Title: PYRIMIDINDIONE DERIVATIVES AS PROKINETICIN 2 RECEPTOR ANTAGONISTS

Abstract: The present invention relates to certain novel compounds of Formula (I), which are suitable for the treatment of prokineticin 2 or prokinin 2 receptor mediated disorders.
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 Kalthenthaler, 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.

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.


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.; Hiroto, 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 ISD. 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):

\[
\begin{array}{c}
\text{O} \\
\text{A}_1 \\
\text{L}_1 \\
\text{N} \\
\text{W} \\
\text{O} \\
\text{D} \\
\text{L}_2 \\
\text{Q}
\end{array}
\]

Formula (I)

wherein:

A₁ is hydrogen; aryl; heteroaryl; C₅₋₈ cycloalkyl; or heterocycl; provided that A₁ is other than piperidin-4-yl, N-t-butoxycarbonyl-piperidin-4-yl, or N-methyl-piperidin-3-yl; and wherein substituents of A₁ other than hydrogen are optionally
substituted with one to three substituents independently selected from the group consisting of C₃₋₆ alkyl, hydroxy(C₁₋₆) alkyl, C₁₋₆ alkoxy, halogen, nitro, halogenated C₁₋₆ alkyl, halogenated C₁₋₆ alkoxy, C₁₋₆ alkythio, C₁₋₆ alkoxy carbonyl, amino, C₁₋₆ alkylation, di(C₁₋₆ alkyl) amino, cyano, hydroxy, aminocarbonyl, C₁₋₆ aminocarbonyl, di(C₁₋₆ alkyl)aminocarbonyl, C₁₋₆ alkylicarbonyl, C₁₋₆ alkylicarbonyl, formyl, C₁₋₆ alkyl sulfanyl, C₁₋₆ alkyl sulfonamino, amino sulfonamino, C₁₋₆ alkylaminosulfonamino, and di(C₁₋₆ alkyl)aminosulfonamino;

L₁ is −CH₂− or −CH₂CH₂X(CH₂)₆−, optionally substituted with one to three substituents independently selected from the group consisting of C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, and halogen; provided that when A₁ 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;

D is −P−A₂; wherein when A₂ is hydrogen, P is −(CH₂)₄−, and when A₂ is other than hydrogen, P is −(CH₂)₁₋₂− or −CH₂CH=CH−;

A₂ is hydrogen; benzodioxalyl; heteroaryl other than unsubstituted pyridin-2-yl; C₃₋₆ cycloalkyl; or phenyl optionally substituted at the meta and para positions with one to three substituents independently selected from the group consisting of C₁₋₆ alkyl, C₁₋₆ alkoxy, halogen, halogenated C₁₋₆ alkyl, halogenated C₁₋₆ alkoxy, aryl(C₁₋₆) alkoxy, phenyl, C₁₋₆ alkythio, C₁₋₆ alkoxy carbonyl, amino, C₁₋₆ alkylation, di(C₁₋₆ alkyl) amino, cyano, hydroxy, nitro, C₁₋₆ alkylicarbonyl, C₁₋₆ alkylicarbonyl, aminocarbonyl, C₁₋₆ alkylationaminocarbonyl, di(C₁₋₆ alkyl)aminocarbonyl, C₁₋₆ alkylicarbonyl amino, and a non fused C₃₋₆ cycloalkoxy; wherein benzodioxalyl, heteroaryl, and C₃₋₆ cycloalkyl are optionally substituted with one to three substituents independently selected from the group consisting of C₁₋₆ alkyl, C₁₋₆ alkoxy, halogen, halogenated C₁₋₆ alkyl, halogenated C₁₋₆ alkoxy, aryl(C₁₋₆) alkoxy, phenyl, C₁₋₆ alkythio, C₁₋₆ alkoxy carbonyl, amino, C₁₋₆ alkylation, and di(C₁₋₆ alkyl)aminosulfonamino.
alkyl)amino, cyano, hydroxy, nitro, C₆-alkylcarbonyl, C₁₋₆-alkythiocarbonyl, aminocarbonyl, C₁₋₆-alkylaminocarbonyl, di(C₁₋₆-alkyl)aminocarbonyl, C₁₋₆-alkylcarbonylamino, and a non fused C₃₋₆-cycloalkylxoy; provided that no more than two substituents on A₂ are aryl(C₁₋₆)alkoxy, phenyl, or a non fused C₃₋₆-cycloalkylxoy; provided that when A₁ is unsubstituted phenyl and L₂ is \(-X₁-CH(R^1)-(CR^1R^2)\) - wherein \(X₁\) is NH, and \(R^x, R^y,\) and \(R^z\) are each hydrogen, A₂ is other than unsubstituted phenyl; phenyl substituted with aryl(C₁₋₆)alkoxy or phenyl; or phenyl substituted at the meta position with cyano; and, further provided that when A₁ is unsubstituted phenyl and L₂ is \(-X₁-CH(R^1)-(CR^1R^2)\)_₂ - wherein \(X₁\) is NH and \(R^x, R^y,\) and \(R^z\) are each hydrogen, A₂ is other than phenyl substituted with methoxy; and, provided that when A₁ is 3,4-dichloro-phenyl and P is \(-CH₂⁻\), A₂ is other than phenyl substituted at the meta position with trifluoromethyl or trifluoromethoxy; and, further provided that when A₁ is 3,4-dichloro-phenyl and P is \(-(CH₂)₂⁻\), A₂ is other than 4-methoxy-phenyl; W is N or C(R₆); wherein R₆ is H or C₁₋₆-alkyl; L₂ 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 \(-(CH₂)₀⁻\); \(-NH-C₅₋₇-cycloalkyl-(CH₂)₀⁻\); such that when C₅₋₇-cycloalkyl is cyclohexyl, Q is attached at either the 2- or cis-4-position relative to the position of \(-NH⁻\); \(-X₁-(CH₂)ₓ⁻X₂-(CH₂)ᵧ⁻\); wherein \(x\) is an integer of 1 to 3; and wherein \(y\) is an integer of 1 to 4; provided that when \(X₁\) is a direct bond and W is C(R₆), then \(x\) is 1 and \(y\) is 2 to 4; \(-X₂-(CH₂)₀⁻\); \(-X₁-(CH₂)₂⁻X₃-(CH₂)₂⁻\).
-NH(CH₂)₁₋₄ C(=O)-, provided that at least one of R⁺, R⁻, or R⁰ is other than hydrogen and m is 0;
-NHC(=O)-(CH₂)₁₋₄ -;
-C(=O)NH(CR'R₂)₂₋₅ -;

and

-X₁-CH(R³)-(CR'R²)₁₋₅ -; such that when X₁ is a direct bond and W is C(R_w), then R³ is hydrogen;

wherein X₁ is –NH₂, O, S, or a direct bond, such that X₁ is other than O when W is N;

X₂ is –CH=CH₂;

X₃ is O, S, NH, or C=O;

R⁺, R⁻, and R⁰ are independently H or C₁₋₄alkyl;

and provided that L₂ in any instance does not exceed 7 atoms in length;

and further provided that when L₂ is -X₂-(CH₂)₀₋₄ - or -C(=O)NH(CR'R²)₂₋₅ -, then R_w is hydrogen;

Q is -(O)ᵣ₋₅N(Rᵣ)-G; and m is 0 or 1;

G is –C(=NRᵣNRᵣ)NRᵣRᵣ;

Rᵣ and R⁰ are independently hydrogen, C₁₋₄alkyl, C₂₋₆alkenyl, or C₃₋₆alkynyl, wherein substituents of Rᵣ and R⁰ other than hydrogen are optionally substituted with one to three substituents independently selected from the group consisting of hydroxy, C₁₋₄alkoxy, fluoro, amino, C₁₋₄alkylamino, dC₁₋₄alkylamino, and C₁₋₄alkylcarbonyl; or Rᵣ and R⁰ are taken together with the atoms to which they are attached to form a 5-8 membered monocyclic ring optionally substituted with oxo;

R⁻ is hydrogen, C₁₋₄alkyl, C₂₋₆alkenyl, C₃₋₆alkynyl, C₂₋₆alkoxycarbonyl, or cyano; or, R⁺ and R⁻ are taken together with the atoms to which they are attached to form a 5-8 membered monocyclic ring optionally substituted with oxo;

R⁺ is hydrogen, C₁₋₁₀alkyl, C₂₋₁₀alkenyl, C₃₋₁₀alkynyl, C₃₋₇cycloalkyl, adamantyl, amino, C₁₋₄alkylamino, d(C₁₋₄alkyl)amino, C₁₋₄alkylcarbonyl, C₁₋₄alkoxycarbonyl, 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}alkylsulfonlamino, 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)_{2}amino- 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, monocyclic 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 "heterocycyl" 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 heterocycyl includes a heterocycyl ring fused to a benzene ring (benzo fused heterocycyl), 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 heterocycyl 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 heterocycyl ring to form a spiro moiety. For instant compounds of the invention, the carbon atom ring members that form the heterocycyl ring are fully saturated. Other compounds of the invention may have a partially saturated heterocycyl ring. Additionally, heterocycyl includes a heterocyclic ring bridged to form
bicyclic rings. Preferred partially saturated heterocyclcyl 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 heterocyclcyl groups include, and are not limited to, pyrrolinyl (including 2H-pyrrole, 2-pyrrolinyl or 3-pyrrolinyl), pyrroldinyl, 2-imidazoliny, imidazolidinyl, 2-pyrazolinyl, pyrazolidinyl, piperidinyl, morpholiny, 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, thiophenyl, 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, benzoazolyl, 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 $\text{O=}$ 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., $\text{C}_1$-$\text{C}_6$) 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 $\text{C}_1$-$\text{C}_6$ alkyl would include methyl, ethyl, propyl, butyl, penty1 and hexyl individually as well as sub-combinations thereof (e.g. $\text{C}_1$-$\text{C}_2$, $\text{C}_1$-$\text{C}_3$, $\text{C}_1$-$\text{C}_4$, $\text{C}_1$-$\text{C}_5$, $\text{C}_2$-$\text{C}_6$, $\text{C}_3$-$\text{C}_6$, $\text{C}_4$-$\text{C}_6$, $\text{C}_5$-$\text{C}_6$, $\text{C}_2$-$\text{C}_6$, 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\textsubscript{1-6}alkylaminocarbonylC\textsubscript{1-6}alkyl" substituent refers to a group of the formula

![Chemical Structure](image)

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

![Chemical Structure](image)
Formulá (I)

wherein:

A₁ is hydrogen; aryl; heteroaryl; C₅-₈cycloalkyl; or heterocycl; provided that A₁ is
other than piperidin-4-yl, N,N-t-butoxycarbonyl-piperidin-4-yl, or N-methyl-piperidin-
3-yl; and wherein substituents of A₁ other than hydrogen are optionally
substituted with one to three substituents independently selected from the group
consisting of C₁-₆alkyl, hydroxy(C₁-₆alkyl, C₁-₆alkoxy, halogen, nitro, halogenated
C₁-₆alkyl, halogenated C₁-₆alkoxy, C₁-₆alkylthio, C₁-₆alkoxycarbonyl, amino, C₁-
₆alkylamino, di(C₁-₆alkyl)amino, cyano, hydroxy, aminocarbonyl, C₁-
₆alkylaminocarbonyl, di(C₁-₆alkyl)aminocarbonyl, C₁-₆alkoxycarbonylamino, C₁-
₆alkylcarbonyl, C₁-₆alkylthiocarbonyl, formyl, C₁-₆alkylsulfonyl, C₁-
₆alkylsulfonlamino, aminosulfonyl, C₁-₆alkylaminosulfonyl, and di(C₁-
₆alkyl)aminosulfonyl;

