydrogen, A_2 is other than phenyl substituted with methoxy;

and, provided that when A_1 is 3,4-dichloro-phenyl and P is $-CH_2-$, A_2 is other than phenyl substituted at the meta position with trifluoromethyl or trifluoromethoxy

and, further provided that when A_1 is 3,4-dichloro-phenyl and P is $-(CH_2)_2-$, A_2 is other than 4-methoxy-phenyl;

W is N or $C(R_W)$; wherein R_W is H or C_{1-2}alkyl;

L_2 is a bivalent radical selected from the group consisting of

pyrrolidinyl or piperidinyl attached to the triazine ring of Formula (I) via its nitrogen atom, wherein said pyrrolidinyl or piperidinyl is substituted on a carbon atom with $-(CH_2)_{0-2}-$;

$-NH-C_{5-7}$cycloalkyl$-(CH_2)_{0-2}-$; provided that when C_{5-7}cycloalkyl is cyclohexyl, Q is attached at either the 2- or cis-4-position relative to the position of –NH-;

$-X_1-C_{2-6}$alkyl-;

$-X_1-(CH_2)_u-X_2-(CH_2)_v-$; wherein u is an integer of 1 to 3; and wherein v is an integer of 1 to 4; provided that when X_1 is a direct bond and W is $C(R_w)$, then u is 1 and v is 2 to 4;

$-X_2-(CH_2)_{0-4}-$;

$-X_1-(CH_2)_{2-3}-X_3-(CH_2)_{2-3}-$;

$-NH(CH_2)_{1-4}C(=O)-$, provided that at least one of R^b, R^c, or R^d is other than hydrogen and m is 0;

$-NHC(=O)-(CH_2)_{1-4}-$;

$-C(=O)NH(CR^yR^z)_{2-5}-$;

and

$-X_1-CH(R^x)-(CR^yR^z)_{1-5}-$; such that when X_1 is a direct bond and W is $C(R_w)$, then R^x is hydrogen;

wherein X_1 is –NH-, O, S, or a direct bond, such that X_1 is other than O when W is N;

X_2 is –CH=CH-;

X_3 is O, S, NH, or C=O;

R^x, R^y, and R^z are independently H or C_{1-4}alkyl;

and provided that L_2 in any instance does not exceed 7 atoms in length;

and further provided that when L_2 is $-X_2-(CH_2)_{0-4}-$ or $-C(=O)NH(CR^yR^z)_{2-5}-$, then R_W is hydrogen;

Q is $-(O)_mN(R^a)-G$; and m is 0 or 1;

G is $-C(=NR^b)NR^cR^d$;

R^a and R^d are independently hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, or C_{3-6}alkynyl, wherein substituents of R^a and R^d other than hydrogen are optionally substituted with one to three substituents independently selected from the group consisting of hydroxy, C_{1-4}alkoxy, fluoro, amino, C_{1-4}alkylamino, diC_{1-4}alkylamino, and C_{1-4}alkylcarbonyl; or R^a and R^c are taken together with the atoms to which they are attached to form a 5-8 membered monocyclic ring optionally substituted with oxo;

R^b is hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-6}alkynyl, C_{2-6}alkoxycarbonyl, or cyano; or, R^b and R^c are taken together with the atoms to which they are attached to form a 5-8 membered monocyclic ring, optionally substituted with oxo;

R^c is hydrogen, C_{1-10}alkyl, C_{2-10}alkenyl, C_{3-10}alkynyl, C_{3-7}cycloalkyl, adamantyl, amino, C_{1-6}alkylamino, di(C_{1-6}alkyl)amino, C_{1-6}alkylcarbonyl, C_{1-6}alkoxycarbonyl, arylcarbonyl, heteroarylcarbonyl, heterocyclylcarbonyl, aryl, heteroaryl, or heterocyclyl; wherein C_{1-10}alkyl, C_{2-10}alkenyl, and C_{2-10}alkynyl are optionally substituted with one to three substituents independently selected from the group consisting of hydroxy, C_{1-6}alkoxy, trifluoromethyl, aryl, heteroaryl, and heterocyclyl; and wherein any aryl- or heteroaryl-containing substituents of R^c are optionally substituted with one to three substituents independently selected from the group consisting of C_{1-6}alkyl, C_{1-6}alkoxy, halogen, fluorinated C_{1-6}alkyl, fluorinated C_{1-6}alkoxy, C_{1-6}alkylcarbonyl, C_{1-6}alkoxycarbonyl, aminocarbonyl, C_{1-}

$_{6}$alkylaminocarbonyl, di(C_{1-6}alkyl)aminocarbonyl, C_{1-6}alkoxycarbonylamino, formyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, aminosulfonyl, C_{1-6}alkylaminosulfonyl, and di(C_{1-6}alkyl)aminosulfonyl, nitro, methylthio, hydroxy, and cyano; or, R^c and R^d are taken together with the atoms to which they are attached to form a 5-8 membered monocyclic ring that optionally includes 1 to 2 O or S heteroatoms within the ring, and said ring is optionally substituted with oxo;

with the proviso that in any instance, only one ring optionally exists between R^a and R^b, R^b and R^c, or R^c and R^d;

and enantiomers, diastereomers, tautomers, solvates, and pharmaceutically acceptable salts thereof.

2. The compound according to claim 1 wherein the compound of Formula (I) is other than a compound wherein A_1 is phenyl, L is $-CH_2-$, D is $-CH_2-$(4-methoxy-phenyl), W is N, L_2 is $-NH(CH_2)_2-$, and Q is $-NHC(=NH)NH_2$.

3. The compound according to claim 1 wherein A_1 is hydrogen; aryl; heteroaryl; or C_{5-8}cycloalkyl; wherein substituents of A_1 other than hydrogen are optionally substituted with one to three substituents independently selected from the group consisting of C_{1-6}alkyl, hydroxy(C_{1-6})alkyl, C_{1-6}alkoxy, halogen, nitro, halogenated C_{1-6}alkyl, halogenated C_{1-6}alkoxy, C_{1-6}alkylthio, C_{1-6}alkoxycarbonyl, amino, C_{1-6}alkylamino, di(C_{1-6}alkyl)amino, cyano, hydroxy, aminocarbonyl, C_{1-6}alkylaminocarbonyl, di(C_{1-6}alkyl)aminocarbonyl, C_{1-6}alkoxycarbonylamino, C_{1-6}alkylcarbonyl, C_{1-6}alkylthiocarbonyl, formyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, aminosulfonyl, C_{1-6}alkylaminosulfonyl, and di(C_{1-6}alkyl)aminosulfonyl.

4. The compound according to claim 1 wherein A_1 is hydrogen; aryl; heteroaryl; C_{5-8}cycloalkyl; or heterocyclyl; provided that A_1 is other than piperidin-4-yl, *N*-t-butoxycarbonyl-piperidin-4-yl, or *N*-methyl-piperidin-3-yl; and wherein substituents of A_1 other than hydrogen are optionally substituted with one to three substituents independently selected from the group consisting of C_{1-6}alkyl, hydroxy(C_{1-6})alkyl, C_{1-6}alkoxy, halogen, nitro, halogenated C_{1-6}alkyl, halogenated C_{1-6}alkoxy, C_{1-6}alkylthio, C_{1-6}alkoxycarbonyl, amino, cyano, hydroxy, aminocarbonyl, C_{1-6}alkylaminocarbonyl, di(C_{1-6}alkyl)aminocarbonyl, and C_{1-6}alkylcarbonyl.

5. The compound according to claim 1 wherein A_1 is hydrogen; aryl; heteroaryl; C_{5-8}cycloalkyl; or heterocyclyl other than piperidinyl; wherein substituents of A_1 other than hydrogen are optionally substituted with one to three substituents independently selected from the group consisting of C_{1-6}alkyl, hydroxy(C_{1-6})alkyl, C_{1-6}alkoxy, halogen, nitro, halogenated C_{1-6}alkyl, halogenated C_{1-6}alkoxy, C_{1-6}alkylthio, C_{1-6}alkoxycarbonyl, amino, cyano, hydroxy, aminocarbonyl, C_{1-6}alkylaminocarbonyl, di(C_{1-6}alkyl)aminocarbonyl, and C_{1-6}alkylcarbonyl.

6. The compound according to claim 1 wherein A_1 is hydrogen, substituted phenyl, benzofuranyl, furanyl, thiazolyl, thiophenyl, or cyclopentyl; wherein substituents of A_1 other than hydrogen are optionally substituted and phenyl is substituted with one to two substituents independently selected from the group consisting of C_{1-4}alkyl, C_{1-4}alkoxy, halogen, nitro, halogenated C_{1-4}alkyl, halogenated C_{1-4}alkoxy, methylthio, C_{1-4}alkoxycarbonyl, amino, cyano, hydroxy, aminocarbonyl, and C_{1-4}alkylcarbonyl.

7. The compound according to claim 1 wherein A_1 is substituted phenyl, benzofuranyl, thiazolyl, or thiophenyl; wherein phenyl is substituted with, and

benzofuranyl, thiazolyl, and thiophenyl are optionally substituted with one to two substituents independently selected from the group consisting of C_{1-4}alkyl, C_{1-4}alkoxy, halogen, nitro, halogenated C_{1-4}alkyl, halogenated C_{1-4}alkoxy, methylthio, amino, cyano, and C_{1-4}alkylcarbonyl.

8. The compound according to claim 1 wherein A_1 is phenyl or benzofuranyl; wherein phenyl is substituted at either the 4-position or 3- and 4-positions with one to two substituents independently selected from the group consisting of ethyl, methoxy, fluoro, chloro, nitro, difluoromethoxy, and methylthio.

9. The compound according to claim 1 wherein L_1 is $-(CH_2)_r-$, optionally substituted with one to three substituents independently selected from the group consisting of C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, and halogen; provided that when A_1 is hydrogen, r is greater than or equal to 4.

10. The compound according to claim 1 wherein L_1 is $-(CH_2)_r-$, optionally substituted with a substituent selected from the group consisting of C_{1-4}alkyl, C_{2-4}alkenyl, and C_{2-4}alkynyl; provided that r is 1 to 3 when A_1 is other than hydrogen; or r is greater than or equal to 4 when A_1 is hydrogen.

11. The compound according to claim 1 wherein L_1 is $-(CH_2)_r-$ optionally substituted with a substituent selected from the group consisting of methyl and allyl; provided that r is 1 to 3 when A_1 is other than hydrogen.

12. The compound according to claim 1 wherein L_1 is $-CH_2-$ optionally substituted with methyl or allyl.

13. The compound according to claim 1 wherein A_2 is hydrogen, heteroaryl other than unsubstituted pyridin-2-yl, C_{3-8}cycloalkyl, or phenyl optionally substituted at the meta and para positions with one to three substituents independently

selected from the group consisting of C_{1-6}alkyl, C_{1-6}alkoxy, halogen, halogenated C_{1-6}alkyl, halogenated C_{1-6}alkoxy, aryl(C_{1-6})alkoxy, phenyl, C_{1-6}alkylthio, C_{1-6}alkoxycarbonyl, amino, cyano, hydroxy, nitro, aminocarbonyl, C_{1-6}alkylcarbonylamino, and a non fused C_{3-6}cycloalkyloxy; wherein heteroaryl other than unsubstituted pyridin-2-yl and C_{3-8}cycloalkyl are optionally substituted with one to three substituents independently selected from the group consisting of C_{1-6}alkyl, C_{1-6}alkoxy, halogen, halogenated C_{1-6}alkyl, halogenated C_{1-6}alkoxy, aryl(C_{1-6})alkoxy, phenyl, C_{1-6}alkylthio, C_{1-6}alkoxycarbonyl, amino, cyano, hydroxy, nitro, aminocarbonyl, C_{1-6}alkylcarbonylamino, and a non fused C_{3-6}cycloalkyloxy;

provided that no more than two substituents on A_2 are aryl(C_{1-6})alkoxy, phenyl, or a non fused C_{3-6}cycloalkyloxy;

provided that when A_1 is unsubstituted phenyl and L_2 is $-X_1-CH(R^x)-(CR^yR^z)-$ wherein X_1 is NH and R^x, R^y, and R^z are each hydrogen, A_2 is other than unsubstituted phenyl; phenyl substituted with aryl(C_{1-6})alkoxy or phenyl; or phenyl substituted at the meta position with cyano;

and, further provided that when A_1 is unsubstituted phenyl and L_2 is $-X_1-CH(R^x)-(CR^yR^z)_2-$ wherein X_1 is NH and R^x, R^y, and R^z are each hydrogen, A_2 is other than phenyl substituted with methoxy;

and, provided that when A_1 is 3,4-dichloro-phenyl and P is $-CH_2-$, A_2 is other than phenyl substituted at the meta position with trifluoromethyl or trifluoromethoxy

and, further provided that when A_1 is 3,4-dichloro-phenyl and P is $-(CH_2)_2-$, A_2 is other than 4-methoxy-phenyl; and

in addition, when A_2 is hydrogen, P is $-(CH_2)_{4-6}-$, and when A_2 is other than hydrogen, P is $-(CH_2)_{1-2}-$ or $-CH_2CH=CH-$.

14. The compound according to claim 1 wherein A_2 is is a heteroaryl other than unsubstituted pyridin-2-yl, a non fused C_{3-8}cycloalkyl, or phenyl optionally

substituted at the meta and para positions with one to three substituents independently selected from the group consisting of C_{1-6}alkyl, C_{1-6}alkoxy, halogen, halogenated C_{1-6}alkyl, halogenated C_{1-6}alkoxy, C_{1-6}alkylthio, C_{1-6}alkoxycarbonyl, amino, hydroxy, nitro, aminocarbonyl, C_{1-6}alkylcarbonylamino, and a non fused C_{3-6}cycloalkyloxy; wherein heteroaryl other than unsubstituted pyridin-2-yl and a non fused C_{3-8}cycloalkyl are optionally substituted with one to three substituents independently selected from the group consisting of C_{1-6}alkyl, C_{1-6}alkoxy, halogen, halogenated C_{1-6}alkyl, halogenated C_{1-6}alkoxy, C_{1-6}alkylthio, C_{1-6}alkoxycarbonyl, amino, hydroxy, nitro, aminocarbonyl, C_{1-6}alkylcarbonylamino, and a non fused C_{3-6}cycloalkyloxy;

provided that no more than two substituents on A_2 are non fused C_{3-6}cycloalkyloxy;

provided that when A_1 is unsubstituted phenyl and L_2 is $-X_1-CH(R^x)-(CR^yR^z)-$ wherein X_1 is NH and R^x, R^y, and R^z are each hydrogen, A_2 is other than unsubstituted phenyl;

and, further provided that when A_1 is unsubstituted phenyl and L_2 is $-X_1-CH(R^x)-(CR^yR^z)_2-$ wherein X_1 is NH and R^x, R^y, and R^z are each hydrogen, A_2 is other than phenyl substituted with methoxy;

and, provided that when A_1 is 3,4-dichloro-phenyl, A_2 is other than phenyl substituted at the meta position with trifluoromethyl or trifluoromethoxy;

and, further provided that when A_1 is 3,4-dichloro-phenyl and P is $-(CH_2)_2-$, A_2 is other than 4-methoxy-phenyl.

15. The compound according to claim 1 wherein A_2 is furanyl, pyridin-3-yl, pyridin-4-yl, or phenyl optionally substituted at the meta and para positions with one to three substituents independently selected from the group consisting of C_{1-4}alkyl, C_{1-4}alkoxy, halogen, halogenated C_{1-3}alkoxy, C_{1-3}alkylthio, hydroxy, amino, aminocarbonyl, C_{1-3}alkylcarbonylamino, and a non fused C_{3-}

$_6$cycloalkyloxy; and wherein furanyl, pyridin-3-yl, and pyridin-4-yl are optionally substituted with one to three substituents independently selected from the group consisting of C_{1-4}alkyl, C_{1-4}alkoxy, halogen, halogenated C_{1-3}alkoxy, C_{1-3}alkylthio, hydroxy, amino, aminocarbonyl, C_{1-3}alkylcarbonylamino, and a non fused C_{3-6}cycloalkyloxy;

provided that no more than two substituents on A_2 are non fused C_{3-6}cycloalkyloxy;

provided that when A_1 is unsubstituted phenyl and L_2 is $-X_1-CH(R^x)-(CR^yR^z)-$ wherein X_1 is NH and R^x, R^y, and R^z are each hydrogen, A_2 is other than unsubstituted phenyl;

and, further provided that when A_1 is unsubstituted phenyl and L_2 is $-X_1-CH(R^x)-(CR^yR^z)_2-$ wherein X_1 is NH and R^x, R^y, and R^z are each hydrogen, A_2 is other than phenyl substituted with methoxy;

and, provided that when A_1 is 3,4-dichloro-phenyl, A_2 is other than phenyl substituted in the meta position with trifluoromethoxy.

16. The compound according to claim 1 wherein A_2 is pyridin-3-yl, pyridin-4-yl, or phenyl optionally substituted at the meta and para positions with one to two substituents independently selected from the group consisting of methyl, ethyl, methoxy, ethoxy, isopropyloxy, trifluoromethoxy, difluoromethoxy, hydroxy, aminocarbonyl, and methylcarbonylamino; wherein pyridin-3-yl and pyridin-4-yl are optionally substituted with one to two substituents independently selected from the group consisting of methyl, ethyl, methoxy, ethoxy, isopropyloxy, trifluoromethoxy, difluoromethoxy, hydroxy, aminocarbonyl, and methylcarbonylamino;

provided that when A_1 is unsubstituted phenyl and L_2 is $-X_1-CH(R^x)-(CR^yR^z)-$ wherein X_1 is NH and R^x, R^y, and R^z are each hydrogen, A_2 is other than unsubstituted phenyl;

and, further provided that when A_1 is unsubstituted phenyl and L_2 is

$-X_1-CH(R^x)-(CR^yR^z)_2-$ wherein X_1 is NH and R^x, R^y, and R^z are each hydrogen, A_2 is other than phenyl substituted with methoxy;

and, further provided that when A_1 is 3,4-dichloro-phenyl, A_2 is other than phenyl substituted at the meta position with trifluoromethoxy

17. The compound according to claim 1 wherein A_2 is phenyl substituted at the para position with a substituent selected from the group consisting of methoxy, ethoxy, isopropyloxy, difluoromethoxy, hydroxy, and aminocarbonyl; or A_2 is pyridin-3-yl or pyridin-4-yl substituted with methoxy.

18. The compound according to claim 1 wherein P is $-CH_2-$.

19. The compound according to claim 1 wherein W is N or $C(R_W)$ wherein R_W is H.

20. The compound according to claim 1 wherein L_2 is a bivalent radical selected from the group consisting of

$-NH-C_{5-7}$cycloalkyl$-(CH_2)_{0-2}-$; such that when C_{5-7}cycloalkyl is cyclohexyl, Q is attached at either the 2- or cis-4-position relative to the position of –NH-;

$-X_2-(CH_2)_{0-4}-$;

$-X_1-(CH_2)_{2-3}-X_3-(CH_2)_{2-3}-$;

$-NH(CH_2)_{1-4}C(=O)-$ provided that at least one of R^b, R^c, or R^d is other than hydrogen and m is 0;

$-NHC(=O)-(CH_2)_{1-4}-$;

$-C(=O)NH(CR^yR^z)_{2-5}-$;

and

$-X_1-CH(R^x)-(CR^yR^z)_{1-5}-$; such that when X_1 is a direct bond and W is $C(R_w)$, then R^x of $CH(R^x)$ is hydrogen;

wherein X_1 is –NH-, O, S, or a direct bond; such that X_1 is other than O when W is N;

X_2 is –CH=CH-;

X_3 is O, S, NH, or C=O;

R^x, R^y, and R^z are independently H or C_{1-4}alkyl;

and provided that L_2 in any instance does not exceed 7 atoms in length;

and further provided that when L_2 is $-X_2-(CH_2)_{0-4}-$ or $-C(=O)NH(CR^yR^z)_{2-5}-$, then R_W is hydrogen.

21. The compound according to claim 1 wherein L_2 is a bivalent radical selected from the group consisting of -NH-C_{5-6}cycloalkyl–$(CH_2)_{0-2}$- provided that when C_{5-6}cycloalkyl is cyclohexyl, Q is attached at either the 2- or cis-4-position relative to the position of –NH-;

$-X_1-CH(R^x)-(CR^yR^z)_{1-5}-$, wherein X_1 is -NH–, O, or S and R^x, R^y, and R^z are each hydrogen; such that X_1 is other than O when W is N;

$-C(=O)NH(CH_2)_2-$;

and

$-X_1-(R,R\text{-}CH(R^x)CR^y(R^z))-$; wherein X_1 is -NH–, and R^x and R^z are methyl, and R^y is hydrogen;

provided that when L_2 is $-C(=O)NH(CH_2)_2-$, then R_W is hydrogen.

22. The compound according to claim 1 wherein L_2 is a bivalent radical selected from the group consisting of -NH-cyclohexyl–$(CH_2)_{0-2}$– and Q is attached at either the 2- or cis-4-position relative to the position of –NH-;

$-X_1-CH(R^x)-(CR^yR^z)_{1-5}-$; wherein X_1 is –NH- or S; and R^x, R^y, and R^z are each hydrogen;

and

$-X_1-(R,R\text{-}CH(R^x)CR^y(R^z))-$; wherein X_1 is -NH–, and R^x and R^z are methyl, and R^y is hydrogen.

23. The compound according to claim 1 wherein L_2 is a bivalent radical selected from the group consisting of -NH-cyclohexyl–$(CH_2)_{0-2}$– and Q is attached at either the 2- or cis-4-position relative to the position of –NH-;
-X_1-$CH(R^x)$-(CR^yR^z)-; wherein X_1 is -NH– or S and R^x, R^y, and R^z are each hydrogen;
and
-X_1-(*R,R*-$CH(R^x)CR^y(R^z)$)-; wherein X_1 is -NH–, R^x and R^z are methyl, and R^y is hydrogen.

24. The compound according to claim 1 wherein m is 0.

25. The compound according to claim 1 wherein R^a and R^d are independently hydrogen or C_{1-6}alkyl, wherein C_{1-6}alkyl is optionally substituted with one to three substituents independently selected from the group consisting of hydroxy, C_{1-4}alkoxy, fluoro, amino, C_{1-4}alkylamino, diC_{1-4}alkylamino, and C_{1-4}alkylcarbonyl; or R^a and R^c are taken together with the atoms to which they are attached to form a 5-8 membered monocyclic ring optionally substituted with oxo.

26. The compound according to claim 1 wherein R^a and R^d are independently hydrogen or C_{1-3}alkyl, wherein C_{1-3}alkyl is optionally substituted with one to three substituents independently selected from the group consisting of hydroxy, C_{1-4}alkoxy, fluoro, amino, C_{1-4}alkylamino, diC_{1-4}alkylamino, and C_{1-4}alkylcarbonyl; or R^a and R^c are taken together with the atoms to which they are attached to form a 5-8 membered monocyclic ring optionally substituted with oxo.

27. The compound according to claim 1 wherein R^a and R^d are independently hydrogen, methyl or ethyl; or R^a and R^c are taken together with the atoms to which they are attached to form a 5-8 membered monocyclic ring optionally substituted with oxo.

28. The compound according to claim 1 wherein R^a and R^d are independently hydrogen, methyl or ethyl.

29. The compound according to claim 1 wherein R^b is hydrogen, C_{1-6}alkyl, C_{2-6}alkoxycarbonyl, or cyano; or, R^b and R^c are taken together with the atoms to which they are attached to form a 5-8 membered monocyclic ring, optionally substituted with oxo.

30. The compound according to claim 1 wherein R^b is hydrogen or C_{1-4}alkyl; or, R^b and R^c are taken together with the atoms to which they are attached to form a 5-8 membered monocyclic ring, optionally substituted with oxo.