L₁ is (CH₂)_r or (CH₂)ᵦ(CH₂)ᵦ, optionally substituted with one to three
substituents independently selected from the group consisting of C₁-₆alkyl, C₂-
₆alkenyl, C₂-₆alkynyl, and halogen; provided that when A₁ 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–A₂; wherein when A₂ is hydrogen, P is –(CH₂)₄₋₅₋, and when A₂ is other than
hydrogen, P is –(CH₂)₁₋₂₋ or –CH₂CH=CH–;

A₂ is hydrogen; benzodioxalyl; heteroaryl other than unsubstituted pyridin-2-yl; C₃-
₆cycloalkyl; or phenyl optionally substituted at the meta and para positions with
one to three substituents independently selected from the group consisting of C₁-
₆alkyl, C₁-₆alkoxy, halogen, halogenated C₁-₆alkyl, halogenated C₁-₆alkoxy,
aryl(C₁-₆)alkoxy, phenyl, C₁-₆alkylthio, C₁-₆alkoxycarbonyl, amino, C₁-₆alkylamino,
di(C₁-₆alkyl)amino, cyano, hydroxy, nitro, C₁-₆alkylcarbonyl, C₁-₆alkylthiocarbonyl,
aminocarbonyl, C₁-₆alkylaminocarbonyl, di(C₁-₆alkyl)aminocarbonyl, C₁-

alkylcarbonylamino, and a non fused C₃-₆cycloalkyloxy; wherein benzodioxalyl, heteroaryl, and C₃-₆cycloalkyl are optionally substituted with one to three substituents independently selected from the group consisting of C₁-₆alkyl, C₁-₆alkoxy, halogen, halogenated C₁-₆alkyl, halogenated C₁-₆alkoxy, aryl(C₁-₆)alkoxy, phenyl, C₁-₆alkythio, C₁-₆alkoxycarbonyl, amino, C₁-₆alkylamino, di(C₁-₆alkyl)amino, cyano, hydroxy, nitro, C₁-₆alkylcarbonyl, C₁-₆alkylthiocarbonyl, aminocarbonyl, C₁-₆alkylaminocarbonyl, di(C₁-₆alkyl)aminocarbonyl, C₁-₆alkylcarbonylamino, and a non fused C₃-₆cycloalkyloxy; provided that no more than two substituents on A₂ are aryl(C₁-₆)alkoxy, phenyl, or a non fused C₃-₆cycloalkyloxy;

provided that when A₁ is unsubstituted phenyl and L₂ is -X₁CH(R¹)-(CR⁴R³)- wherein X₁ is NH, and R¹, R⁴, and R³ are each hydrogen, A₂ is other than unsubstituted phenyl; phenyl substituted with aryl(C₁-₆)alkoxy or phenyl; or phenyl substituted at the meta position with cyano;

and, further provided that when A₁ is unsubstituted phenyl and L₂ is -X₁CH(R⁷)-(CR⁴R³)₂- wherein X₁ is NH and R⁷, R⁴, and R³ are each hydrogen, A₂ is other than phenyl substituted with methoxy;

and, provided that when A₁ is 3,4-dichloro-phenyl and P is -(CH₂)₁₋₂, A₂ is other than phenyl substituted at the meta position with trifluoromethyl or trifluoromethoxy;

and, further provided that when A₁ is 3,4-dichloro-phenyl and P is -(CH₂)₁₋₂, A₂ is other than 4-methoxy-phenyl;

W is N or C(R₆); wherein R₆ is H or C₁-₂alkyl;

L₂ 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 -(CH₂)₀₋₂ -;

-NH-C₅₋₇cycloalkyl-(CH₂)₀₋₂ -, such that when C₅₋₇cycloalkyl is cyclohexyl, Q is attached at either the 2- or cis-4-position relative to the position of -NH-;
\[-X_1-(\text{CH}_2)_u-\text{X}_2-(\text{CH}_2)_v-;\] 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;

\[-X_2-(\text{CH}_2)_{0.4}-;\]
\[-X_1-(\text{CH}_2)_{0.2-3}-X_3-(\text{CH}_2)_{2.3}-;\]
\[-\text{NH}(\text{CH}_2)_{1.4} \text{C}(=\text{O})-\], provided that at least one of \(R^b\), \(R^c\), or \(R^d\) is other than hydrogen and \(m\) is 0;

\[-\text{NHC}(=\text{O})-(\text{CH}_2)_{1.4}-;\]
\[-\text{C}(=\text{O})\text{NH}(\text{CR}^b\text{R}^c)_{2.5}-;\]

and

\[-X_1-\text{CH}(\text{R}^a)-(\text{CR}^b\text{R}^c)_{1.5}-;\] such that when \(X_1\) is a direct bond and \(W\) is \(C(R_w)\), then \(R^a\) is hydrogen;

wherein \(X_1\) is \(-\text{NH}-, \text{O}, \text{S},\) or a direct bond, such that \(X_1\) is other than \(\text{O}\) when \(W\) is \(\text{N}\);

\(X_2\) is \(-\text{CH}=\text{CH}-;\)

\(X_3\) is \(\text{O}, \text{S}, \text{NH},\) or \(\text{C}=\text{O};\)

\(R^a, R^b,\) and \(R^c\) are independently \(\text{H}\) or \(\text{C}_1\text{H}_4\text{alkyl};\)

and provided that \(L_2\) in any instance does not exceed 7 atoms in length; and further provided that when \(L_2\) is \(-X_2-(\text{CH}_2)_{0.4}-\) or \(-\text{C}(=\text{O})\text{NH}(\text{CR}^b\text{R}^c)_{2.5}-\), then \(R_w\) of \(W\) is hydrogen;

\(Q\) is \(-\text{(O)}_m\text{N}(\text{R}^a)-\text{G};\) and \(m\) is 0 or 1;

\(G\) is \(-\text{C}(=\text{NR}^a)\text{NR}^a\text{R}^d;\)

\(R^a\) and \(R^d\) are independently hydrogen, \(\text{C}_1\text{H}_4\text{alkyl}, \text{C}_2\text{H}_5\text{alkenyl},\) or \(\text{C}_3\text{H}_6\text{alkynyl},\) 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, \(\text{C}_1\text{H}_4\text{alkoxy}, \text{fluoro, amino, C}_1\text{H}_4\text{alkylamino, diC}_1\text{H}_4\text{alkylamino, and C}_1\text{H}_4\text{alkylcarbonyl};\) 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}alkoxy carbonyl, 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, C_{1-6}alkylamino, di(C_{1-6}alkyl)amino, C_{1-6}alkyl carbonyl, C_{1-6}alkoxy carbonyl, arylcarbonyl, heteroaryl carbonyl, heterocyclyl carbonyl, aroyl, 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, aroyl, 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}alkyl carbonyl, C_{1-6}alkoxy carbonyl, aminocarbonyl, C_{1-6}alkylaminocarbonyl, di(C_{1-6}alkyl)aminocarbonyl, C_{1-6}alkoxy carbonylamino, formyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonlamino, 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 A₁ is phenyl, L is -CH₂-, D is -CH₂-(4-methoxy-phenyl), W is N, L₂ is -NH(CH₂)₂-, and Q is -NHC(=NH)NH₂.

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$_5$-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$_1$-alkyl, hydroxy(C$_1$-alkyl), C$_1$-alkoxy, halogen, nitro, halogenated C$_1$-alkyl, halogenated C$_1$-alkoxy, C$_1$-alkylthio, C$_1$-alkoxycarbonyl, amino, C$_1$-alkylamino, di(C$_1$-alkyl)amino, cyano, hydroxy, aminocarbonyl, C$_1$-alkylaminocarbonyl, di(C$_1$-alkyl)aminocarbonyl, C$_1$-alkoxycarbonylamino, C$_1$-alkylcarbonyl, C$_1$-alkylthiocarbonyl, formyl, C$_1$-alkylsulfonyl, C$_1$-alkylsulfonylamino, aminosulfonyl, C$_1$-alkylaminosulfonyl, and di(C$_1$-alkyl)aminosulfonyl;

b) $A_1$ is hydrogen; aryl; heteroaryl; C$_5$-cycloalkyl; or heterocycl(yl); 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$_1$-alkyl, hydroxy(C$_1$-alkyl), C$_1$-alkoxy, halogen, nitro, halogenated C$_1$-alkyl, halogenated C$_1$-alkoxy, C$_1$-alkylthio, C$_1$-alkoxycarbonyl, amino, cyano, hydroxy, aminocarbonyl, C$_1$-alkylaminocarbonyl, di(C$_1$-alkyl)aminocarbonyl, and C$_1$-alkylcarbonyl;

c) $A_1$ is hydrogen; aryl; heteroaryl; C$_5$-cycloalkyl; or heterocycl(yl) 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$_1$-alkyl, hydroxy(C$_1$-alkyl), C$_1$-alkoxy, halogen, nitro, halogenated C$_1$-alkyl, halogenated C$_1$-alkoxy, C$_1$-alkylthio, C$_1$-alkoxycarbonyl, amino,
cyano, hydroxy, aminocarbonyl, C₁₋₆alkylaminocarbonyl, di(C₁₋₆alkyl)aminocarbonyl, and C₁₋₆alkylcarbonyl;

d) A₁ is hydrogen, substituted phenyl, benzofuranyl, furanyl, thiazolyl, thiophenyl, or cyclopentyl; wherein substituents of A₁ other than hydrogen are optionally substituted and phenyl is substituted with one to two substituents independently selected from the group consisting of C₁₋₄alkyl, C₁₋₄alkoxy, halogen, nitro, halogenated C₁₋₄alkyl, halogenated C₁₋₄alkoxy, methylthio, C₁₋₄alkoxycarbonyl, amino, cyano, hydroxy, aminocarbonyl, and C₁₋₄alkylcarbonyl;

e) A₁ 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 C₁₋₄alkyl, C₁₋₄alkoxy, halogen, nitro, halogenated C₁₋₄alkyl, halogenated C₁₋₄alkoxy, methylthio, amino, cyano, and C₁₋₄alkylcarbonyl;

f) A₁ 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) L₁ is –(CH₂)ᵣ–, optionally substituted with one to three substituents independently selected from the group consisting of C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, and halogen; provided that when A₁ is hydrogen, r is greater than or equal to 4;

h) L₁ is –(CH₂)ᵣ–, optionally substituted with a substituent selected from the group consisting of C₁₋₄alkyl, C₂₋₄alkenyl, and C₂₋₄alkynyl, provided that r is 1 to 3 when A₁ is other than hydrogen; or r is greater than or equal to 4 when A₁ is hydrogen;

i) L₁ is –(CH₂)ᵣ– optionally substituted with a substituent selected from the group consisting of methyl and allyl, provided that r is 1 to 3 when A₁ is other than hydrogen;

j) L₁ is –CH₂– optionally substituted with methyl or allyl;