31. The compound according to claim 1 wherein R^b is hydrogen.

32. The compound according to claim 1 wherein R^c is hydrogen, C_{1-10}alkyl, C_{2-10}alkenyl, C_{3-7}cycloalkyl, adamantyl, amino, arylcarbonyl, aryl, heteroaryl, or heterocyclyl; wherein C_{1-10}alkyl is optionally substituted with one to two substituents independently selected from the group consisting of C_{1-4}alkoxy, trifluoromethyl, aryl, heteroaryl, and heterocyclyl; and wherein any aryl- or heteroaryl-containing substituents of R^c are optionally substituted with one to three substituents independently selected from the group consisting of C_{1-6}alkyl, C_{1-6}alkoxy, halogen, fluorinated C_{1-6}alkyl, fluorinated C_{1-6}alkoxy, C_{1-6}alkylcarbonyl, C_{1-6}alkoxycarbonyl, nitro, methylthio, hydroxy, and cyano; or, R^c and R^d are taken together with the atoms to which they are attached to

form a 5-8 membered monocyclic ring that optionally includes 1 to 2 O or S heteroatoms within the ring, and said ring is optionally substituted with oxo.

33. The compound according to claim 1 wherein R^c is hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-7}cycloalkyl, adamantyl, heterocyclyl, arylcarbonyl, phenyl, or heteroaryl; wherein C_{1-6}alkyl is optionally substituted with one to two substituents independently selected from the group consisting of C_{1-3}alkoxy, trifluoromethyl, phenyl, heteroaryl, and heterocyclyl; and wherein any aryl-, phenyl-, or heteroaryl-containing substituents of R^c are optionally substituted with one to three substituents independently selected from the group consisting of C_{1-6}alkyl, C_{1-6}alkoxy, halogen, fluorinated C_{1-6}alkyl, fluorinated C_{1-6}alkoxy, C_{1-6}alkylcarbonyl, C_{1-6}alkoxycarbonyl, nitro, methylthio, hydroxy, and cyano; or, R^c and R^d are taken together with the atoms to which they are attached to form a 5-8 membered monocyclic ring and said ring is optionally substituted with oxo.

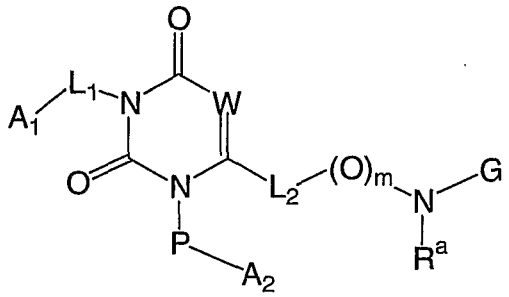
34. The compound according to claim 1 wherein R^c is hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-7}cycloalkyl, heterocyclyl, phenylcarbonyl, phenyl, or heteroaryl; wherein C_{1-6}alkyl is optionally substituted with one to two substituents independently selected from the group consisting of C_{1-3}alkoxy, phenyl, pyridinyl, furanyl, and tetrahydrofuranyl; and wherein any phenyl- or heteroaryl-containing substituents of R^c are optionally substituted with one to two substituents independently selected from the group consisting of C_{1-6}alkyl, C_{1-6}alkoxy, chloro, fluoro, bromo, fluorinated C_{1-3}alkoxy, nitro, methylthio, hydroxy, and cyano; or, R^c and R^d are taken together with the atoms to which they are attached to form a 5-8 membered monocyclic ring.

35. The compound according to claim 1 wherein R^c is hydrogen, C_{1-4}alkyl, C_{2-4}alkenyl, cyclohexyl, phenylcarbonyl, phenyl, pyrimidinyl, furanyl,

benzo[1,3]dioxolyl, or pyridinyl; wherein C_{1-4}alkyl is optionally substituted with one to two substituents independently selected from the group consisting of C_{1-3}alkoxy, phenyl, pyridinyl, furanyl, and tetrahydrofuranyl; and wherein any phenyl- or heteroaryl-containing substituents of R^c are optionally substituted with one to two substituents independently selected from the group consisting of C_{1-6}alkyl, C_{1-6}alkoxy, chloro, fluoro, bromo, fluorinated C_{1-3}alkoxy, nitro, methylthio, hydroxy, and cyano; or, R^c and R^d are taken together with the atoms to which they are attached to form a 5-8 membered monocyclic ring.

36. The compound according to claim 1 wherein R^c is hydrogen, C_{1-4}alkyl, C_{2-4}alkenyl, cyclohexyl, phenylcarbonyl, phenyl, pyrimidinyl, furanyl, benzo[1,3]dioxolyl, or pyridinyl; wherein C_{1-4}alkyl is optionally substituted with one to two substituents independently selected from the group consisting of methoxy, phenyl, pyridinyl, furanyl, and tetrahydrofuranyl; and wherein any phenyl- or heteroaryl-containing substituents of R^c are optionally substituted with one to two substituents independently selected from the group consisting of C_{1-3}alkyl, C_{1-3}alkoxy, chloro, fluoro, bromo, trifluoromethoxy, nitro, hydroxy, and cyano; or, R^c and R^d are taken together with the atoms to which they are attached to form a 5-6 membered monocyclic ring.

37. A compound of Formula (Ia):



Formula (Ia)

wherein:

A_1 is hydrogen; aryl; heteroaryl; C_{5-8}cycloalkyl; or heterocyclyl provided that A_1 is other than piperidin-4-yl, *N*-t-butoxycarbonyl-piperidin-4-yl, or *N*-methyl-piperidin-3-yl; and wherein substituents of A_1 other than hydrogen are optionally substituted with one to three substituents independently selected from the group consisting of C_{1-6}alkyl, hydroxy(C_{1-6})alkyl, C_{1-6}alkoxy, halogen, nitro, halogenated C_{1-6}alkyl, halogenated C_{1-6}alkoxy, C_{1-6}alkylthio, C_{1-6}alkoxycarbonyl, amino, cyano, hydroxy, aminocarbonyl, C_{1-6}alkylaminocarbonyl, di(C_{1-6}alkyl)aminocarbonyl, and C_{1-6}alkylcarbonyl;

L_1 is $-(CH_2)_r-$ optionally substituted with one to three substituents independently selected from the group consisting of C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, and halogen; provided that when A_1 is hydrogen, r is greater than or equal to 4;

r is an integer of 1 to 5;

P is $-(CH_2)_{4-6}-$ when A_2 is hydrogen; and P is $-(CH_2)_{1-2}-$ or $-CH_2CH=CH-$ when A_2 is other than hydrogen;

A_2 is hydrogen, heteroaryl other than unsubstituted pyridin-2-yl, C_{3-8}cycloalkyl, or phenyl optionally substituted at the meta and para positions with one to three substituents independently selected from the group consisting of C_{1-6}alkyl, C_{1-6}alkoxy, halogen, halogenated C_{1-6}alkyl, halogenated C_{1-6}alkoxy, aryl(C_{1-6})alkoxy, phenyl, C_{1-6}alkylthio, C_{1-6}alkoxycarbonyl, amino, cyano, hydroxy, nitro, aminocarbonyl, C_{1-6}alkylcarbonylamino, and a non fused C_{3-6}cycloalkyloxy; wherein heteroaryl other than unsubstituted pyridin-2-yl and C_{3-8}cycloalkyl are optionally substituted with one to three substituents independently selected from the group consisting of C_{1-6}alkyl, C_{1-6}alkoxy, halogen, halogenated C_{1-6}alkyl, halogenated C_{1-6}alkoxy, aryl(C_{1-6})alkoxy, phenyl, C_{1-6}alkylthio, C_{1-6}alkoxycarbonyl, amino, cyano, hydroxy, nitro, aminocarbonyl, C_{1-6}alkylcarbonylamino, and a non fused C_{3-6}cycloalkyloxy;

provided that no more than two substituents on A_2 are aryl(C_{1-6})alkoxy, phenyl, or a non fused C_{3-6}cycloalkyloxy;

provided that when A_1 is unsubstituted phenyl and L_2 is $-X_1-CH(R^x)-(CR^yR^z)-$ wherein X_1 is NH and R^x, R^y, and R^z are each hydrogen, A_2 is other than unsubstituted phenyl; phenyl substituted with aryl(C_{1-6})alkoxy or phenyl; or phenyl substituted at the meta position with cyano;

and, further provided that when A_1 is unsubstituted phenyl and L_2 is $-X_1-CH(R^x)-(CR^yR^z)_2-$ wherein X_1 is NH and R^x, R^y, and R^z are each hydrogen, A_2 is other than phenyl substituted with methoxy;

and, provided that when A_1 is 3,4-dichloro-phenyl and P is $-CH_2-$, A_2 is other than phenyl substituted at the meta position with trifluoromethyl or trifluoromethoxy;

and, further provided that when A_1 is 3,4-dichloro-phenyl and P is $-(CH_2)_2-$, A_2 is other than 4-methoxy-phenyl;

W is N or CH;

L_2 is a bivalent radical selected from the group consisting of

$-NH-C_{5-7}$cycloalkyl$-(CH_2)_{0-2}-$; provided that when C_{5-7}cycloalkyl is cyclohexyl, Q is attached at either the 2- or cis-4-position relative to the position of –NH-;

$-X_2-(CH_2)_{0-4}-$;

$-X_1-(CH_2)_{2-3}-X_3-(CH_2)_{2-3}-$;

$-NH(CH_2)_{1-4}C(=O)-$ provided that at least one of R^b, R^c, or R^d is other than hydrogen and m is 0;

$-NHC(=O)-(CH_2)_{1-4}-$;

$-C(=O)NH(CR^yR^z)_{2-5}$;

and

$-X_1-CH(R^x)-(CR^yR^z)_{1-5}-$; such that when X_1 is a direct bond and W is $C(R_w)$, then R^x of $CH(R^x)$ is hydrogen;

wherein X_1 is –NH-, O, S, or a direct bond; such that X_1 is other than O when W is N;

X_2 is –CH=CH-;

X_3 is O, S, NH, or C=O;

R^x, R^y, and R^z are independently H or C_{1-4}alkyl;

and provided that L_2 in any instance does not exceed 7 atoms in length;

and further provided that when L_2 is $-X_2-(CH_2)_{0-4}-$ or $-C(=O)NH(CR^yR^z)_{2-5}-$, then R_W is hydrogen;;

m is 0 or 1;

G is $-C(=NR^b)NR^cR^d$;

R^a and R^d are independently hydrogen or C_{1-6}alkyl, wherein C_{1-6}alkyl is optionally substituted with one to three substituents independently selected from the group consisting of hydroxy, C_{1-4}alkoxy, fluoro, amino, C_{1-4}alkylamino, diC_{1-4}alkylamino, and C_{1-4}alkylcarbonyl; or R^a and R^c are taken together with the atoms to which they are attached to form a 5-8 membered monocyclic ring optionally substituted with oxo;

R^b is hydrogen, C_{1-6}alkyl, C_{2-6}alkoxycarbonyl, or cyano; or, R^b and R^c are taken together with the atoms to which they are attached to form a 5-8 membered monocyclic ring optionally substituted with oxo;

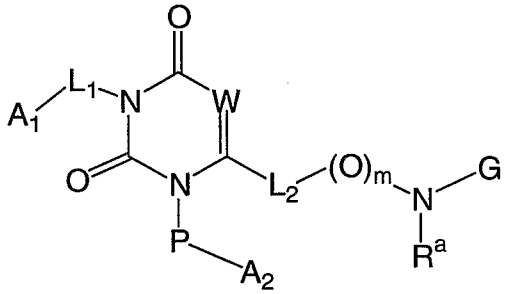
R^c is hydrogen, C_{1-10}alkyl, C_{2-10}alkenyl, C_{3-7}cycloalkyl, adamantyl, amino, arylcarbonyl, aryl, heteroaryl, or heterocyclyl; wherein C_{1-10}alkyl is optionally substituted with one to two substituents independently selected from the group consisting of C_{1-4}alkoxy, trifluoromethyl, aryl, heteroaryl, and heterocyclyl; and wherein any aryl- or heteroaryl-containing substituents of R^c are optionally substituted with one to three substituents independently selected from the group consisting of C_{1-6}alkyl, C_{1-6}alkoxy, halogen, fluorinated C_{1-6}alkyl, fluorinated C_{1-6}alkoxy, C_{1-6}alkylcarbonyl, C_{1-6}alkoxycarbonyl, nitro, methylthio, hydroxy, and cyano; or, R^c and R^d are taken together with the atoms to which they are attached to form a 5-8

membered monocyclic ring that optionally includes 1 to 2 O or S heteroatoms within the ring, and said ring is optionally substituted with oxo;

with the proviso that in any instance, only one ring optionally exists between R^a and R^b, R^b and R^c, or R^c and R^d;

and enantiomers, diastereomers, tautomers, solvates, and pharmaceutically acceptable salts thereof.

38. A compound of Formula (Ia)



Formula (Ia)

wherein:

A_1 is hydrogen; aryl; heteroaryl; C_{5-8}cycloalkyl; or heterocyclyl other than piperidinyl; wherein substituents of A_1 other than hydrogen are optionally substituted with one to three substituents independently selected from the group consisting of C_{1-6}alkyl, hydroxy(C_{1-6})alkyl, C_{1-6}alkoxy, halogen, nitro, halogenated C_{1-6}alkyl, halogenated C_{1-6}alkoxy, C_{1-6}alkylthio, C_{1-6}alkoxycarbonyl, amino, cyano, hydroxy, aminocarbonyl, C_{1-6}alkylaminocarbonyl, di(C_{1-6}alkyl)aminocarbonyl, and C_{1-6}alkylcarbonyl;

L_1 is $-(CH_2)_r-$ optionally substituted with a substituent selected from the group consisting of C_{1-4}alkyl, C_{2-4}alkenyl, and C_{2-4}alkynyl; provided that r is 1 to 3 when A_1 is other than hydrogen; or r is 4 or 5 when A_1 is hydrogen;

P is $-CH_2-$;

A_2 is heteroaryl other than unsubstituted pyridin-2-yl, a non fused C_{3-8}cycloalkyl, or phenyl optionally substituted at the meta and para positions with one to

three substituents independently selected from the group consisting of C_{1-6}alkyl, C_{1-6}alkoxy, halogen, halogenated C_{1-6}alkyl, halogenated C_{1-6}alkoxy, C_{1-6}alkylthio, C_{1-6}alkoxycarbonyl, amino, hydroxy, nitro, aminocarbonyl, C_{1-6}alkylcarbonylamino, and a non fused C_{3-6}cycloalkyloxy; wherein heteroaryl other than unsubstituted pyridin-2-yl and a non fused C_{3-8}cycloalkyl are optionally substituted with one to three substituents independently selected from the group consisting of C_{1-6}alkyl, C_{1-6}alkoxy, halogen, halogenated C_{1-6}alkyl, halogenated C_{1-6}alkoxy, C_{1-6}alkylthio, C_{1-6}alkoxycarbonyl, amino, hydroxy, nitro, aminocarbonyl, C_{1-6}alkylcarbonylamino, and a non fused C_{3-6}cycloalkyloxy;

provided that no more than two substituents on A_2 are non fused C_{3-6}cycloalkyloxy;

provided that when A_1 is unsubstituted phenyl and L_2 is $-X_1-CH(R^x)-(CR^yR^z)-$ wherein X_1 is -NH– or S and R^x, R^y, and R^z are each hydrogen, A_2 is other than unsubstituted phenyl;

and, further provided that when A_1 is unsubstituted phenyl and L_2 is $-X_1-CH(R^x)-(CR^yR^z)_2-$ wherein X_1 is NH and R^x, R^y, and R^z are each hydrogen, A_2 is other than phenyl substituted with methoxy;

and, further provided that when A_1 is 3,4-dichloro-phenyl, A_2 is other than phenyl substituted at the meta position with trifluoromethoxy;

W is N or CH;

L_2 is a bivalent radical selected from the group consisting of

$-NH-C_{5-6}$cycloalkyl–$(CH_2)_{0-2}-$; provided that when C_{5-6}cycloalkyl is cyclohexyl, Q is attached at either the 2- or cis-4-position relative to the position of –NH-;

$-X_1-CH(R^x)-(CR^yR^z)_{1-5}-$, wherein X_1 is -NH–, O, or S; and R^x, R^y, and R^z are each hydrogen; such that X_1 is other than O when W is N;

$-C(=O)NH(CH_2)_2-$;

and

-X_1-(*R,R*-CH(R^x)CR^y(R^z))-; wherein X_1 is -NH–, and R^x and R^z are methyl, and R^y is hydrogen;

provided that when L_2 is -C(=O)NH$(CH_2)_2$-, then R_W is hydrogen;

m is 0 or 1;

G is –C(=NR^b)N$R^c R^d$;

R^a and R^d are independently hydrogen or C_{1-3}alkyl, wherein C_{1-3}alkyl is optionally substituted with one to three substituents independently selected from the group consisting of hydroxy, C_{1-4}alkoxy, fluoro, amino, C_{1-4}alkylamino, diC_{1-4}alkylamino, and C_{1-4}alkylcarbonyl; or R^a and R^c are taken together with the atoms to which they are attached to form a 5-8 membered monocyclic ring optionally substituted with oxo;

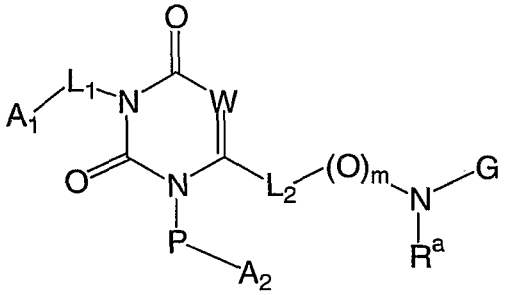
R^b is hydrogen or C_{1-4}alkyl; or, R^b and R^c are taken together with the atoms to which they are attached to form a 5-8 membered monocyclic ring, optionally substituted with oxo;

R^c is hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-7}cycloalkyl, adamantyl, heterocyclyl, arylcarbonyl, phenyl, or heteroaryl; wherein C_{1-6}alkyl is optionally substituted with one to two substituents independently selected from the group consisting of C_{1-3}alkoxy, trifluoromethyl, phenyl, heteroaryl, and heterocyclyl; and wherein any aryl-, phenyl-, or heteroaryl-containing substituents of R^c are optionally substituted with one to three substituents independently selected from the group consisting of C_{1-6}alkyl, C_{1-6}alkoxy, halogen, fluorinated C_{1-6}alkyl, fluorinated C_{1-6}alkoxy, C_{1-6}alkylcarbonyl, C_{1-6}alkoxycarbonyl, nitro, methylthio, hydroxy, and cyano; or, R^c and R^d are taken together with the atoms to which they are attached to form a 5-8 membered monocyclic ring and said ring is optionally substituted with oxo;

with the proviso that in any instance, only one ring optionally exists between R^a and R^b, R^b and R^c, or R^c and R^d;

and enantiomers, diastereomers, tautomers, solvates, and pharmaceutically acceptable salts thereof.

39. A compound of Formula (Ia)



Formula (Ia)

wherein:

A_1 is substituted phenyl, benzofuranyl, thiazolyl, or thiophenyl; wherein phenyl is substituted with, and benzofuranyl, thiazolyl, and thiophenyl are optionally substituted with, one to two substituents independently selected from the group consisting of C_{1-4}alkyl, C_{1-4}alkoxy, halogen, nitro, halogenated C_{1-4}alkyl, halogenated C_{1-4}alkoxy, methylthio, amino, cyano, and C_{1-4}alkylcarbonyl;

L_1 is $-(CH_2)_r-$ optionally substituted with a substituent selected from the group consisting of methyl and allyl, and r is 1 to 3;

P is $-CH_2-$;

A_2 is pyridin-3-yl, pyridin-4-yl, or phenyl optionally substituted at the meta and para positions with one to two substituents independently selected from the group consisting of methyl, ethyl, methoxy, ethoxy, isopropyloxy, trifluoromethoxy, difluoromethoxy, hydroxy, aminocarbonyl, and methylcarbonylamino; wherein pyridin-3-yl and pyridin-4-yl are optionally substituted with one to two substituents independently selected from the group consisting of methyl, ethyl, methoxy, ethoxy, isopropyloxy, trifluoromethoxy, difluoromethoxy, hydroxy, aminocarbonyl, and

methylcarbonylamino; provided that when A_1 is 3,4-dichloro-phenyl, A_2 is other than phenyl substituted at the meta position with trifluoromethoxy;

W is N or CH;

L_2 is a bivalent radical selected from the group consisting of

-NH-cyclohexyl–$(CH_2)_{0-2}$– and Q is attached at either the 2- or cis-4-position relative to the position of –NH-;

$-X_1-CH(R^x)-(CR^yR^z)_{1-5}-$; wherein X_1 is –NH- or S; and R^x, R^y, and R^z are each hydrogen;

and

- X_1-(*R,R*-$CH(R^x)CR^y(R^z)$)-; wherein X_1 is -NH–, and R^x and R^z are methyl, and R^y is hydrogen;

m is 0;

G is $-C(=NR^b)NR^cR^d$;

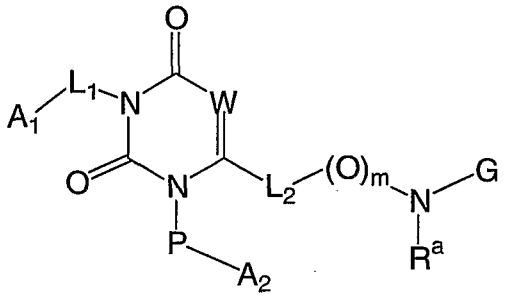
R^a and R^d are independently hydrogen, methyl or ethyl; or R^a and R^c are taken together with the atoms to which they are attached to form a 5-8 membered monocyclic ring optionally substituted with oxo;

R^b is hydrogen;

R^c is hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-7}cycloalkyl, heterocyclyl, phenylcarbonyl, phenyl, or heteroaryl; wherein C_{1-6}alkyl is optionally substituted with one to two substituents independently selected from the group consisting of C_{1-3}alkoxy, phenyl, pyridinyl, furanyl, and tetrahydrofuranyl; and wherein any phenyl- or heteroaryl-containing substituents of R^c are optionally substituted with one to two substituents independently selected from the group consisting of C_{1-6}alkyl, C_{1-6}alkoxy, chloro, fluoro, bromo, fluorinated C_{1-3}alkoxy, nitro, methylthio, hydroxy, and cyano; or, R^c and R^d are taken together with the atoms to which they are attached to form a 5-8 membered monocyclic ring;

and enantiomers, diastereomers, tautomers, solvates, and pharmaceutically acceptable salts thereof.