k) P is –CH₂–
1) \( A_2 \) is hydrogen, heteroaryl other than unsubstituted pyridin-2-yl, \( C_{3-6} \) 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, \( C_1 \) \( \delta \) alkoxy, halogen, halogenated \( C_{1-6} \) alkyl, halogenated \( C_{1-6} \) alkoxy, aryl(\( C_{1-6} \) alkoxy, phenyl, \( C_1 \) \( \delta \) alkylthio, \( C_{1-6} \) alkoxy carbonyl, amino, cyano, hydroxy, nitro, aminocarbonyl, \( C_{1-6} \) alkyl carbonyl amino, and a non fused \( C_{3-6} \) cycloalkyloxy; wherein heteroaryl other than unsubstituted pyridin-2-yl and \( C_{3-6} \) 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, \( C_1 \) \( \delta \) alkoxy carbonyl, amino, cyano, hydroxy, nitro, aminocarbonyl, \( C_1 \) \( \delta \) 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 \(-X_1-CH(R^\delta)-(CR^3R^2)^-\)

wherein \( X_1 \) is NH and \( R^\delta \), \( R^3 \), and \( R^2 \) 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 \(-X_1-CH(R^\delta)-(CR^3R^2)^2 \)

wherein \( X_1 \) is NH and \( R^\delta \), \( R^3 \), \( R^3 \), and \( R^2 \) 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 \(-(CH_2)_4-\), and when \( A_2 \) is other than hydrogen, \( P \) is \(-(CH_2)_{1-2}-\) or \(-CH_2 CH=CH-\);
m) \(A_2\) is heteroaryl other than unsubstituted pyridin-2-yl, a non fused C\(_3\)

cycloalkyl, or phenyl optionally substituted at the meta and para positions
with one to three substituents independently selected from the group
consisting of C\(_1\)-alkyl, C\(_1\)-alkoxy, halogen, halogenated C\(_1\)-alkyl,
ahalogenated C\(_1\)-alkoxy, C\(_1\)-alkoxycarbonyl, amino, hydroxy,
nitro, aminocarbonyl, C\(_1\)-alkylcarbonylamino, and a non fused C\(_3\)
cycloalkoxy; wherein heteroaryl other than unsubstituted pyridin-2-yl and a
non fused C\(_3\)-cycloalkyl are optionally substituted with one to three
substituents independently selected from the group consisting of C\(_1\)-alkyl, C\(_1\)
alkoxy, halogen, halogenated C\(_1\)-alkyl, halogenated C\(_1\)-alkoxy, C\(_1\)-alkylthio,
C\(_1\)-alkoxycarbonyl, amino, hydroxy, nitro, aminocarbonyl, C\(_1\)
carbonylamino, and a non fused C\(_3\)-cycloalkylxy; provided that no
more than two substituents on \(A_2\) are non fused C\(_3\)-cycloalkoxy;
provided that when \(A_1\) is unsubstituted phenyl and \(L_2\) is \(-X_1-CH(R^x)-(CR^rR^z)-\)
wherein \(X_1\) is NH and \(R\), \(R\), and \(R\) are each hydrogen, \(A_2\) is other than
unsubstituted phenyl;
and, further provided that when \(A_1\) is unsubstituted phenyl and \(L_2\) is \(-X_1-CH(R^3)-(CR^rR^z)-\)
wherein \(X_1\) is NH and \(R\), \(R\), and \(R\) 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\(_1\)-alkyl, C\(_1\)-alkoxy, halogen, halogenated C\(_1\)-alkoxy, C\(_1\)
alkylthio, hydroxy, amino, aminocarbonyl, C\(_1\)-alkylcarbonylamino, and a non
fused C\(_3\)-cycloalkoxy; 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 C₄₋₅alkyl, C₄₋₅alkoxy, halogen, halogenated C₁₋₃alkoxy, C₁₋₃alkylthio, hydroxy, amino, aminocarboxyl, C₁₋₃alkylcarboxylamino, and a non-fused C₃₋₆cycloalkylcycloalkyloxy;

provided that no more than two substituents on A₂ are non-fused C₉-
6 cycloalkyloxy;

provided that when A₁ is unsubstituted phenyl and L₂ is -X₁₋₁(CH(R¹)-(CR²R²)⁻
wherein X₁ is NH and R⁺, R⁻, and R² are each hydrogen, A₂ is other than unsubstituted phenyl;

and, further provided that when A₁ is unsubstituted phenyl and L₂ is -X₁₋₁(CH(R²)-
(CR²R²)⁻ where X₁ is NH and R⁺, R⁻, and R² are each hydrogen, A₂ is other then phenyl substituted with methoxy;

and, provided that when A₁ is 3,4-dichloro-phenyl, A₂ is other than phenyl substituted in the meta position with trifluoromethoxy;

do) A₂ 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, isopropoxy, trifluoromethoxy, difluoromethoxy, hydroxy, aminocarboxyl, and methylcarboxylamino; 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, isopropoxy, trifluoromethoxy, difluoromethoxy, hydroxy, aminocarboxyl, and methylcarboxylamino;

provided that when A₁ is unsubstituted phenyl and L₂ is -X₁₋₁(CH(R⁺)-(CR²R²)⁻
wherein X₁ is NH and R⁺, R⁻, and R² are each hydrogen, A₂ is other than unsubstituted phenyl;

and, further provided that when A₁ is unsubstituted phenyl and L₂ is -X₁₋₁(CH(R³)-
(CR²R²)⁻ where X₁ is NH and R⁺, R⁻, and R² are each hydrogen, A₂ is other then phenyl substituted with methoxy;

and, provided that when A₁ is 3,4-dichloro-phenyl, A₂ 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, isopropoxy, 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

- $\text{NH-}C_6$-cycloalkyl–(CH$_2$)$_0$-; provided that when C$_5$-cycloalkyl is cyclohexyl, Q is attached at either the 2- or cis-4-position relative to the position of $\text{NH}$;
  - $X_2^-$–(CH$_2$)$_0$-;
  - $X_1^-$–(CH$_2$)$_{2-3}$–;
  - $\text{NH}$(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;
  - $\text{NHC}(=O)$–(CH$_2$)$_{1-4}$–;
  - C(=O)NH(CR$^b$R$^d$)$_{2-6}$–;

and

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

wherein $X_1$ is $\text{NH}$, O, S, or a direct bond; such that $X_1$ is other than O when $W$ is N;

- $X_2$ is $\text{CH}=\text{CH}$-

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

- $\text{NH-}C_6$-cycloalkyl–(CH$_2$)$_0$-; provided that when C$_5$-cycloalkyl is cyclohexyl, Q is attached at either the 2- or cis-4-position relative to the position of $\text{NH}$–;
  - $X_1^-$–CH(R$^d$)-(CR$^b$R$^d$)$_{1-5}$–, wherein $X_1$ is $\text{NH}$–, 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(CH₂)₂-;

and

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

provided that when \(L_2\) is \(-\text{C}(=O)\text{NH}(\text{CH}_2)_2\)-, then \(R_w\) is hydrogen

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

-\(\text{NH-cyclohexyl-(CH}_2)_{0-2}-\) and \(Q\) is attached at either the 2- or cis-4-position relative to the position of \(-\text{NH-}\);

-\(X_1-\text{CH}(R^x)-(\text{CR}^yR^z)_1-5-\); wherein \(X_1\) is \(-\text{NH-}\) or \(S\); and \(R^x\), \(R^y\), and \(R^z\) are each hydrogen;

and

-\(X_1-(R,\overline{R}-\text{CH}(R^x)\text{CR}^y(R^z))\)-; wherein \(X_1\) is \(-\text{NH-}\), 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

-\(\text{NH-cyclohexyl-(CH}_2)_{0-2}-\) and \(Q\) is attached at either the 2- or cis-4-position relative to the position of \(-\text{NH-}\);

-\(X_1-\text{CH}(R^x)-(\text{CR}^yR^z)_1-5-\); wherein \(X_1\) is \(-\text{NH-}\) or \(S\) and \(R^x\), \(R^y\), and \(R^z\) are each hydrogen;

and

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

v) \(m\) is 0;

w) \(R^x\) and \(R^z\) 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, di\(C_{1-4}\)-alkylamino, and \(C_{1-4}\)-alkylcarbonyl; or \(R^x\) and \(R^z\) 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;

c) $R^b$ 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 (la):

![Formula (la)]

wherein:

a) \( A_1 \) 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<sub>1</sub>-alkylaminocarbonyl, di(C<sub>1</sub>
alkyl)aminocarbonyl, and C<sub>1</sub>-alkylcarbonyl;
L<sub>1</sub> is \(-(CH_2)_{r}\) -- optionally substituted with one to three substituents independently
selected from the group consisting of C<sub>1</sub>-alkyl, C<sub>2</sub>-alkenyl, C<sub>2</sub>-alkynyl, and
halogen; provided that when A<sub>1</sub> 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<sub>2</sub> is hydrogen; and P is \(-(CH_2)_{1-2}\) -- or \(-CH_2CH=CH-\) when A<sub>2</sub>
is other than hydrogen;
A<sub>2</sub> is hydrogen, heteroaryl other than unsubstituted pyridin-2-yl, C<sub>3</sub>-cycloalkyl, or
phenyl optionally substituted at the meta and para positions with one to three
substituents independently selected from the group consisting of C<sub>1</sub>-alkyl, C<sub>1</sub>
alkoxy, halogen, halogenated C<sub>1</sub>-alkyl, halogenated C<sub>1</sub>-alkoxy, aryl(C<sub>1</sub>-alkoxy,
phenyl, C<sub>1</sub>-alkylthio, C<sub>1</sub>-alkoxycarbonyl, amino, cyano, hydroxy, nitro,
aminocarbonyl, C<sub>1</sub>-alkylcarbonylamino, and a non fused C<sub>3</sub>-cycloalkyloxy;
wherein heteroaryl other than unsubstituted pyridin-2-yl and C<sub>3</sub>-cycloalkyl are
optionally substituted with one to three substituents independently selected from
the group consisting of C<sub>1</sub>-alkyl, C<sub>1</sub>-alkoxy, halogen, halogenated C<sub>1</sub>-alkyl,
halogenated C<sub>1</sub>-alkoxy, aryl(C<sub>1</sub>-alkoxy, phenyl, C<sub>1</sub>-alkylthio, C<sub>1</sub>
alkoxycarbonyl, amino, cyano, hydroxy, nitro, aminocarbonyl, C<sub>1</sub>
alkylcarbonylamino, and a non fused C<sub>3</sub>-cycloalkyloxy;
provided that no more than two substituents on A<sub>2</sub> are aryl(C<sub>1</sub>-alkoxy, phenyl, or a
non fused C<sub>3</sub>-cycloalkyloxy;
provided that when A<sub>1</sub> is unsubstituted phenyl and L<sub>2</sub> is \(-X_1\cdot CH(R^x)-(CR^yR^z)-\)
wherein X<sub>1</sub> is NH, and R<sup>x</sup>, R<sup>y</sup>, and R<sup>z</sup> are each hydrogen, A<sub>2</sub> is other than
unsubstituted phenyl; phenyl substituted with aryl(C<sub>1</sub>-alkoxy or phenyl; or
phenyl substituted at the meta position with cyano;
and, further provided that when A<sub>1</sub> is unsubstituted phenyl and L<sub>2</sub> is \(-X_1\cdot CH(R^x)-(CR^yR^z)-\)
wherein X<sub>1</sub> is NH and R<sup>x</sup>, R<sup>y</sup>, and R<sup>z</sup> are each hydrogen, A<sub>2</sub> is
other than phenyl substituted with methoxy;
and, provided that when \(A_1\) is 3,4-dichloro-phenyl and \(P\) is \(-\text{CH}_2\)\(-\text{CH}_2\)\(-\text{CH}_2\)\(-\text{CH}_2\), \(A_2\) 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 \(-(\text{CH}_2)_2\)\(-\text{CH}_2\)\(-\text{CH}_2\), \(A_2\) is other than 4-methoxy-phenyl;

5  \(W\) is N or CH;

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

- \(-\text{NH}-\text{C}_{5,7}\text{cycloalkyl}\)-(\text{CH}_2)\(_{0,2}\)-; provided that when \(\text{C}_{5,7}\text{cycloalkyl}\) is cyclohexyl, \(Q\) is attached at either the 2- or cis-4-position relative to the position of \(-\text{NH}-\);

- \(-\text{X}_2\)-(\text{CH}_2)\(_{0,4}\)-;

- \(-\text{X}_1\)-(\text{CH}_2)\(_{2,3}\)-\(-\text{X}_3\)-(\text{CH}_2)\(_{2,3}\)-;

- \(-\text{NH}(\text{CH}_2)\(_{1,4}\)\text{C}(=\text{O})\)- provided that at least one of \(R^b\), \(R^c\), or \(R^d\) is not hydrogen 
and \(m\) is 0;

- \(-\text{NHC}(=\text{O})-(\text{CH}_2)\(_{1,4}\)-;

- \(-\text{C}(=\text{O})\text{NH}(\text{CR}^x\text{R}^z)\(_{2,5}\)-;

and

- \(-\text{X}_1\cdot\text{CH}(\text{R}^x\text{)}\)-(\text{CR}^y\text{R}^z)\(_{1,5}\)-; such that when \(X_1\) is a direct bond and \(W\) is \(C(\text{R}_w)\), then \(R^x\) of \(\text{CH}(\text{R}^x)\) is hydrogen;

wherein \(X_1\) is \(-\text{NH}-\), O, S, or a direct bond; such that \(X_1\) is other than O when \(W\) is N;

20  \(X_2\) is \(-\text{CH}=\text{CH}\)-;

\(X_3\) 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 \(-\text{X}_2\)-(CH\(_{2,4}\))\(-\text{C}(=\text{O})\text{NH}(\text{CR}^y\text{R}^z)\(_{2,5}\)-, then \(R_w\)

25  is hydrogen;

\(m\) is 0 or 1;

\(G\) is \(-\text{C}(=\text{NR}^b)\text{NR}^c\text{R}^d\);

\(R^a\) 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;

5  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$_{5-7}$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$_{1-6}$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, 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;

10 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.

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

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A₁ is hydrogen; aryl; heteroaryl; C₅₋₆-cycloalkyl; or heterocycyl other than piperidinyl; where substituents of A₁ other than hydrogen are optionally substituted with one to three substituents independently selected from the group consisting of C₁₋₆-alkyl, hydroxy(C₁₋₆-alkyl, C₁₋₆-alkoxy, halogen, nitro, halogenated C₁₋₆-alkyl, halogenated C₁₋₆-alkoxy, C₁₋₆-alkylthio, C₁₋₆-alkoxycarbonyl, amino, cyano, hydroxy, aminocarbonyl, C₁₋₆-alkylaminocarbonyl, di(C₁₋₆-alkyl)aminocarbonyl, and C₁₋₆-alkylcarbonyl;

L₁ is -(CH₂)ᵣ- optionally substituted with a substituent selected from the group consisting of C₁₋₄-alkyl, C₂₋₄-alkenyl, and C₂₋₄-alkynyl; provided that r is 1 to 3 when A₁ is other than hydrogen; or r is 4 or 5 when A₁ is hydrogen;
P is -CH₂₋₋;

A₂ 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 C₁₋₆-alkyl, C₁₋₆-alkoxy, halogen, halogenated C₁₋₆-alkoxy, C₁₋₆-alkylthio, hydroxy, amino, aminocarbonyl, C₁₋₆-alkylcarbonylamino, and a non fused C₃₋₆-cycloalkoxy; 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 C₁₋₄-alkyl, C₁₋₄-alkoxy, halogen, halogenated C₁₋₄-alkoxy, C₁₋₄-alkylthio, hydroxy, amino, aminocarbonyl, C₁₋₄-alkylcarbonylamino, and a non fused C₃₋₆-cycloalkoxy;

provided that no more than two substituents on A₂ are non fused C₃₋₆-cycloalkoxy; provided that when A₁ is unsubstituted phenyl and L₂ is -X₁-CH(R¹)⁻(CR²'R³')⁻ wherein X₁ is NH, and R¹', R²', and R³' are each hydrogen, A₂ is other than unsubstituted phenyl;

and, further provided that when A₁ is unsubstituted phenyl and L₂ is -X₁-CH(R¹)'⁻(CR²'R³')₂⁻ wherein X₁ is NH and R¹', R²', and R³' are each hydrogen, A₂ is other than phenyl substituted with methoxy;

and, provided that when A₁ is 3,4-dichloro-phenyl, A₂ 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$^y$R$^z$)$_{1-5}$, 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$^z$))$_n$; 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 $C_{1-9}$alkyl, wherein $C_{1-9}$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, di$C_{1-4}$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 $C_{1-6}$alkynyl, and fluorinated $C_{1-6}$alkenyl.
alkoxy, C₁₆alkylcarbonyl, C₁₆alkoxycarbonyl, nitro, methylthio, hydroxy, and
cyano; or, R⁵ and R⁶ 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;

5 with the proviso that in any instance, only one ring optionally exists between R⁶ and
R⁸, R⁶ and R⁸, or R⁷ and R⁹;
and enantiomers, diastereomers, tautomers, solvates, and pharmaceutically
acceptable salts thereof.

10 A further aspect of the present invention is directed to a compound of
Formula Ia wherein:
A₁ 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 C₁₆alkyl, C₁₆alkoxy, halogen, nitro, halogenated C₁₆alkyl,
halogenated C₁₆alkoxy, methylthio, amino, cyano, and C₁₆alkylcarbonyl;
L₁ is -(CH₂)ᵣ optionally substituted with a substituent selected from the group
consisting of methyl and allyl, and r is 1 to 3;
P is -(CH₂)ᵩ;

20 A₂ 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, isopropoxy, trifluoromethoxy,
difluoromethoxy, hydroxy, aminocarbonyl, and methylcarbamoylamino; 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, isopropoxy, trifluoromethoxy, difluoromethoxy, hydroxy, aminocarbonyl,
and methylcarbamoylamino; provided that when A₁ is 3,4-dichloro-phenyl, A₂ is
other than phenyl substituted in the meta position with trifluoromethoxy;
W is N or CH;
L₂ is a bivalent radical selected from the group consisting of
-NH-cyclohexyl-(CH₂)₀₋₂-- and Q is attached at either the 2- or cis-4-position
relative to the position of –NH–;
-X₁-CH(R₆)¹-(CR₂[R₆]²)-₁₋₅--; wherein X₁ is –NH– or S; and R₆, R₂₀ and R² are each
hydrogen;
and
-X₁-(R,R-CH(R₆)²)CR₆[R₂₀]⁻; wherein X₁ is –NH–, and R₆ and R² are methyl, and R₂₀ is
hydrogen;
m is 0;
G is –C(=NR₆[R₂₀]²)NR₆[R₂₀]²;
R₆ and R₂₀ are independently hydrogen, methyl or ethyl; or R₆ and R₂₀ are taken
together with the atoms to which they are attached to form a 5-8 membered
monocyclic ring optionally substituted with oxo;
R₆ is hydrogen,
C₁₋₆alkyl, C₂₋₆alkenyl, C₃₋₇cycloalkyl, heterocyclyl, phenylcarbonyl,
phenyl, or heteroaryl; wherein C₁₋₆alkyl is optionally substituted with one to two
substituents independently selected from the group consisting of C₁₋₆alkoxy,
phenyl, pyridinyl, furanyl, and tetrahydrofuranyl; and wherein any phenyl- or
heteroaryl-containing substituents of R₂₀ are optionally substituted with one to two
substituents independently selected from the group consisting of C₁₋₆alkyl, C₁₋₆alkoxy,
chloro, fluoro, bromo, fluorinated C₁₋₆alkoxy, nitro, methylthio, hydroxy,
and cyano; or, R₂₀ and R₂₀ 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 R₆ and
R₆, R₂₀ and R₂₀, or R₂₀ and R₂₀;
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:

A₁ 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;

L₁ is –CH₂- optionally substituted with methyl or allyl; P is –CH₂-;

A₂ is phenyl substituted at the para position with a substituent selected from the group consisting of methoxy, ethoxy, isopropoxy, difluoromethoxy, hydroxy, and aminocarbonyl; or A₂ is pyridin-3-yl or pyridin-4-yl substituted with methoxy;

W is N or CH;

L₂ is a bivalent radical selected from the group consisting of -NH-cyclohexyl-(CH₂)₀₋₂ – and Q is attached at either the 2- or cis-4-position relative to the position of –NH–;

-X₁-CH(R⁻)- (CR⁻R⁻)-; wherein X₁ is -NH– or S and R⁻, ᵃ, ᵃ', and ᵃ'' are each hydrogen;

and

-X₁-(R, R'-CH (R⁻)CR⁻(R⁻))⁻; wherein X₁ is -NH–, R⁻ and R² are methyl, and ᵃ is hydrogen;

m is 0;

G is –C(NR⁻)Nᵐ⁻R⁻;

R⁻ and ᵃ are independently hydrogen, methyl or ethyl;

R⁻ is hydrogen;

R⁻ is hydrogen, C₃₋₄-alkyl, C₂₋₃-alkenyl, cyclohexyl, phenylcarbonyl, phenyl, pyrimidinyl, furanyl, benzo[1,3]dioxolyl, or pyridinyl; wherein C₃₋₄-alkyl is optionally substituted with one to two substituents independently selected from the group consisting of C₁₋₃-alkoxy, phenyl, pyridinyl, furanyl, and tetrahydrofuranyl; and wherein any phenyl- or heteroaryl-containing substituents of ᵃ⁻ are optionally
substituted with one to two substituents independently selected from the group consisting of C<sub>1</sub>-alkyl, C<sub>1</sub>-alkoxy, chloro, fluoro, bromo, fluorinated C<sub>1</sub>-alkoxy, nitro, methylthio, hydroxy, and cyano; or, R<sup>e</sup> and R<sup>d</sup> 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<sub>1</sub>, L<sub>1</sub>, D, W, L<sub>2</sub>, and Q are as defined in the present invention.