40. A compound of Formula (Ia)



Formula (Ia)

wherein:

A_1 is phenyl or benzofuranyl; wherein phenyl is substituted at either the 4-position or 3- and 4-positions with one to two substituents independently selected from the group consisting of ethyl, methoxy, fluoro, chloro, nitro, difluoromethoxy, and methylthio;

L_1 is $-CH_2-$ optionally substituted with methyl or allyl;P is $-CH_2-$;

A_2 is phenyl substituted at the para position with a substituent selected from the group consisting of methoxy, ethoxy, isopropyloxy, difluoromethoxy, hydroxy, and aminocarbonyl; or A_2 is pyridin-3-yl or pyridin-4-yl substituted with methoxy;

W is N or CH;

L_2 is a bivalent radical selected from the group consisting of

-NH-cyclohexyl–$(CH_2)_{0-2}$– and Q is attached at either the 2- or cis-4-position relative to the position of –NH-;

$-X_1-CH(R^x)-(CR^yR^z)-$; wherein X_1 is –NH- or S; and R^x, R^y, and R^z are each hydrogen;

and

$- X_1-(R,R-CH(R^x)CR^y(R^z))-$; wherein X_1 is -NH–, and R^x and R^z are methyl, and R^y is hydrogen;

m is 0;

G is $-C(=NR^b)NR^cR^d$;

R^a and R^d are independently hydrogen, methyl or ethyl;

R^b is hydrogen;

R^c is hydrogen, C_{1-4}alkyl, C_{2-4}alkenyl, cyclohexyl, phenylcarbonyl, phenyl, pyrimidinyl, furanyl, benzo[1,3]dioxolyl, or pyridinyl; wherein C_{1-4}alkyl is optionally substituted with one to two substituents independently selected from the group consisting of C_{1-3}alkoxy, phenyl, pyridinyl, furanyl, and tetrahydrofuranyl; and wherein any phenyl- or heteroaryl-containing substituents of R^c are optionally substituted with one to two substituents independently selected from the group consisting of C_{1-6}alkyl, C_{1-6}alkoxy, chloro, fluoro, bromo, fluorinated C_{1-3}alkoxy, nitro, methylthio, hydroxy, and cyano; or, R^c and R^d are taken together with the atoms to which they are attached to form a 5-8 membered monocyclic ring;

and enantiomers, diastereomers, tautomers, solvates, and pharmaceutically acceptable salts thereof.

41. A compound according to claim 1 selected from the group consisting of:

a compound of Formula (I) wherein A_1 is phenyl, L_1 is $-CH_2-$, D is $-CH_2-$(4-fluoro-phenyl), W is N, L_2 is $-NH(CH_2)_2-$, and Q is $-NHC(=NH)NH_2$;

a compound of Formula (I) wherein A_1 is phenyl, L_1 is $-CH_2-$, D is $-CH_2-$(4-methoxy-phenyl), W is N, L_2 is $-NH(CH_2)_2-$, and Q is $-NHC(=NH)NH_2$;

a compound of Formula (I) wherein A_1 is phenyl, L_1 is $-CH_2-$, D is $-CH_2-$(4-methylcarboxy-phenyl), W is N, L_2 is $-NH(CH_2)_2-$, and Q is $-NHC(=NH)NH_2$;

a compound of Formula (I) wherein A_1 is phenyl, L_1 is $-(CH_2)_2-$, D is $-CH_2-$(4-methoxy-phenyl), W is N, L_2 is $-NH(CH_2)_2-$, and Q is $-NHC(=NH)NH_2$;

a compound of Formula (I) wherein A_1 is H, L_1 is $-(CH_2)_4-$, D is $-CH_2-$(4-methoxy-phenyl), W is N, L_2 is $-NH(CH_2)_2-$, and Q is $-NHC(=NH)NH_2$;

a compound of Formula (I) wherein A_1 is furan-2-yl, L_1 is $-CH_2-$, D is $-CH_2-$(4-methoxy-phenyl), W is N, L_2 is $-NH(CH_2)_2-$, and Q is $-NHC(=NH)NH_2$;

a compound of Formula (I) wherein A_1 is phenyl, L_1 is $-CH_2-$, D is $-CH_2-$(3-trifluoromethyl-phenyl), W is N, L_2 is $-NH(CH_2)_2-$, and Q is $-NHC(=NH)NH_2$;

a compound of Formula (I) wherein A_1 is phenyl, L_1 is $-CH_2-$, D is $-CH_2-$(4-t-butyl-phenyl), W is N, L_2 is $-NH(CH_2)_2-$, and Q is $-NHC(=NH)NH_2$;

a compound of Formula (I) wherein A_1 is phenyl, L_1 is $-CH_2-$, D is $-CH_2-$(4-nitro-phenyl), W is N, L_2 is $-NH(CH_2)_2-$, and Q is $-NHC(=NH)NH_2$;

a compound of Formula (I) wherein A_1 is phenyl, L_1 is $-CH_2-$, D is $-CH_2-$(4-methoxy-phenyl), W is N, L_2 is $-NH(CH_2)_2-$, and Q is $-ONHC(=NH)NH_2$;

a compound of Formula (I) wherein A_1 is phenyl, L_1 is $-CH_2-$, D is $-CH_2-$pyridin-4-yl, W is N, L_2 is $-NH(CH_2)_2-$, and Q is $-NHC(=NH)NH_2$;

a compound of Formula (I) wherein A_1 is phenyl, L_1 is $-CH_2-$, D is $-CH_2-$(4-ethoxy-phenyl), W is N, L_2 is $-NH(CH_2)_2-$, and Q is $-NHC(=NH)NH_2$;

a compound of Formula (I) wherein A_1 is phenyl, L_1 is $-CH_2-$, D is $-CH_2-$(4-difluoromethoxy-phenyl), W is N, L_2 is $-NH(CH_2)_2-$, and Q is $-NHC(=NH)NH_2$;

a compound of Formula (I) wherein A_1 is phenyl, L_1 is $-CH_2-$, D is $-CH_2-$(4-n-butyl-phenyl), W is N, L_2 is $-NH(CH_2)_2-$, and Q is $-NHC(=NH)NH_2$;

a compound of Formula (I) wherein A_1 is phenyl, L_1 is $-CH_2-$, D is $-CH_2-$(4-trifluoromethyl-phenyl), W is N, L_2 is $-NH(CH_2)_2-$, and Q is $-NHC(=NH)NH_2$;

a compound of Formula (I) wherein A_1 is 2-fluoro-phenyl, L_1 is $-CH_2-$, D is $-CH_2-$(4-methoxy-phenyl), W is N, L_2 is $-NH(CH_2)_2-$, and Q is $-NHC(=NH)NH_2$;

a compound of Formula (I) wherein A_1 is 4-fluoro-phenyl, L_1 is $-CH_2-$, D is $-CH_2-$(4-methoxy-phenyl), W is N, L_2 is $-NH(CH_2)_2-$, and Q is $-NHC(=NH)NH_2$;

a compound of Formula (I) wherein A_1 is 3,4-dichloro-phenyl, L_1 is -CH_2-, D is -CH_2-(4-methoxy-phenyl), W is N, L_2 is -$NH(CH_2)_2$-, and Q is -$NHC(=NH)NH_2$;

a compound of Formula (I) wherein A_1 is phenyl, L_1 is -CH_2-, D is -CH_2-(4-trifluoromethoxy-phenyl), W is N, L_2 is -$NH(CH_2)_2$-, and Q is -$NHC(=NH)NH_2$;

a compound of Formula (I) wherein A_1 is 3-methoxy-phenyl, L_1 is -CH_2-, D is -CH_2-(4-methoxy-phenyl), W is N, L_2 is -$NH(CH_2)_2$-, and Q is -$NHC(=NH)NH_2$;

a compound of Formula (I) wherein A_1 is 2-methoxy-phenyl, L_1 is -CH_2-, D is -CH_2-(4-methoxy-phenyl), W is N, L_2 is -$NH(CH_2)_2$-, and Q is -$NHC(=NH)NH_2$;

a compound of Formula (I) wherein A_1 is phenyl, L_1 is -CH_2-, D is -CH_2-(4-aminocarbonyl-phenyl), W is N, L_2 is -$NH(CH_2)_2$-, and Q is -$NHC(=NH)NH_2$;

a compound of Formula (I) wherein A_1 is phenyl, L_1 is -CH_2-, D is -CH_2-(4-methylcarboxylamino-phenyl), W is N, L_2 is -$NH(CH_2)_2$-, and Q is -$NHC(=NH)NH_2$;

a compound of Formula (I) wherein A_1 is 4-fluoro-phenyl, L_1 is -CH_2-, D is -CH_2-(4-ethoxy-phenyl), W is N, L_2 is -$NH(CH_2)_2$-, and Q is -$NHC(=NH)NH_2$;

a compound of Formula (I) wherein A_1 is phenyl, L_1 is -(*R,R*–$CH(CH_3)CH(CH_3)$)-, D is -CH_2-(4-methoxy-phenyl), W is N, L_2 is -$NH(CH_2)_2$-, and Q is -$NHC(=NH)NH_2$;

a compound of Formula (I) wherein A_1 is phenyl, L_1 is -(*R,R*–$CH(CH_3)CH(CH_3)$)-, D is -CH_2-(4-methoxy-phenyl), W is N, L_2 is -$NH(CH_2)_2$-, and Q is -$NHC(=NH)NH_2$;

a compound of Formula (I) wherein A_1 is 3,4-dichloro-phenyl, L_1 is -CH_2-, D is -CH_2-(4-methoxy-phenyl), W is N, L_2 is -$NH(CH_2)_2$-, and Q is -$ONHC(=NH)NH_2$;

a compound of Formula (I) wherein A_1 is 3,4-dichloro-phenyl, L_1 is $-CH_2-$, D is $-CH_2-$(4-methoxy-phenyl), W is N, L_2 is $-NH(CH_2)_2-$, and Q is $-NHC(=N-CN)NH_2$;

a compound of Formula (I) wherein A_1 is 3,4-dichloro-phenyl, L_1 is $-CH_2-$, D is $-CH_2-$(4-ethoxy-phenyl), W is N, L_2 is $-NH(CH_2)_2-$, and Q is $-NHC(=NH)NH_2$;

a compound of Formula (I) wherein A_1 is 4-chloro-phenyl, L_1 is $-CH_2-$, D is $-CH_2-$(4-methoxy-phenyl), W is N, L_2 is $-NH(CH_2)_2-$, and Q is $-NHC(=NH)NH_2$;

a compound of Formula (I) wherein A_1 is 4-methoxy-phenyl, L_1 is $-CH_2-$, D is $-CH_2-$(4-methoxy-phenyl), W is N, L_2 is $-NH(CH_2)_2-$, and Q is $-NHC(=NH)NH_2$;

a compound of Formula (I) wherein A_1 is 3,4-dichloro-phenyl, L_1 is $-CH_2-$, D is $-CH_2-$(4-methoxy-phenyl), W is N, L_2 is $-NH(CH_2)_4-$, and Q is $-NHC(=NH)NH_2$;

a compound of Formula (I) wherein A_1 is 4-fluoro-phenyl, L_1 is $-CH_2-$, D is $-(CH_2)_2-$(4-methoxy-phenyl), W is N, L_2 is $-NH(CH_2)_2-$, and Q is $-NHC(=NH)NH_2$;

a compound of Formula (I) wherein A_1 is 3,4-dichloro-phenyl, L_1 is $-CH_2-$, D is $-CH_2-$(4-n-propyl-phenyl), W is N, L_2 is $-NH(CH_2)_2-$, and Q is $-NHC(=NH)NH_2$;

a compound of Formula (I) wherein A_1 is 3,4-dichloro-phenyl, L_1 is $-CH_2-$, D is $-CH_2-$(4-*i*-propyl-phenyl), W is N, L_2 is $-NH(CH_2)_2-$, and Q is $-NHC(=NH)NH_2$;

a compound of Formula (I) wherein A_1 is 3,4-dichloro-phenyl, L_1 is $-CH_2-$, D is $-CH_2-$(4-cyclopentyloxy-phenyl), W is N, L_2 is $-NH(CH_2)_2-$, and Q is $-NHC(=NH)NH_2$;

a compound of Formula (I) wherein A_1 is 3,4-dichloro-phenyl, L_1 is $-CH_2-$, D is $-CH_2$-(4-methylthio-phenyl), W is N, L_2 is $-NH(CH_2)_2-$, and Q is $-NHC(=NH)NH_2$;

a compound of Formula (I) wherein A_1 is 3,4-dichloro-phenyl, L_1 is $-CH_2-$, D is $-CH_2$-(4-ethyl-phenyl), W is N, L_2 is $-NH(CH_2)_2-$, and Q is $-NHC(=NH)NH_2$;

a compound of Formula (I) wherein A_1 is 3-chloro-phenyl, L_1 is $-CH_2-$, D is $-CH_2$-(4-methoxy-phenyl), W is N, L_2 is $-NH(CH_2)_2-$, and Q is $-NHC(=NH)NH_2$;

a compound of Formula (I) wherein A_1 is 3,4-dichloro-phenyl, L_1 is $-CH_2-$, D is $-CH_2$-(4-trifluoromethoxy-phenyl), W is N, L_2 is $-NH(CH_2)_2-$, and Q is $-NHC(=NH)NH_2$;

a compound of Formula (I) wherein A_1 is 3,4-dichloro-phenyl, L_1 is $-CH_2-$, D is $-CH_2$-(4-difluoromethoxy-phenyl), W is N, L_2 is $-NH(CH_2)_2-$, and Q is $-NHC(=NH)NH_2$;

a compound of Formula (I) wherein A_1 is 3,4-dichloro-phenyl, L_1 is $-CH_2-$, D is $-CH_2$-(4-methoxy-phenyl), W is N, L_2 is cis-racemic-1,2-cyclohexyl, and Q is $-NHC(=NH)NH_2$;

a compound of Formula (I) whereinA_1 is 3,4-dichloro-phenyl, L_1 is $-CH_2-$, D is $-CH_2$-(4-methoxy-phenyl), W is N, L_2 is trans (1S, 2S)-cyclohexyl-, and Q is $-NHC(=NH)NH_2$;

a compound of Formula (I) wherein A_1 is 3,4-dichloro-phenyl, L_1 is $-CH_2-$, D is $-CH_2$-(4-methoxy-phenyl), W is N, L_2 is $-NH(CH_2)_2-$, and Q is $-NHC(=NH)NH_2$;

a compound of Formula (I) whereinA_1 is 4-methylthio-phenyl, L_1 is $-CH_2-$, D is $-CH_2$-(4-methoxy-phenyl), W is N, L_2 is $-NH(CH_2)_2-$, and Q is $-NHC(=NH)NH_2$;

a compound of Formula (I) wherein A_1 is 4-ethyl-phenyl, L_1 is $-CH_2-$, D is $-CH_2$-(4-methoxy-phenyl), W is N, L_2 is $-NH(CH_2)_2-$, and Q is $-NHC(=NH)NH_2$;

a compound of Formula (I) wherein A_1 is 3,4-dichloro-phenyl, L_1 is -CH_2-, D is -CH_2-(4-methoxy-phenyl), W is N, L_2 is trans(1R, 2R)-cyclohexyl-, and Q is -NHC(=NH)NH_2;

a compound of Formula (I) wherein A_1 is 3,4-dichloro-phenyl, L_1 is -CH_2-, D is -CH_2-(4-methoxy-phenyl), W is N, L_2 is -NH$(CH_2)_2$-, and Q is -NH(3,5-dihydro-imidazol-4-on-2-yl);

a compound of Formula (I) wherein A_1 is 3,4-dichloro-phenyl, L_1 is -CH_2-, D is -CH_2-(4-methoxy-phenyl), W is N, L_2 is -NH$(CH_2)_2$-, and Q is -NH(4,5-dihydro-1*H*-imidazol-2-yl);

a compound of Formula (I) wherein A_1 is 3,4-dichloro-phenyl, L_1 is -CH_2-, D is -CH_2-(4-methylcarbonylamino-phenyl), W is N, L_2 is -NH$(CH_2)_2$-, and Q is -NHC(=NH)NH_2;

a compound of Formula (I) wherein A_1 is 3,4-dichloro-phenyl, L_1 is -CH_2-, D is -CH_2-(4-aminocarbonyl-phenyl), W is N, L_2 is -NH$(CH_2)_2$-, and Q is -NHC(=NH)NH_2;

a compound of Formula (I) wherein A_1 is 3,4-dichloro-phenyl, L_1 is -CH_2-, D is -CH_2-(3-ethoxy-phenyl), W is N, L_2 is -NH$(CH_2)_2$-, and Q is -NHC(=NH)NH_2;

a compound of Formula (I) wherein A_1 is 3,4-dichloro-phenyl, L_1 is -CH_2-, D is -CH_2-(4-ethoxy-phenyl), W is N, L_2 is -NH$(CH_2)_2$-, and Q is -NHC(=NH)NH-ethyl;

a compound of Formula (I) wherein A_1 is 3,4-dichloro-phenyl, L_1 is -CH_2-, D is -CH_2-(4-methoxy-phenyl), W is N, L_2 is -NH$(CH_2)_2$-, and Q is -NHC(=NH)NH-propyl;

a compound of Formula (I) wherein A_1 is 3,4-dichloro-phenyl, L_1 is -CH_2-, D is -CH_2-(4-methoxy-phenyl), W is N, L_2 is pyrrolindin-1-yl, and Q is 3-NHC(=NH)NH_2;

a compound of Formula (I) wherein A_1 is 4-chloro-phenyl, L_1 is $-CH_2-$, D is $-CH_2$-(4-methoxy-phenyl), W is N, L_2 is trans (1R, 2R)-cyclohexyl-, and Q is $-NHC(=NH)NH_2$;

a compound of Formula (I) wherein A_1 is 3,4-dichloro-phenyl, L_1 is $-CH_2-$, D is $-CH_2$-(3-difluoromethoxy-phenyl), W is N, L_2 is $-NH(CH_2)_2-$, and Q is $-NHC(=NH)NH_2$;

a compound of Formula (I) wherein A_1 is 3,4-dichloro-phenyl, L_1 is $-CH_2-$, D is $-CH_2$-(4-methoxy-phenyl), W is N, L_2 is $-NH(CH_2)_2-$, and Q is -NHC(=NH)NH(*i*-propyl);

a compound of Formula (I) wherein A_1 is 3,4-dichloro-phenyl, L_1 is $-CH_2-$, D is $-CH_2$-(4-methoxy-phenyl), W is N, L_2 is $-NH(CH_2)_2-$, and Q is -N(ethyl)C(=NH)NH_2;

a compound of Formula (I) wherein A_1 is 3,4-dichloro-phenyl, L_1 is $-CH_2-$, D is $-CH_2$-(4-methoxy-phenyl), W is N, L_2 is $-NH(CH_2)_2-$, and Q is 2-imino-imidazolid-1-yl;

a compound of Formula (I) wherein a compound of Formula (I) wherein A_1 is 3,4-dichloro-phenyl, L_1 is $-CH_2-$, D is $-CH_2$-(4-methoxy-phenyl), W is N, L_2 is $-NH(CH_2)_2-$, and Q is -NHC(=NH)NH(n-butyl);

a compound of Formula (I) wherein A_1 is 3,4-dichloro-phenyl, L_1 is $-CH_2-$, D is $-CH_2$-(4-methoxy-phenyl), W is N, L_2 is $-NH(CH_2)_2-$, and Q is -NHC(=NH)NH(cyclohexyl);

a compound of Formula (I) wherein A_1 is 3,4-dichloro-phenyl, L_1 is $-CH_2-$, D is $-CH_2$-(4-methoxy-phenyl), W is N, L_2 is $-NH(CH_2)_2-$, and Q is -NHC(=NH)NH(benzyl);

a compound of Formula (I) wherein A_1 is 3,4-dichloro-phenyl, L_1 is $-CH_2-$, D is $-CH_2$-(4-methoxy-phenyl), W is N, L_2 is $-NH(CH_2)_2-$, and Q is -NHC(=NH)NH(tetrahydrofuran-2-ylmethyl);

a compound of Formula (I) wherein A_1 is 3,4-dichloro-phenyl, L_1 is $-CH_2-$, D is $-CH_2$-(4-methoxy-phenyl), W is N, L_2 is $-NH(CH_2)_2-$, and Q is -NHC(=NH)NH(phenylethyl);

a compound of Formula (I) wherein A_1 is 3,4-dichloro-phenyl, L_1 is $-CH_2-$, D is $-CH_2$-(4-methoxy-phenyl), W is N, L_2 is $-NH(CH_2)_2-$, and Q is -NHC(=NH)NH(furan-2-ylmethyl);

a compound of Formula (I) wherein A_1 is 3,4-dichloro-phenyl, L_1 is $-CH_2-$, D is $-CH_2$-(4-methoxy-phenyl), W is N, L_2 is $-NH(CH_2)_2-$, and Q is -NHC(=NH)NH(2-methoxy-ethyl);

a compound of Formula (I) wherein A_1 is 3,4-dichloro-phenyl, L_1 is $-CH_2-$, D is $-CH_2$-(4-methoxy-phenyl), W is N, L_2 is $-NH(CH_2)_3-$, and Q is $-NHC(=NH)NH_2$;

a compound of Formula (I) wherein A_1 is 3,4-dichloro-phenyl, L_1 is $-CH_2-$, D is $-(CH_2)_6$-H, W is N, L_2 is $-NH(CH_2)_3-$, and Q is $-NHC(=NH)NH_2$;

a compound of Formula (I) wherein A_1 is 3,4-dichloro-phenyl, L_1 is $-CH_2-$, D is $-CH_2$-(4-methoxy-phenyl), W is N, L_2 is $-NH(CH_2)_2-$, and Q is -NHC(=NH)NH(allyl);

a compound of Formula (I) wherein A_1 is 3,4-dichloro-phenyl, L_1 is $-CH_2-$, D is $-CH_2$-(4-methoxy-phenyl), W is N, L_2 is $-NH(CH_2)_2-$, and Q is -NHC(=NH)NH(phenyl);

a compound of Formula (I) wherein A_1 is 3,4-dichloro-phenyl, L_1 is $-CH_2-$, D is $-CH_2$-(4-methoxy-phenyl), W is N, L_2 is $-NH(CH_2)_2-$, and Q is -NHC(=NH)NH(4-methoxy-phenyl);

a compound of Formula (I) wherein A_1 is 3,4-dichloro-phenyl, L_1 is $-CH_2-$, D is $-CH_2$-(4-methoxy-phenyl), W is N, L_2 is $-NH(CH_2)_2-$, and Q is -NHC(=NH)NH(4-chloro-phenyl);

a compound of Formula (I) wherein A_1 is 3,4-dichloro-phenyl, L_1 is $-CH_2-$, D is $-CH_2$-(4-methoxy-phenyl), W is N, L_2 is $-NH(CH_2)_2-$, and Q is -NHC(=NH)NH(4-trifluoromethyl-phenyl);

a compound of Formula (I) wherein A_1 is 3,4-dichloro-phenyl, L_1 is $-CH_2-$, D is $-CH_2-$(4-methoxy-phenyl), W is N, L_2 is $-NH(CH_2)_2-$, and Q is -NHC(=NH)NH(pyridin-3-yl);

a compound of Formula (I) wherein A_1 is 3,4-dichloro-phenyl, L_1 is $-CH_2-$, D is $-CH_2-$(4-methoxy-phenyl), W is N, L_2 is $-NH(CH_2)_2-$, and Q is -NHC(=NH)NH(4-methylcarbonyl-phenyl);

a compound of Formula (I) wherein A_1 is furan-3-yl, L_1 is $-CH_2-$, D is $-CH_2-$(4-methoxy-phenyl), W is N, L_2 is $-NH(CH_2)_2-$, and Q is $-NHC(=NH)NH_2$;

a compound of Formula (I) wherein A_1 is thiophen-2-yl, L_1 is $-CH_2-$, D is $-CH_2-$(4-methoxy-phenyl), W is N, L_2 is $-NH(CH_2)_2-$, and Q is $-NHC(=NH)NH_2$;

a compound of Formula (I) wherein A_1 is 4-methoxy-phenyl, L_1 is R,S-mixture $-CH(CH_3)-$, D is $-CH_2-$(4-methoxy-phenyl), W is N, L_2 is $-NH(CH_2)_2-$, and Q is $-NHC(=NH)NH_2$;

a compound of Formula (I) wherein A_1 is 4-difluoromethoxy-phenyl, L_1 is $-CH_2-$, D is $-CH_2-$(4-methoxy-phenyl), W is N, L_2 is $-NH(CH_2)_2-$, and Q is -NHC(=NH)NH_2;

a compound of Formula (I) wherein A_1 is phenyl, L_1 is $-CH_2-$, D is $-CH_2-$(4-methoxy-phenyl), W is CH, L_2 is $-NH(CH_2)_2-$, and Q is $-NHC(=NH)NH_2$;