**Table 1**

<table>
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<th>Cpd #</th>
<th>A&lt;sub&gt;1&lt;/sub&gt;</th>
<th>L&lt;sub&gt;1&lt;/sub&gt;</th>
<th>D</th>
<th>W</th>
<th>L&lt;sub&gt;2&lt;/sub&gt;</th>
<th>Q</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>phenyl</td>
<td>-CH&lt;sub&gt;2&lt;/sub&gt;-</td>
<td>-CH&lt;sub&gt;2&lt;/sub&gt;-(4-fluoro-phenyl)</td>
<td>N</td>
<td>-NH(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;-</td>
<td>-NHC(=NH)NH&lt;sub&gt;2&lt;/sub&gt;</td>
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<td>-CH&lt;sub&gt;2&lt;/sub&gt;-</td>
<td>-CH&lt;sub&gt;2&lt;/sub&gt;-(4-methoxy-phenyl)</td>
<td>N</td>
<td>-NH(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;-</td>
<td>-NHC(=NH)NH&lt;sub&gt;2&lt;/sub&gt;</td>
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<tr>
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<td>-CH&lt;sub&gt;2&lt;/sub&gt;-</td>
<td>-CH&lt;sub&gt;2&lt;/sub&gt;-(4-methylcarboxy-phenyl)</td>
<td>N</td>
<td>-NH(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;-</td>
<td>-NHC(=NH)NH&lt;sub&gt;2&lt;/sub&gt;</td>
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<tr>
<td>4</td>
<td>phenyl</td>
<td>-(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;4&lt;/sub&gt;-</td>
<td>-CH&lt;sub&gt;2&lt;/sub&gt;-(4-methoxy-phenyl)</td>
<td>N</td>
<td>-NH(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;-</td>
<td>-NHC(=NH)NH&lt;sub&gt;2&lt;/sub&gt;</td>
</tr>
<tr>
<td>5</td>
<td>H</td>
<td>-(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;4&lt;/sub&gt;-</td>
<td>-CH&lt;sub&gt;2&lt;/sub&gt;-(4-methoxy-phenyl)</td>
<td>N</td>
<td>-NH(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;-</td>
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<td>-CH&lt;sub&gt;2&lt;/sub&gt;-</td>
<td>-CH&lt;sub&gt;2&lt;/sub&gt;-(4-methoxy-phenyl)</td>
<td>N</td>
<td>-NH(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;-</td>
<td>-NHC(=NH)NH&lt;sub&gt;2&lt;/sub&gt;</td>
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<td>-CH₂-(4-methoxy-phenyl)</td>
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<td>-NH(CH₂)₂⁻</td>
<td>-NHC(=NH)NH₂</td>
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<td>-CH₂⁻(4-methoxy-phenyl)</td>
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<td>-CH₂⁻(4-methoxy-phenyl)</td>
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<td>-CH₂⁻(4-aminocarbonyl-phenyl)</td>
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<td>-NH(CH₂)₂⁻</td>
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<td>-CH₂⁻(4-methylcarboxyl-amino-phenyl)</td>
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<td>-CH₂⁻(4-ethoxy-phenyl)</td>
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<td>-NH(CH₂)₂⁻</td>
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<td>-CH₂⁻(4-methoxy-phenyl)</td>
<td>N</td>
<td>-NH(CH₂)₂⁻</td>
<td>-NHC(=NH)NH₂</td>
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<td>26</td>
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<td>-CH₂⁻(4-methoxy-phenyl)</td>
<td>N</td>
<td>-NH(CH₂)₂⁻</td>
<td>-NHC(=NH)NH₂</td>
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<td>27</td>
<td>3,4-dichloro-phenyl</td>
<td>-CH₂⁻</td>
<td>-CH₂⁻(4-methoxy-phenyl)</td>
<td>N</td>
<td>-NH(CH₂)₂⁻</td>
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<td>-CH₂⁻(4-methoxy-phenyl)</td>
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<td>-NH(CH₂)₂⁻</td>
<td>-NHC(=N-CN)NH₂</td>
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<td>29</td>
<td>3,4-dichloro-phenyl</td>
<td>-CH₂⁻</td>
<td>-CH₂⁻(4-ethoxy-phenyl)</td>
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<td>-NH(CH₂)₂⁻</td>
<td>-NHC(=NH)NH₂</td>
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<td>-CH₂⁻(4-methoxy-phenyl)</td>
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<td>-CH₂⁻(4-methoxy-phenyl)</td>
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<td>-NH(CH₂)₂⁻</td>
<td>-NHC(=NH)NH₂</td>
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<td>-CH₂⁻(4-methoxy-phenyl)</td>
<td>N</td>
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<td>-NHC(=NH)NH₂</td>
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<td>33</td>
<td>4-fluoro-phenyl</td>
<td>-CH₂⁻</td>
<td>-(CH₂)₆⁻(4-methoxy-phenyl)</td>
<td>N</td>
<td>-NH(CH₂)₂⁻</td>
<td>-NHC(=NH)NH₂</td>
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<td>34</td>
<td>3,4-dichloro-phenyl</td>
<td>-CH₂⁻</td>
<td>-CH₂⁻(4-n-propyl-phenyl)</td>
<td>N</td>
<td>-NH(CH₂)₂⁻</td>
<td>-NHC(=NH)NH₂</td>
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<td>35</td>
<td>3,4-dichloro-phenyl</td>
<td>-CH₂⁻</td>
<td>-CH₂⁻(4-i-propyl-phenyl)</td>
<td>N</td>
<td>-NH(CH₂)₂⁻</td>
<td>-NHC(=NH)NH₂</td>
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<td>36</td>
<td>3,4-dichloro-phenyl</td>
<td>-CH₂⁻</td>
<td>-CH₂⁻(4-cyclopentyl(oxo)-phenyl)</td>
<td>N</td>
<td>-NH(CH₂)₂⁻</td>
<td>-NHC(=NH)NH₂</td>
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<tr>
<td>37</td>
<td>3,4-dichloro-phenyl</td>
<td>-CH₂⁻</td>
<td>-CH₂⁻(4-methylthio-phenyl)</td>
<td>N</td>
<td>-NH(CH₂)₂⁻</td>
<td>-NHC(=NH)NH₂</td>
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<td>38</td>
<td>3,4-dichloro-phenyl</td>
<td>-CH₂⁻</td>
<td>-CH₂⁻(4-ethyl-phenyl)</td>
<td>N</td>
<td>-NH(CH₂)₂⁻</td>
<td>-NHC(=NH)NH₂</td>
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<td>39</td>
<td>3-chloro-phenyl</td>
<td>-CH₂⁻</td>
<td>-CH₂⁻(4-methoxy-phenyl)</td>
<td>N</td>
<td>-NH(CH₂)₂⁻</td>
<td>-NHC(=NH)NH₂</td>
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<td>40</td>
<td>3,4-dichloro-phenyl</td>
<td>-CH₂⁻</td>
<td>-CH₂⁻(4-trifluoromethoxy-phenyl)</td>
<td>N</td>
<td>-NH(CH₂)₂⁻</td>
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<td>41</td>
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<td>-CH₂⁻</td>
<td>-CH₂⁻(4-difluoromethoxy-phenyl)</td>
<td>N</td>
<td>-NH(CH₂)₂⁻</td>
<td>-NHC(=NH)NH₂</td>
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<tr>
<td>42</td>
<td>3,4-dichloro-phenyl</td>
<td>-CH₂⁻</td>
<td>-CH₂⁻(4-methoxy-phenyl)</td>
<td>N</td>
<td>cis-racemic-1,2-cyclohexyl</td>
<td>-NHC(=NH)NH₂</td>
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<td>43</td>
<td>3,4-dichloro-phenyl</td>
<td>-CH₂⁻</td>
<td>-CH₂⁻(4-methoxy-phenyl)</td>
<td>N</td>
<td>trans (1S, 2S)-cyclohexyl</td>
<td>-NHC(=NH)NH₂</td>
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<td>44</td>
<td>3,4-dichloro-phenyl</td>
<td>-CH₂⁻</td>
<td>-CH₂⁻(4-methoxy-phenyl)</td>
<td>N</td>
<td>-NH(CH₂)₂⁻</td>
<td>-NHC(=NH)NH₂</td>
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<td>-CH₂⁻</td>
<td>-CH₂⁻(4-methoxy-phenyl)</td>
<td>N</td>
<td>-NH(CH₂)₂⁻</td>
<td>-NHC(=NH)NH₂</td>
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<td>46</td>
<td>4-ethyl-phenyl -CH₂⁻</td>
<td>-CH₂⁻-(4-methoxy-phenyl)</td>
<td>N</td>
<td>-NH(CH₂)₂⁻</td>
<td>-NHC(=NH)NH₂</td>
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<td>47</td>
<td>3,4-dichloro-phenyl -CH₂⁻</td>
<td>-CH₂⁻-(4-methoxy-phenyl)</td>
<td>N</td>
<td>trans(1R, 2R)-cyclohexyl⁻</td>
<td>-NHC(=NH)NH₂</td>
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<tr>
<td>48</td>
<td>3,4-dichloro-phenyl -CH₂⁻</td>
<td>-CH₂⁻-(4-methoxy-phenyl)</td>
<td>N</td>
<td>-NH(CH₂)₂⁻</td>
<td>-NH(3,5-dihydro-imidazol-4-on-2-yl)</td>
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<td>3,4-dichloro-phenyl -CH₂⁻</td>
<td>-CH₂⁻-(4-methoxy-phenyl)</td>
<td>N</td>
<td>-NH(CH₂)₂⁻</td>
<td>-NH(4,5-dihydro-1H-imidazol-2-yl)</td>
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<td>-NH(CH₂)₂⁻</td>
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<td>51</td>
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<td>-CH₂⁻-(4-aminocarbonyl-phenyl)</td>
<td>N</td>
<td>-NH(CH₂)₂⁻</td>
<td>-NHC(=NH)NH₂</td>
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<tr>
<td>52</td>
<td>3,4-dichloro-phenyl -CH₂⁻</td>
<td>-CH₂⁻-(3-ethoxy-phenyl)</td>
<td>N</td>
<td>-NH(CH₂)₂⁻</td>
<td>-NHC(=NH)NH₂</td>
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<td>3,4-dichloro-phenyl -CH₂⁻</td>
<td>-CH₂⁻-(4-ethoxy-phenyl)</td>
<td>N</td>
<td>-NH(CH₂)₂⁻</td>
<td>-NHC(=NH)NH-ethyl</td>
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<td>-CH₂⁻-(4-methoxy-phenyl)</td>
<td>N</td>
<td>-NH(CH₂)₂⁻</td>
<td>-NHC(=NH)NH-propyl</td>
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<td>N</td>
<td>pyrrolindin-1-yl</td>
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<td>N</td>
<td>trans (1R, 2R)-cyclohexyl⁻</td>
<td>-NHC(=NH)NH₂</td>
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<td>-CH₂⁻-(3-difluoromethoxy-phenyl)</td>
<td>N</td>
<td>-NH(CH₂)₂⁻</td>
<td>-NHC(=NH)NH₂</td>
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<td>58</td>
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<td>-CH₂⁻-(4-methoxy-phenyl)</td>
<td>N</td>
<td>-NH(CH₂)₂⁻</td>
<td>-NHC(=NH)NH (i-propyl)</td>
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<td>N</td>
<td>-NH(CH₂)₂^N</td>
<td>-N(ethyl)</td>
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<td>-CH₂-(4-methoxy-phenyl)</td>
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<td>-NH(CH₂)₂^N</td>
<td>2-iminoimidazolid-1-yl</td>
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<td>-CH₂-(4-methoxy-phenyl)</td>
<td>N</td>
<td>-NH(CH₂)₂^N</td>
<td>-NHC(=NH)NH</td>
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<td>-NH(CH₂)₂^N</td>
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<td>-CH₂-(4-methoxy-phenyl)</td>
<td>N</td>
<td>-NH(CH₂)₂^N</td>
<td>-NHC(=NH)NH</td>
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<td>-CH₂-(4-methoxy-phenyl)</td>
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<td>-NH(CH₂)₂^N</td>
<td>(cyclohexyl)</td>
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<td>-CH₂-(4-methoxy-phenyl)</td>
<td>N</td>
<td>-NH(CH₂)₂^N</td>
<td>-NHC(=NH)NH</td>
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<td>-CH₂-(4-methoxy-phenyl)</td>
<td>N</td>
<td>-NH(CH₂)₂^N</td>
<td>(benzyl)</td>
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<td>-CH₂-(4-methoxy-phenyl)</td>
<td>N</td>
<td>-NH(CH₂)₂^N</td>
<td>-NHC(=NH)NH</td>
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<td>68</td>
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<td>-CH₂-(4-methoxy-phenyl)</td>
<td>N</td>
<td>-NH(CH₂)₂^N</td>
<td>(tetrahydrofuran-2-ylmethyl)</td>
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<td>-CH₂-(4-methoxy-phenyl)</td>
<td>N</td>
<td>-NH(CH₂)₂^N</td>
<td>-NHC(=NH)NH</td>
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<td>70</td>
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<td>-NH(CH₂)₂^N</td>
<td>(furan-2-ylmethyl)</td>
</tr>
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<td>-CH₂-(4-methoxy-phenyl)</td>
<td>N</td>
<td>-NH(CH₂)₂^N</td>
<td>(2-methoxy-ethyl)</td>
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<td>-NH(CH₂)₂^N</td>
<td>-NHC(=NH)NH</td>
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<td>-NH(CH₂)₂^N</td>
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<td>-NH(CH₂)₂^N</td>
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<td>-NH(CH₂)₂^N</td>
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<td>-CH₂-(4-methoxy-phenyl)</td>
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<td>-NH(CH₂)₂^N</td>
<td>(phenyl)</td>
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<td>-NH(CH₂)₂⁺</td>
<td>-NHC(=NH)NH(4-methoxy-phenyl)</td>
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<td>-CH₂-(4-methoxy-phenyl)</td>
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<td>-NH(CH₂)₂⁺</td>
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<td>-CH₂-(4-methoxy-phenyl)</td>
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<td>-CH₂-(6-methoxy-pyridin-3-yl)</td>
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<td>-CH₂-(4-nitrophenyl)</td>
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<td>-NH(CH₂)₂⁺</td>
<td>-NHC(=NH)NH₂</td>
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<td>-CH₂-(4-methoxy-phenyl)</td>
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<td>-NH(CH₂)₂⁺</td>
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<td>-CH₂-(4-methoxy-phenyl)</td>
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<td>-CH₂-(4-methoxy-phenyl)</td>
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<td>-NH(CH₂)₂⁺</td>