a compound of Formula (I) wherein A_1 is 4-methoxy-phenyl, L_1 is R,S-mixture -CH(allyl)-, D is $-CH_2-$(4-methoxy-phenyl), W is N, L_2 is $-NH(CH_2)_2-$, and Q is $-NHC(=NH)NH_2$;

a compound of Formula (I) wherein A_1 is 4-chloro-phenyl, L_1 is R,S-mixture -CH(allyl)-, D is $-CH_2-$(4-methoxy-phenyl), W is N, L_2 is $-NH(CH_2)_2-$, and Q is $-NHC(=NH)NH_2$;

a compound of Formula (I) wherein A_1 is 4-methoxy-phenyl, L_1 is $-CH_2-$, D is $-CH_2-$(4-methoxy-phenyl), W is CH, L_2 is $-NH(CH_2)_2-$, and Q is -NHC(=NH)NH_2;

a compound of Formula (I) wherein A_1 is 4-methoxy-phenyl, L_1 is -CH_2-, D is -CH_2-(6-methoxy-pyridin-3-yl), W is N, L_2 is -NH$(CH_2)_2$-, and Q is -NHC(=NH)NH_2;

a compound of Formula (I) wherein A_1 is 4-methoxy-phenyl, L_1 is -CH_2-, D is -CH_2-(4-methoxy-cyclohexyl), W is N, L_2 is -NH$(CH_2)_2$-, and Q is -NHC(=NH)NH_2;

a compound of Formula (I) wherein A_1 is 4-fluoro-phenyl, L_1 is -CH_2-, D is -CH_2-(4-nitro-phenyl), W is N, L_2 is -NH$(CH_2)_2$-, and Q is -NHC(=NH)NH_2;

a compound of Formula (I) wherein A_1 is 4-fluoro-phenyl, L_1 is -CH_2-, D is -CH_2-(4-methoxy-phenyl), W is N, L_2 is -NH$(CH_2)_2$-, and Q is -NHC(=NH)NH(2-(morpholin-4-yl)-eth-1-yl);

a compound of Formula (I) wherein A_1 is 4-fluoro-phenyl, L_1 is -CH_2-, D is -CH_2-(4-methoxy-phenyl), W is N, L_2 is -NH$(CH_2)_2$-, ;
and Q is -NHC(=NH)NH(3-(morpholin-4-yl)-prop-1-yl);

a compound of Formula (I) wherein A_1 is 4-fluoro-phenyl, L_1 is -CH_2-, D is -CH_2-(4-methoxy-phenyl), W is N, L_2 is -NH$(CH_2)_2$-, and Q is -NHC(=NH)NH(4-cyano-phenyl);

a compound of Formula (I) wherein A_1 is 4-fluoro-phenyl, L_1 is -CH_2-, D is -CH_2-(4-methoxy-phenyl), W is N, L_2 is -NH$(CH_2)_2$-, and Q is -NHC(=NH)NH(4-nitro-phenyl);

a compound of Formula (I) wherein A_1 is 4-fluoro-phenyl, L_1 is -CH_2-, D is -CH_2-(4-methoxy-phenyl), W is N, L_2 is -NH$(CH_2)_2$-,
and Q is -NHC(=NH)NH(1,3-benzodioxol-5-yl);

a compound of Formula (I) wherein A_1 is 4-fluoro-phenyl, L_1 is -CH_2-, D is -CH_2-(4-methoxy-phenyl), W is N, L_2 is -NH$(CH_2)_2$-, and Q is -NHC(=NH)$NHNH_2$;

a compound of Formula (I) wherein A_1 is 3-nitro-phenyl, L_1 is -CH_2-, D is -CH_2-(4-methoxy-phenyl), W is N, L_2 is -NH$(CH_2)_2$-, and Q is -NHC(=NH)NH_2;

a compound of Formula (I) wherein A_1 is 4-nitro-phenyl, L_1 is -CH_2-, D is -CH_2-(4-methoxy-phenyl), W is N, L_2 is -$NH(CH_2)_2$-, and Q is -$NHC(=NH)NH_2$;

a compound of Formula (I) wherein A_1 is 3-amino-phenyl, L_1 is -CH_2-, D is -CH_2-(4-methoxy-phenyl), W is N, L_2 is -$NH(CH_2)_2$-, and Q is -$NHC(=NH)NH_2$;

a compound of Formula (I) wherein A_1 is 4-cyano-phenyl, L_1 is -CH_2-, D is -CH_2-(4-methoxy-phenyl), W is N, L_2 is v-$NH(CH_2)_2$-, and Q is -$NHC(=NH)NH_2$;

a compound of Formula (I) wherein A_1 is 3-cyano-phenyl, L_1 is -CH_2-, D is -CH_2-(4-methoxy-phenyl), W is N, L_2 is -$NH(CH_2)_2$-, and Q is -$NHC(=NH)NH_2$;

a compound of Formula (I) wherein A_1 is 4-methoxycarbonyl-phenyl, L_1 is -CH_2-, D is -CH_2-(4-methoxy-phenyl), W is N, L_2 is -$NH(CH_2)_2$-, and Q is -$NHC(=NH)NH_2$;

a compound of Formula (I) wherein A_1 is 3-methoxycarbonyl-phenyl, L_1 is -CH_2-, D is -CH_2-(4-methoxy-phenyl), W is N, L_2 is -$NH(CH_2)_2$-, and Q is -$NHC(=NH)NH_2$;

a compound of Formula (I) wherein A_1 is 4-carboxy-phenyl, L_1 is -CH_2-, D is -CH_2-(4-methoxy-phenyl), W is N, L_2 is -$NH(CH_2)_2$-, and Q is -$NHC(=NH)NH_2$;

a compound of Formula (I) wherein A_1 is 3,4-dichloro-phenyl, L_1 is -CH_2-, D is -CH_2-(4-methoxy-phenyl), W is N, L_2 is -$NH(CH_2)C(Me)_2$-, and Q is -$NHC(=NH)NH_2$;

a compound of Formula (I) wherein A_1 is 4-fluoro-phenyl, L_1 is -CH_2-, D is -CH_2-(4-methoxy-phenyl), W is N, L_2 is -$NH(CH_2)_2$-, and Q is -$NHC(=NH)NH$(4-bromo-phenyl);

a compound of Formula (I) wherein A_1 is 4-fluoro-phenyl, L_1 is -CH_2-, D is -CH_2-(4-methoxy-phenyl), W is N, L_2 is -$NH(CH_2)_2$-, and Q is -$NHC(=NH)NH$(pyridin-2-yl);

a compound of Formula (I) wherein A_1 is 4-fluoro-phenyl, L_1 is $-CH_2-$, D is $-CH_2$-(4-methoxy-phenyl), W is N, L_2 is $-NH(CH_2)_2-$, and Q is -NHC(=NH)NH(pyridin-2-yl-ethyl);

a compound of Formula (I) wherein A_1 is 4-fluoro-phenyl, L_1 is $-CH_2-$, D is $-CH_2$-(4-methoxy-phenyl), W is N, L_2 is $-NH(CH_2)_2-$, and Q is -NHC(=NH)NH(4-ethoxycarbonyl-phenyl);

a compound of Formula (I) wherein A_1 is 4-fluoro-phenyl, L_1 is $-CH_2-$, D is $-CH_2$-(4-methoxy-phenyl), W is N, L_2 is $-NH(CH_2)_2-$, and Q is-NHC(=NH)NH(2,4-difluoro-phenyl);

a compound of Formula (I) wherein A_1 is 4-fluoro-phenyl, L_1 is $-CH_2-$, D is $-CH_2$-(4-methoxy-phenyl), W is N, L_2 is $-NH(CH_2)_2-$, and Q is -NHC(=NH)NH(*n*-decanyl);

a compound of Formula (I) wherein A_1 is 4-t-butoxy-phenyl, L_1 is $-CH_2-$, D is $-CH_2$-(4-methoxy-phenyl), W is N, L_2 is $-NH(CH_2)_2-$, and Q is -NHC(=NH)NH_2;

a compound of Formula (I) whereinA$_1$ is 4-hydroxy-phenyl, L_1 is $-CH_2-$, D is $-CH_2$-(4-methoxy-phenyl), W is N, L_2 is $-NH(CH_2)_2-$, and Q is -NHC(=NH)NH_2;

a compound of Formula (I) wherein A_1 is 2-chloro-thiazol-4-yl, L_1 is $-CH_2-$, D is $-CH_2$-(4-methoxy-phenyl), W is N, L_2 is $-NH(CH_2)_2-$, and Q is -NHC(=NH)NH_2;

a compound of Formula (I) wherein A_1 is benzofuran-2-yl, L_1 is $-CH_2-$, D is $-CH_2$-(4-methoxy-phenyl), W is N, L_2 is $-NH(CH_2)_2-$, and Q is -NHC(=NH)NH_2;

a compound of Formula (I) wherein A_1 is 3,4-dichloro-phenyl, L_1 is $-CH_2-$, D is $-CH_2$-(4-methoxy-phenyl), W is N, L_2 is $-NH(CH_2)_2-$, and Q is -N(Me)C(=NH)NH_2;

a compound of Formula (I) wherein A_1 is 4-fluoro-phenyl, L_1 is -CH_2-, D is -CH_2-(4-methoxy-phenyl), W is N, L_2 is -NH$(CH_2)_2$-, and Q is -NHC(=NH)NH(CH_2CF_3);

a compound of Formula (I) wherein A_1 is 4-fluoro-phenyl, L_1 is -CH_2-, D is -CH_2-(4-methoxy-phenyl), W is N, L_2 is -NH$(CH_2)_2$-, and Q is -NHC(=NH)NH(3-methoxypropyl);

a compound of Formula (I) wherein A_1 is 4-fluoro-phenyl, L_1 is -CH_2-, D is -CH_2-(4-methoxy-phenyl), W is N, L_2 is -NH$(CH_2)_2$-, and Q is -NHC(=NH)piperidin-1-yl;

a compound of Formula (I) wherein A_1 is 4-fluoro-phenyl, L_1 is -CH_2-, D is -CH_2-(4-methoxy-phenyl), W is N, L_2 is -NH$(CH_2)_2$-, and Q is -NHC(=NH)N(Me)phenyl;

a compound of Formula (I) wherein A_1 is 4-fluoro-phenyl, L_1 is -CH_2-, D is -CH_2-(4-methoxy-phenyl), W is N, L_2 is -NH$(CH_2)_2$-, and Q is -NHC(=NH)NH(2-fluoro-phenyl);

a compound of Formula (I) wherein A_1 is 4-fluoro-phenyl, L_1 is -CH_2-, D is -CH_2-(4-methoxy-phenyl), W is N, L_2 is -NH$(CH_2)_2$-, and Q is -NHC(=NH)NH(4-fluoro-phenyl);

a compound of Formula (I) wherein A_1 is 4-fluoro-phenyl, L_1 is -CH_2-, D is -CH_2-(4-methoxy-phenyl), W is N, L_2 is -NH$(CH_2)_2$-, and Q is -NHC(=NH)NH(4-methyl-phenyl);

a compound of Formula (I) wherein A_1 is 4-fluoro-phenyl, L_1 is -CH_2-, D is -CH_2-(4-methoxy-phenyl), W is N, L_2 is -NH$(CH_2)_2$-, and Q is -NHC(=NH)NH(t-butyl);

a compound of Formula (I) wherein A_1 is 4-chloro-phenyl, L_1 is -CH_2-, D is -CH_2-(4-amino-phenyl), W is N, L_2 is -NH$(CH_2)_2$-, and Q is -NHC(=NH)NH_2;

a compound of Formula (I) wherein A_1 is t-butyl, L_1 is -CH_2-, D is -CH_2-(4-methoxy-phenyl), W is N, L_2 is -NH$(CH_2)_2$-, and Q is -NHC(=NH)NH_2;

a compound of Formula (I) wherein A_1 is cyclopentyl, L_1 is $-CH_2-$, D is $-CH_2-$(4-methoxy-phenyl), W is N, L_2 is $-NH(CH_2)_2-$, and Q is $-NHC(=NH)NH_2$;

a compound of Formula (I) wherein A_1 is A_1 is 4-amino-phenyl, L_1 is $-CH_2-$, D is $-CH_2-$(4-methoxy-phenyl), W is N, L_2 is $-NH(CH_2)_2-$, and Q is $-NHC(=NH)NH_2$;

a compound of Formula (I) wherein A_1 is 4-fluoro-phenyl, L_1 is $-CH_2-$, D is $-CH_2-$(4-methoxy-phenyl), W is N, L_2 is $-NH(CH_2)_2-$, and Q is -NHC(=NH)NH(adamantan-2-yl);

a compound of Formula (I) wherein A_1 is 4-fluoro-phenyl, L_1 is $-CH_2-$, D is $-CH_2-$(4-methoxy-phenyl), W is N, L_2 is $-NH(CH_2)_2-$, and Q is -NHC(=NH)NH(4-trifluoromethoxy-phenyl);

a compound of Formula (I) wherein A_1 is 4-fluoro-phenyl, L_1 is $-CH_2-$, D is $-CH_2-$(4-methoxy-phenyl), W is N, L_2 is $-NH(CH_2)_2-$, and Q is -NHC(=NH)NH(4-hydroxy-phenyl);

a compound of Formula (I) wherein A_1 is 4-chloro-phenyl, L_1 is $-CH_2-$, D is $-CH_2-$phenyl, W is N, L_2 is $-NH(CH_2)_2-$, and Q is $-NHC(=NH)NH_2$;

a compound of Formula (I) wherein A_1 is 4-chloro-phenyl, L_1 is $-CH_2-$, D is $-CH_2-$furan-3-yl, W is N, L_2 is $-NH(CH_2)_2-$, and Q is $-NHC(=NH)NH_2$;

a compound of Formula (I) wherein A_1 is 4-fluoro-phenyl, L_1 is $-CH_2-$, D is $-CH_2-$(4-methoxy-phenyl), W is N, L_2 is 1,4-cyclohexyl, and Q is $-NHC(=NH)NH_2$;

a compound of Formula (I) wherein A_1 is 4-fluoro-phenyl, L_1 is $-CH_2-$, D is $-CH_2-$(4-methoxy-phenyl), W is N, L_2 is $-NHCH_2C(=O)-$, and Q is $-NHC(=NC(=O)O$-t-butyl$)NH_2$;

a compound of Formula (I) wherein A_1 is 4-fluoro-phenyl, L_1 is $-CH_2-$, D is $-CH_2-$(4-methoxy-phenyl), W is N, L_2 is $-NH(CH_2)_2-$, and Q is -NHC(=NH)NH(2-methylthio-phenyl);

a compound of Formula (I) wherein A_1 is 4-fluoro-phenyl, L_1 is -CH_2-, D is -CH_2-(4-methoxy-phenyl), W is N, L_2 is -NH$(CH_2)_2$-, and Q is -NHC(=NH)NH(C(=O)phenyl);

a compound of Formula (I) wherein A_1 is 4-fluoro-phenyl, L_1 is -CH_2-, D is -CH_2-(4-methoxy-phenyl), W is N, L_2 is -NH$(CH_2)_2$-, and Q is -NHC(=NH)NH(pyrimidin-2-yl);

a compound of Formula (I) wherein A_1 is 4-fluoro-phenyl, L_1 is -CH_2-, D is -CH_2-(4-methoxy-phenyl), W is N, L_2 is -NH((*S*)-CHMe)$_2$-, and Q is -NHC(=NH)NH_2;

a compound of Formula (I) wherein A_1 is 4-fluoro-phenyl, L_1 is -CH_2-, D is -CH_2-(4-methoxy-phenyl), W is N, L_2 is -NH((*R*)-CHMe)$_2$-, and Q is -NHC(=NH)NH_2;

a compound of Formula (I) wherein A_1 is 4-fluoro-phenyl, L_1 is -CH_2-, D is -CH_2-(4-methoxy-phenyl), W is N, L_2 is -NH$(CH_2)_2$-, and Q is -NH(=NH)NH(4-trifluoromethyl-5,6,7,8-tetrahydro-quinazolin-2-yl);

a compound of Formula (I) wherein A_1 is 4-fluoro-phenyl, L_1 is -CH_2-, D is -CH_2-(4-methoxy-phenyl), W is N, L_2 is -NH$(CH_2)_2$-, and Q is -NHC(=NH)NH(5-methyl-pyridin-2-yl);

a compound of Formula (I) wherein A_1 is 4-fluoro-phenyl, L_1 is -CH_2-, D is -CH_2-(4-methoxy-phenyl), W is N, L_2 is -NH$(CH_2)_2$-, and Q is -NHC(=NH)morpholin-4-yl;

a compound of Formula (I) wherein A_1 is 4-chloro-phenyl, L_1 is -CH_2-, D is -CH_2-furan-2-yl, W is N, L_2 is -NH$(CH_2)_2$-, and and Q is -NHC(=NH)NH_2;

a compound of Formula (I) wherein A_1 is 4-chloro-phenyl, L_1 is -CH_2-, D is -CH_2-(4-methoxy-phenyl), W is N, L_2 is -NH$(CH_2)_5$-, and and Q is -NHC(=NH)NH_2;

a compound of Formula (I) wherein A_1 is 4-methoxy-phenyl, L_1 is -CH_2-, D is -CH_2-(4-hydroxy-phenyl), W is N, L_2 is -NH$(CH_2)_2$-, and and Q is -NHC(=NH)NH_2;

a compound of Formula (I) wherein A_1 is 4-chloro-phenyl, L_1 is $-CH_2-$, D is $-CH_2$-(4-methoxy-phenyl), W is N, L_2 is $-NH(CH_2)_6-$, and Q is $-NHC(=NH)NH_2$;

a compound of Formula (I) wherein A_1 is 4-methoxy-phenyl, L_1 is $-(CH_2)_2-$, D is $-CH_2$-(4-methoxy-phenyl), W is N, L_2 is $-NH(CH_2)_2-$, and Q is $-NHC(=NH)NH_2$;

a compound of Formula (I) wherein A_1 is 4-methoxy-phenyl, L_1 is $-(CH_2)_3-$, D is $-CH_2$-(4-methoxy-phenyl), W is N, L_2 is $-NH(CH_2)_2-$, and Q is $-NHC(=NH)NH_2$;

a compound of Formula (I) wherein A_1 is 3,4-dichloro-phenyl, L_1 is $-CH_2-$, D is $-CH_2$-(4-methoxycarbonyl-phenyl), W is N, L_2 is $-NH(CH_2)_2-$, and Q is $-NHC(=NH)NH_2$;

a compound of Formula (I) wherein A_1 is phenyl, L_1 is $-CH_2-$, D is $-CH_2$-(4-*n*-butyloxy-phenyl), W is N, L_2 is $-NH(CH_2)_2-$, and Q is $-NHC(=NH)NH_2$;

a compound of Formula (I) wherein A_1 is 4-chloro-phenyl, L_1 is $-CH_2-$, D is $-CH_2$-phenyl, W is N, L_2 is $-NH(CH_2)_2-$, and Q is $-NHC(=NH)NH_2$;

a compound of Formula (I) wherein A_1 is 4-chloro-phenyl, L_1 is $-CH_2-$, D is $-CH_2$-furan-3-yl, W is N, L_2 is $-NH(CH_2)_2-$, and Q is $-NHC(=NH)NH_2$;

a compound of Formula (I) wherein A_1 is 4-fluoro-phenyl, L_1 is $-CH_2-$, D is $-CH_2$-(4-methoxy-phenyl), W is N, L_2 is $-NH(CH_2)_2-$, and Q is $-NHC(=NH)NHC(=O)$methyl;

a compound of Formula (I) wherein A_1 is 4-fluoro-phenyl, L_1 is $-CH_2-$, D is $-CH_2$-(4-methoxy-phenyl), W is N, L_2 is $-NH(CH_2)_2-$, and Q is $-NHC(=NH)NH$(allyl);

a compound of Formula (I) wherein A_1 is 4-fluoro-phenyl, L_1 is $-CH_2-$, D is $-CH_2$-(4-methoxy-phenyl), W is N, L_2 is $-NH(CH_2)_2-$, and Q is $-NHC(=NH)NH$(*i*-propyl);

a compound of Formula (I) wherein A_1 is 4-fluoro-phenyl, L_1 is $-CH_2-$, D is $-CH_2$-(4-methoxy-phenyl), W is N, L_2 is $-NH(CH_2)_2-$, and Q is

-NHC(=NH)NH(*n*-propyl);

a compound of Formula (I) wherein A_1 is 4-fluoro-phenyl, L_1 is -CH_2-, D is -CH_2-(4-methoxy-phenyl), W is N, L_2 is -$NH(CH_2)_2$-, and Q is -NHC(=NH)NH(ethyl);

a compound of Formula (I) wherein A_1 is 4-fluoro-phenyl, L_1 is -CH_2-, D is -CH_2-(4-methoxy-phenyl), W is N, L_2 is -$NH(CH_2)_2$-, and Q is -NHC(=NH)NH(methyl);

a compound of Formula (I) wherein A_1 is 4-methoxy-phenyl, L_1 is -CH_2-, D is -CH_2-(4-methoxy-phenyl), W is CH, L_2 is -$C(=O)NH(CH_2)_2$-, and Q is -$NHC(=NH)NH_2$;

a compound of Formula (I) wherein A_1 is 4-methoxy-phenyl, L_1 is -CH_2-, D is -CH_2-(4-methoxy-phenyl), W is CH, L_2 is -$O(CH_2)_2$-, and Q is -$NHC(=NH)NH_2$;

a compound of Formula (I) wherein A_1 is 4-methoxy-phenyl, L_1 is -CH_2-, D is -CH_2-(4-methoxy-phenyl), W is CH, L_2 is -$S(CH_2)_2$-, and Q is -$NHC(=NH)NH_2$; and

a compound of Formula (I) wherein A_1 is 4-methoxy-phenyl, L_1 is -CH_2-, D is -CH_2-(4-methoxy-phenyl), W is CH, L_2 is -$(CH_2)_3$-, and Q is -$NHC(=NH)NH_2$.

42. A pharmaceutical composition comprising a compound, salt or solvate according to any of claims 1 admixed with a pharmaceutically acceptable carrier, excipient or diluent.

43. A veterinary composition comprising a compound, salt or solvate according to claim 1 admixed with a veterinarily acceptable carrier, excipient or diluent.

44. A method of treating or preventing a disease or condition in a mammal in which the disease or condition is affected by the antagonism of prokineticin 2

receptor, which method comprises administering to a mammal in need thereof a therapeutically effective amount of a non-peptidic antagonist of Prokineticin 2 or Prokineticin 2 receptor.

45. A method of treating or preventing a disease or condition in a mammal in which the disease or condition is affected by the antagonism of prokineticin 2 receptors, which method comprises administering to a mammal in need thereof a therapeutically effective amount of a compound, salt or solvate of claim 1.

46. The method of claim 45 wherein the condition is selected from the group consisting of gastrointestinal (GI) diseases, GERD and secretory diarrhea, cancers of the GI tract and reproductive organs, and pain.

47. The method of claim 45 wherein the condition is caused by a disease selected from the group consisting of irritable bowel syndrome (IBS, including diarrhea-predominant, as well as alternating diarrhea/constipation forms of IBS), inflammatory bowel disease (IBD, including ulcerative colitis, and Crohn's disease), secretory bowel disorders induced by pathogens, testicular cancer, ovarian cancer, Leydig cell carcinoma, and cancers of the small or large bowel, polycystic ovary syndrome, and visceral hyperalgesia.

48. The method of claim 45 wherein said therapeutically effective amount comprises a dose range of from about 0.1 mg to about 1,000 mg.

49. The method of claim 45 wherein said therapeutically effective amount comprises a dose range of from about 50 mg to about 1000 mg.

50. The method of claim 45 wherein said therapeutically effective amount comprises a dose range of from about 100 mg to about 1000 mg.