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<tr>
<td>97</td>
<td>4-cyano-phenyl</td>
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<td>CH&lt;sub&gt;2&lt;/sub&gt;-(4-methoxy-phenyl)</td>
<td>N</td>
<td>-NH(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;-</td>
<td>-NHC(=NH)NH&lt;sub&gt;2&lt;/sub&gt;</td>
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<td>3-cyano-phenyl</td>
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<td>CH&lt;sub&gt;2&lt;/sub&gt;-(4-methoxy-phenyl)</td>
<td>N</td>
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<td>-NHC(=NH)NH&lt;sub&gt;2&lt;/sub&gt;</td>
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<td>N</td>
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<td>CH&lt;sub&gt;2&lt;/sub&gt;-(4-methoxy-phenyl)</td>
<td>N</td>
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<td>-NHC(=NH)NH&lt;sub&gt;2&lt;/sub&gt;</td>
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<tr>
<td>102</td>
<td>3,4-dichloro-phenyl</td>
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<td>CH&lt;sub&gt;2&lt;/sub&gt;-(4-methoxy-phenyl)</td>
<td>N</td>
<td>-NH(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;-</td>
<td>-NHC(=NH)NH&lt;sub&gt;2&lt;/sub&gt;</td>
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<tr>
<td>103</td>
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<td>CH&lt;sub&gt;2&lt;/sub&gt;-(4-methoxy-phenyl)</td>
<td>N</td>
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<td>CH&lt;sub&gt;2&lt;/sub&gt;-(4-methoxy-phenyl)</td>
<td>N</td>
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<td>CH&lt;sub&gt;2&lt;/sub&gt;-(4-methoxy-phenyl)</td>
<td>N</td>
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<td>N</td>
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<td>-CH₂⁺(4-methoxy-phenyl)</td>
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<td>-NH(CH₃)₂⁺</td>
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<td>-NH(CH₃)₂⁺</td>
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<td>-NHC(=NH)N(Me) phenyl</td>
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<td>-CH₂⁺(4-methoxy-phenyl)</td>
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<td>-NH(CH₃)₂⁺</td>
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<td>-NHC(=NH)NH(4-fluoro-phenyl)</td>
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<td>-CH₂⁺(4-methoxy-phenyl)</td>
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<td>-CH₂⁺(4-amino-phenyl)</td>
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<td>-NH(CH₃)₂⁺</td>
<td>-NHC(=NH)NH₂</td>
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<td>-NH(C(=NH)NH)&lt;sub&gt;2&lt;/sub&gt;</td>
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<td>cyclopentyl</td>
<td>-CH&lt;sub&gt;2&lt;/sub&gt;-</td>
<td>-CH&lt;sub&gt;2&lt;/sub&gt;-(4-methoxy-phenyl)</td>
<td>N</td>
<td>-NH(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;-</td>
<td>-NH(C(=NH)NH)&lt;sub&gt;2&lt;/sub&gt;</td>
</tr>
<tr>
<td>125</td>
<td>4-amino-phenyl</td>
<td>-CH&lt;sub&gt;2&lt;/sub&gt;-</td>
<td>-CH&lt;sub&gt;2&lt;/sub&gt;-(4-methoxy-phenyl)</td>
<td>N</td>
<td>-NH(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;-</td>
<td>-NH(C(=NH)NH)&lt;sub&gt;2&lt;/sub&gt;</td>
</tr>
<tr>
<td>126</td>
<td>4-fluoro-phenyl</td>
<td>-CH&lt;sub&gt;2&lt;/sub&gt;-</td>
<td>-CH&lt;sub&gt;2&lt;/sub&gt;-(4-methoxy-phenyl)</td>
<td>N</td>
<td>-NH(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;-</td>
<td>-NH(C(=NH)NH)(adamantan-2-yl)</td>
</tr>
<tr>
<td>127</td>
<td>4-fluoro-phenyl</td>
<td>-CH&lt;sub&gt;2&lt;/sub&gt;-</td>
<td>-CH&lt;sub&gt;2&lt;/sub&gt;-(4-methoxy-phenyl)</td>
<td>N</td>
<td>-NH(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;-</td>
<td>-NH(C(=NH)NH)(4-trifluoromethoxy-phenyl)</td>
</tr>
<tr>
<td>128</td>
<td>4-fluoro-phenyl</td>
<td>-CH&lt;sub&gt;2&lt;/sub&gt;-</td>
<td>-CH&lt;sub&gt;2&lt;/sub&gt;-(4-methoxy-phenyl)</td>
<td>N</td>
<td>-NH(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;-</td>
<td>-NH(C(=NH)NH)(4-hydroxy-phenyl)</td>
</tr>
<tr>
<td>129</td>
<td>4-chloro-phenyl</td>
<td>-CH&lt;sub&gt;2&lt;/sub&gt;-</td>
<td>-CH&lt;sub&gt;2&lt;/sub&gt;-phenyl</td>
<td>N</td>
<td>-NH(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;-</td>
<td>-NH(C(=NH)NH)&lt;sub&gt;2&lt;/sub&gt;</td>
</tr>
<tr>
<td>130</td>
<td>4-chloro-phenyl</td>
<td>-CH&lt;sub&gt;2&lt;/sub&gt;-</td>
<td>-CH&lt;sub&gt;2&lt;/sub&gt;-furan-3-yl</td>
<td>N</td>
<td>-NH(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;-</td>
<td>-NH(C(=NH)NH)&lt;sub&gt;2&lt;/sub&gt;</td>
</tr>
<tr>
<td>131</td>
<td>4-fluoro-phenyl</td>
<td>-CH&lt;sub&gt;2&lt;/sub&gt;-</td>
<td>-CH&lt;sub&gt;2&lt;/sub&gt;-(4-methoxy-phenyl)</td>
<td>N</td>
<td>1,4-cyclohexyl</td>
<td>-NH(C(=NH)NH)&lt;sub&gt;2&lt;/sub&gt;</td>
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<tr>
<td>132</td>
<td>4-fluoro-phenyl</td>
<td>-CH&lt;sub&gt;2&lt;/sub&gt;-</td>
<td>-CH&lt;sub&gt;2&lt;/sub&gt;-(4-methoxy-phenyl)</td>
<td>N</td>
<td>-NHCH&lt;sub&gt;2&lt;/sub&gt;C(=O)-butyl</td>
<td>-NH(C(=NC(=O)O-t-butyln)&lt;sub&gt;2&lt;/sub&gt;</td>
</tr>
<tr>
<td>133</td>
<td>4-fluoro-phenyl</td>
<td>-CH&lt;sub&gt;2&lt;/sub&gt;-</td>
<td>-CH&lt;sub&gt;2&lt;/sub&gt;-(4-methoxy-phenyl)</td>
<td>N</td>
<td>-NH(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;-</td>
<td>-NH(C(=NH)NH)(2-methylthio-phenyl)</td>
</tr>
<tr>
<td>134</td>
<td>4-fluoro-phenyl</td>
<td>-CH&lt;sub&gt;2&lt;/sub&gt;-</td>
<td>-CH&lt;sub&gt;2&lt;/sub&gt;-(4-methoxy-phenyl)</td>
<td>N</td>
<td>-NH(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;-</td>
<td>-NH(C(=NH)NH)(C(=O)phenyl)</td>
</tr>
<tr>
<td>135</td>
<td>4-fluoro-phenyl</td>
<td>-CH&lt;sub&gt;2&lt;/sub&gt;-</td>
<td>-CH&lt;sub&gt;2&lt;/sub&gt;-(4-methoxy-phenyl)</td>
<td>N</td>
<td>-NH(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;-</td>
<td>-NH(C(=NH)NH)(pyrimidin-2-yl)</td>
</tr>
<tr>
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<td>L&lt;sub&gt;1&lt;/sub&gt;</td>
<td>D</td>
<td>W</td>
<td>L&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Q</td>
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</tr>
<tr>
<td>136</td>
<td>4-fluoro-phenyl</td>
<td>-CH&lt;sub&gt;2&lt;/sub&gt;-</td>
<td>-CH&lt;sub&gt;2&lt;/sub&gt;-(4-methoxy-phenyl)</td>
<td>N</td>
<td>-NH(((S)-CHMe)&lt;sub&gt;2&lt;/sub&gt;)</td>
<td>-NHC(=NH)NH&lt;sub&gt;2&lt;/sub&gt;</td>
</tr>
<tr>
<td>137</td>
<td>4-fluoro-phenyl</td>
<td>-CH&lt;sub&gt;2&lt;/sub&gt;-</td>
<td>-CH&lt;sub&gt;2&lt;/sub&gt;-(4-methoxy-phenyl)</td>
<td>N</td>
<td>-NH(((R)-CHMe)&lt;sub&gt;2&lt;/sub&gt;)</td>
<td>-NHC(=NH)NH&lt;sub&gt;2&lt;/sub&gt;</td>
</tr>
<tr>
<td>138</td>
<td>4-fluoro-phenyl</td>
<td>-CH&lt;sub&gt;2&lt;/sub&gt;-</td>
<td>-CH&lt;sub&gt;2&lt;/sub&gt;-(4-methoxy-phenyl)</td>
<td>N</td>
<td>-NH(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>-NHC(=NH)NH(4-trifluoromethyl-5,6,7,8-tetrahydro-quinazolin-2-yl)</td>
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<tr>
<td>139</td>
<td>4-fluoro-phenyl</td>
<td>-CH&lt;sub&gt;2&lt;/sub&gt;-</td>
<td>-CH&lt;sub&gt;2&lt;/sub&gt;-(4-methoxy-phenyl)</td>
<td>N</td>
<td>-NH(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>-NHC(=NH)NH(5-methyl-pyridin-2-yl)</td>
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<td>140</td>
<td>4-fluoro-phenyl</td>
<td>-CH&lt;sub&gt;2&lt;/sub&gt;-</td>
<td>-CH&lt;sub&gt;2&lt;/sub&gt;-(4-methoxy-phenyl)</td>
<td>N</td>
<td>-NH(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>-NHC(=NH)morpholin-4-yl</td>
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<td>141</td>
<td>4-chloro-phenyl</td>
<td>-CH&lt;sub&gt;2&lt;/sub&gt;-</td>
<td>-CH&lt;sub&gt;2&lt;/sub&gt;-furan-2-yl</td>
<td>N</td>
<td>-NH(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>-NHC(=NH)NH&lt;sub&gt;2&lt;/sub&gt;</td>
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<td>142</td>
<td>4-chloro-phenyl</td>
<td>-CH&lt;sub&gt;2&lt;/sub&gt;-</td>
<td>-CH&lt;sub&gt;2&lt;/sub&gt;-(4-methoxy-phenyl)</td>
<td>N</td>
<td>-NH(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>-NHC(=NH)NH&lt;sub&gt;2&lt;/sub&gt;</td>
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<td>143</td>
<td>4-methoxy-phenyl</td>
<td>-CH&lt;sub&gt;2&lt;/sub&gt;-</td>
<td>-CH&lt;sub&gt;2&lt;/sub&gt;-(4-hydroxy-phenyl)</td>
<td>N</td>
<td>-NH(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>-NHC(=NH)NH&lt;sub&gt;2&lt;/sub&gt;</td>
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<tr>
<td>144</td>
<td>4-chloro-phenyl</td>
<td>-CH&lt;sub&gt;2&lt;/sub&gt;-</td>
<td>-CH&lt;sub&gt;2&lt;/sub&gt;-(4-methoxy-phenyl)</td>
<td>N</td>
<td>-NH(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>-NHC(=NH)NH&lt;sub&gt;2&lt;/sub&gt;</td>
</tr>
<tr>
<td>145</td>
<td>4-methoxy-phenyl</td>
<td>-(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;-</td>
<td>-CH&lt;sub&gt;2&lt;/sub&gt;-(4-methoxy-phenyl)</td>
<td>N</td>
<td>-NH(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>-NHC(=NH)NH&lt;sub&gt;2&lt;/sub&gt;</td>
</tr>
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<td>146</td>
<td>4-methoxy-phenyl</td>
<td>-(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;3&lt;/sub&gt;-</td>
<td>-CH&lt;sub&gt;2&lt;/sub&gt;-(4-methoxy-phenyl)</td>
<td>N</td>
<td>-NH(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>-NHC(=NH)NH&lt;sub&gt;2&lt;/sub&gt;</td>
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<td>147</td>
<td>3,4-dichloro-phenyl</td>
<td>-CH&lt;sub&gt;2&lt;/sub&gt;-</td>
<td>-CH&lt;sub&gt;2&lt;/sub&gt;-(4-methoxycarbonyl-phenyl)</td>
<td>N</td>
<td>-NH(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>-NHC(=NH)NH&lt;sub&gt;2&lt;/sub&gt;</td>
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<td>148</td>
<td>phenyl</td>
<td>-CH&lt;sub&gt;2&lt;/sub&gt;-</td>
<td>-CH&lt;sub&gt;2&lt;/sub&gt;-(4-n-butoxy-phenyl)</td>
<td>N</td>
<td>-NH(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>-NHC(=NH)NH&lt;sub&gt;2&lt;/sub&gt;</td>
</tr>
<tr>
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<td>A₁</td>
<td>L₁</td>
<td>D</td>
<td>W</td>
<td>L₂</td>
<td>Q</td>
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<tr>
<td>149</td>
<td>4-chloro-phenyl</td>
<td>-CH₂⁻</td>
<td>-CH₂⁻-phenyl</td>
<td>N</td>
<td>-NH(CH₂)₂⁻</td>
<td>-NHC(=NH)NH₂</td>
</tr>
<tr>
<td>150</td>
<td>4-chloro-phenyl</td>
<td>-CH₂⁻</td>
<td>-CH₂⁻-furan-3-yl</td>
<td>N</td>
<td>-NH(CH₂)₂⁻</td>
<td>-NHC(=NH)NH₂</td>
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<tr>
<td>151</td>
<td>4-fluoro-phenyl</td>
<td>-CH₂⁻</td>
<td>-CH₂⁻-(4-methoxy-phenyl)</td>
<td>N</td>
<td>-NH(CH₂)₂⁻</td>
<td>-NHC(=NH)NCH(=O)methyl</td>
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<tr>
<td>152</td>
<td>4-fluoro-phenyl</td>
<td>-CH₂⁻</td>
<td>-CH₂⁻-(4-methoxy-phenyl)</td>
<td>N</td>
<td>-NH(CH₂)₂⁻</td>
<td>-NHC(=NH)NH(allyl)</td>
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<tr>
<td>153</td>
<td>4-fluoro-phenyl</td>
<td>-CH₂⁻</td>
<td>-CH₂⁻-(4-methoxy-phenyl)</td>
<td>N</td>
<td>-NH(CH₂)₂⁻</td>
<td>-NHC(=NH)NH(i-propyl)</td>
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<tr>
<td>154</td>
<td>4-fluoro-phenyl</td>
<td>-CH₂⁻</td>
<td>-CH₂⁻-(4-methoxy-phenyl)</td>
<td>N</td>
<td>-NH(CH₂)₂⁻</td>
<td>-NHC(=NH)NH(n-propyl)</td>
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<td>155</td>
<td>4-fluoro-phenyl</td>
<td>-CH₂⁻</td>
<td>-CH₂⁻-(4-methoxy-phenyl)</td>
<td>N</td>
<td>-NH(CH₂)₂⁻</td>
<td>-NHC(=NH)NH(ethyl)</td>
</tr>
<tr>
<td>156</td>
<td>4-fluoro-phenyl</td>
<td>-CH₂⁻</td>
<td>-CH₂⁻-(4-methoxy-phenyl)</td>
<td>N</td>
<td>-NH(CH₂)₂⁻</td>
<td>-NHC(=NH)NH(methyl)</td>
</tr>
<tr>
<td>157</td>
<td>4-methoxy-phenyl</td>
<td>-CH₂⁻</td>
<td>-CH₂⁻-(4-methoxy-phenyl)</td>
<td>CH</td>
<td>-C(=O)NH(CH₂)₂⁻</td>
<td>-NHC(=NH)NH₂</td>
</tr>
<tr>
<td>158</td>
<td>4-methoxy-phenyl</td>
<td>-CH₂⁻</td>
<td>-CH₂⁻-(4-methoxy-phenyl)</td>
<td>CH</td>
<td>-O(CH₂)₂⁻</td>
<td>-NHC(=NH)NH₂</td>
</tr>
<tr>
<td>159</td>
<td>4-methoxy-phenyl</td>
<td>-CH₂⁻</td>
<td>-CH₂⁻-(4-methoxy-phenyl)</td>
<td>CH</td>
<td>-S(CH₂)₂⁻</td>
<td>-NHC(=NH)NH₂</td>
</tr>
<tr>
<td>160</td>
<td>4-methoxy-phenyl</td>
<td>-CH₂⁻</td>
<td>-CH₂⁻-(4-methoxy-phenyl)</td>
<td>CH</td>
<td>-(CH₂)₂⁻</td>
<td>-NHC(=NH)NH₂</td>
</tr>
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</table>
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:

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
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<tbody>
<tr>
<td>Boc</td>
<td>tert-butoxycarbonyl</td>
</tr>
<tr>
<td>BuLi</td>
<td>n-butyllithium</td>
</tr>
<tr>
<td>Cpd or Cmpd</td>
<td>compound</td>
</tr>
<tr>
<td>d</td>
<td>day/ days</td>
</tr>
<tr>
<td>DCM</td>
<td>dichloromethane</td>
</tr>
<tr>
<td>DIAD</td>
<td>diisopropyl azodicarboxylate</td>
</tr>
<tr>
<td>DIPEA</td>
<td>diisopropylethylamine</td>
</tr>
<tr>
<td>or DIEA</td>
<td>diisopropylethylamine</td>
</tr>
</tbody>
</table>
DMEM = Dulbecco's Modified Eagle Medium
DMF = N,N-dimethylformamide
DMSO = dimethylsulfoxide
EDCI = 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
EtOAc = ethyl acetate
EtOH = ethanol
h = hour/hours
HBTU = O-Benzotriazol-1-yl-N,N',N''-tetramethyluronium hexafluorophosphate
LDA = lithium diisopropylamide
M = molar
MeCN = acetonitrile
MeOH = methanol
min = minutes
NaOMe = sodium methoxide
PyBOP = benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate
rt/RT = room temperature
THF = tetrahydrofuran
TFA = trifluoroacetic acid

GENERAL SCHEMES

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 L₂ is other than -\text{NHC}(=\text{O})-(\text{CH}_2)_{1-4}^\text{a}, -\text{C}(=\text{O})\text{NH}(\text{CR}^\text{b}R^\text{c})_{2-6}^\text{a}, and -X_2^\text{a}(\text{CH}_2)_{0-4}^\text{a}. In Scheme A, \( X_1 \) of L₂ 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 LG₁ is a leaving group, using conventional chemistry known to one versed in the art. For instance, when LG₁ 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, LG₁ may be a halide, tosylate, or the like such that LG₁ 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 X₁ is NH and m is zero) to provide a compound of formula A7. One versed in the art will recognize that when L₂ 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 LG₂ 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 L₂ is -NHC(=O)-(CH₂)₁⁻. 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 LG₃ 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 LG₁ as defined herein, or K is an Rⁿ-substituted amino group protected with an appropriate amino-
protecting group (PG).
To prepare a compound of formula B4, a compound of formula B3 may either be N-deprotected (when $K = -NR^a(PG)$) 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 L2 is a direct bond and L2 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 D illustrates the general synthesis of compounds of the present invention wherein W is C(R<sub>W</sub>), L<sub>2</sub> is other than -NHC(=O)-(CH<sub>2</sub>)<sub>1-4</sub> or -C(=O)NH(CR'<sub>2</sub>R''<sub>2</sub>)<sub>2-5</sub>, and X<sub>1</sub> of L<sub>2</sub> is NH, O, or S. A compound of formula D1 may be condensed with a compound of formula D2 with heating, (wherein LG<sub>2</sub> is C<sub>1-4</sub>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<sub>5</sub>, 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<sub>2</sub> 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<sub>1</sub> 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 E illustrates the general synthesis of compounds of the present
evention wherein W is C(Rw) and L₂ is -NHC(=O)-(CH₂)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 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 an urea of formula F4 to form a cyclic compound of formula F5.

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 $G$-substituent 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 L₂ is \(-X_2-(CH₂)_n-4\). 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.
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 L₂ includes an alkenyl group, X₂. 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 L₂ is "-X₂-(CH₂)₃-". 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 -L₁A₁ 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 L₂ is "-X₂-(CH₂)₃-".
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 L₂ of Formula (I) is one which contains an X₁ group, and W is N. In Scheme I, X₁ is S.

Scheme I
A compound of formula 11 (either commercially available or prepared by known methods described in the scientific literature) may be alkylated under basic conditions with a compound of formula 12 (wherein \( Q_1 \) is \( -(\text{CH}_2)_u\text{-X}_2\text{-(CH}_2)_v \text{-} \)), \( -(\text{CH}_2)_{2-3}\text{-X}_3\text{-(CH}_2)_{2-3} \text{-} \), or \( -\text{CH}(R^\gamma)-(\text{CR}^\gamma\text{R'}^\gamma)_1\text{-} \)) to provide a compound of formula 13. A compound of formula 13 may be condensed with an appropriately substituted isocyanate such as \( N\text{-chlorocarbonyl isocyanate} \) in the presence of excess tertiary amine such as diisopropylethylamine to give a triazine of formula 14. A compound of formula 14 may be alkylated with a compound of formula A4 to provide a compound of formula 15, which may then be guanylated according the methods described herein to provide a compound of formula (I)-1.

Scheme J illustrates the general synthesis of compounds of the present invention wherein \( L_2 \) is \(-\text{C(=O)NH}(\text{CR}^\gamma\text{R'}^\gamma)_{2-5}\text{-} \) 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 $-\text{C}(=\text{O})\text{NH}(\text{CR}^3\text{R}^2_{2-5})$ and $W$ is $\text{CH}$.

A compound of formula $\text{H}_4$ may be treated under Mitsunobu-type coupling conditions (in the presence of a coupling agent and activating agent), with an alcohol of formula $\text{J}_2$ to afford a compound of formula $\text{K}_1$. Oxidation of the aldehyde group using an appropriate oxidizing agent gives a compound of formula $\text{K}_2$, wherein the corresponding carboxylic acid may be coupled with an amine of formula $\text{J}_5$ (PG is an appropriate amino protecting group) to afford a compound of formula $\text{K}_3$. The conventional removal of the amino protecting group, PG, yields the primary amine of formula $\text{K}_4$, 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-1H-[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-1H-[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)-1H-[1,3,5]triazine-2,4-dione (Cpd 1e). To 1-(4-methoxy-benzyl)-6-methylsulfanyl-1H-[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 1H-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, $J = 7.5$Hz), 2.41-2.47 (2H, q, $J = 7.4$Hz), 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)carbonylcarbamimidothioic acid methyl ester (Cpd 2a). S-methylisothiouronium sulfate (10.0 g, 35.9 mmol) was dissolved in 8:2:1 MeOH/ H₂O/ 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 NH₄Cl and extracted with dichloromethane. The combined organic phases were dried over Na₂SO₄, 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 NH₄Cl and extracted with dichloromethane. The combined organic phases were dried over Na₂SO₄, 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-1H-[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-1H-[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), triphenylphosphine (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, δ). 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-2H-[1,3,5]triazin-1-ylmethyl]-benzamide (Cpd 2d). Compound 2c (dichlorobenzyl) (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 NH₄Cl and extracted with ethyl acetate. The combined organic extracts were dried over Na₂SO₄, 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 Na₂SO₄, 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, δ) 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, 26, 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-2H-[1,3,5]triazin-1-yl-methyl]-benzamide δ (DMSO, δ) 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)*

![Reaction Scheme](image)
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. \(^1\text{H NMR (DMSO, } \delta)\). 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. \(^1\text{H NMR (MeOD, } \delta)\). δ 5.04 (s, 2H), 5.87 (s, 1H), 7.25 – 7.38 (m, 5H).
C. 1-(4-Methoxybenzyl)-6-chloro-3-benzyl uracil (Cpd 3c). A stirred solution of Cpd 3b (60 mg, 0.25 mmol) in THF was treated with 4-methoxybenzyl alcohol (35 mg, 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 Na₂SO₄, 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 Na₂SO₄, 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-tetrahydropyrimidin-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. 1H NMR (MeOD, d₄). 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, 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)*

![Chemical structure](image)

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-ylamino]-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. \( ^1 \text{H} \) NMR (methanol-\( d_4 \)): \( \delta \) 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. \( ^1 \text{H} \) NMR (methanol-\( d_4 \)): \( \delta \) 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. \( ^1 \text{H} \) NMR
(methanol-$d_4$): $\delta$ 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-$d_6$): $\delta$ 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-$d_4$): $\delta$ 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-$d_4$): $\delta$ 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)

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-1H-[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 Cs₂CO₃ (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 Cs₂CO₃ (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 CH₃CN. 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 (d₆-DMSO/CDCl₃) 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 C₂₁H₂₈N₇O₄ 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-2H-[1,3,5]triazin-1-ylmethyl]-benzoic acid (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-2H-[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$_2$O 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)

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$_3$CN. 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). $^1$H NMR (DMSO-$d_6$) δ 1.25-1.28 (m, 1H), 3.28-3.31 (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)-1H-[1,3,5]triazine-2,4-dione (Cpd 9a). Compound 1c (200 mg, 0.73 mmol) was dissolved in CH$_2$CN and was treated with 4-nitrobenzyl bromide (168 mg, 0.86 mmol) and 80 \mu L (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)-1H-[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 \mu L, 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. \(N\text{-}[2\text{-}[1\text{-}(4\text{-Methoxy\text{-}benzyl})\text{-}5\text{-}(4\text{-nitro\text{-}benzyl})\text{-}4,6\text{-dioxo\text{-}1,4,5,6\text{-}}\text{tetrahydro\text{-}1,3,5\text{-}triazin\text{-}2\text{-}yamino\text{-}ethyl\text{-}guanidine (Cpd 95). A mixture of}
\)
\(8b\) (51 mg, 0.12 mmol), \(1H\text{-pyrazole\text{-}1\text{-carboxamidine hydrochloride (18 mg, 0.12 mmol), and diisopropylethylamine (26 \(\mu\text{L, 0.36 mmol) in 10 mL of}}\)
\(\text{acetonitrile was allowed to stir at room temperature for several days. The resulting}
\)
\(\text{mixture was concentrated and purified by liquid chromatography. The title}
\)
\(\text{compound 95 was obtained as a white powder (17 mg, 0.036 mmol) and was}
\)
\(\text{submitted as a TFA salt.}^{1}H\text{ NMR (DMSO-}\text{d}_{\text{6}}\text{) }\delta 3.65-3.71 \text{ (m, 4H), 3.85 (s, 3H), 5.30}
\)
\(\text{ (bm, 4H), 6.99-7.02 (m, 2H), 7.26-7.30 (m, 2H), 7.54-7.60 (m, 2H), 8.02-8.20 (bs,}
\)
\(\text{1H), 8.25 (m, 2H).}
\)
\(\text{Using the procedures of Example 8 and the appropriate reagents, starting}
\)
\(\text{materials and purification methods known to those skilled in the art, the following}
\)
\(\text{compounds of the present invention were prepared: compounds 42, 43, 47, 55, 56,}
\)
\(59, 94, 97, 98, 99, 100, 102, \text{and 113.}
\)

\text{EXAMPLE 9}

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

\(\text{A mixture of the crude Compound 95 (39 mg, 0.083 mmol) and tin (II) chloride}
\)
\(\text{dihydrate (94 mg, 0.42 mmol) in 20 mL of EtOH was heated to reflux for 24 h. The}
\)
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-$d_6$) $\delta$ 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)-1H-[1,3,5]triazine-2,4-dione (Cpd 60)

\[
\text{H}_2\text{N} - \text{N} - \text{NH}_2 \\text{toluene, 110°C}
\]

\[
\text{Cl} - \text{C} - \text{O} - \text{N} - \text{N} - \text{S} - \text{Cl} \\text{O} - \text{C} - \text{N} - \text{N} - \text{N} - \text{NH}_2 \\text{CNBr} - \text{benzene}
\]

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)-1H-[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 mmol) 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)-1H-[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-$d_6$) $\delta$ 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), 7.24 (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, d4). 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; 1H NMR (DMSO, 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 NH₄OH (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 C₂₂H₂₅Cl₂N₃O₃ 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)-4H-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]-1H-[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_{2}N_{7}O_{4} m/z 532.1267 (M+H), found: 532.1257.

**EXAMPLE 15**

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

![Chemical structure of 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_{2}N_{7}O_{3} m/z 518.1474 (M+H), found: 518.1479.
EXAMPLE 16

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

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\(_3\)) \(\delta\) 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, \(J = 8.7\) Hz), 6.90-7.03 (2H, m), 7.16 (2H, d, \(J = 8.7\) Hz), 7.48-7.36 (2H, m). HRMS calcd. for C\(_{21}\)H\(_{26}\)FN\(_8\)O\(_3\) m/z 457.2112 (M+H), found: 457.2101.

EXAMPLE 17

\[ N\{2-[5-(4-fluoro-benzyl)-1-(4-methoxy-benzyl)-4,6-dioxo-1,4,5,6-tetrahydro-[1,3,5]triazin-2-ylamino]-acetyl\}-N'-boc-guanidine \text{ (Cpd 132)} \]
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_{25}FN_{4}O_{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, 0.091 mmol) 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_{2}SO_{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$_3$N) to EtOAc (with 0.1% Et$_3$N) to give the title compound 132 (85% pure by HPLC, 0.0263 g). $^1$H NMR (CDCl$_3$) $\delta$ 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$_7$O$_6$ 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 H₂O (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 H₂O and dried. The solid was crystallized from EtOAc, providing compound 18b. ¹H NMR (DMSO-d₆) 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), PPh₃ (4.00 g) were dissolved in dry THF (25 mL) under an atmosphere of N₂. 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. ¹H NMR (CDCl₃) 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 NaHCO₃. 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 MgSO₄, filtered and evaporated, providing compound 18d as white solid (10.1 g, 65% yield). ¹H NMR (CDCl₃) 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 Et₃N (2 mL). Pd(PPh₃)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 N₂ 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 (CDCl₃) 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 (CDCl₃) 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 1H-pyrazole-1-carboxamide 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$_3$CN) $\delta$ 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)

![Chemical Reaction Diagram]

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. 1H NMR (methanol-d4). 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-dioso-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), benzyltriethylammonium 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. 1H NMR (DMSO, d6). 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. 1H NMR (methanol-d4). 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, 0.05 mmol), 1H-pyrazole-1-carboxamidine HCl (8.7 mg, 0.06 mmol), and DIEA (16.5 μL, 0.15 mmol) in acetonitrile (5 mL) was allowed to stir at rt overnight. The mixture was concentrated and purified by reverse phase chromatography to obtain the title compound 158 as a white solid. M+ (ES+) = 453.9. 1H NMR (DMSO, d6). δ 3.57 (t, 2H, J = 4.7, 5.2 Hz), 3.71 (s, 3H), 3.72 (s, 3H), 4.20 (t, 2H, J = 4.9, 4.6 Hz), 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, 5.6 Hz).

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 benzyltriethylammonium 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. ¹H NMR (methanol-d₄). 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), 1H-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. ¹H NMR (DMSO, d₆). 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 PPh₃ (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 MgSO₄, filtered and evaporated, providing compound 21c as white solid. M+ (ES+) = 453.3. ¹H NMR (CDCl₃). 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. 'H NMR (DMSO, 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-MRGATRVSIMLLLLVTVSDCDYKDDDKAVITGACERDQGAGTCCASLWLRGLRMCTPLGREGEECHPGSHKVPFFRKHKHTCPCLPNLLCSRFDPGDGYRCMSDLK 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, 20 mM 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 4 units/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:
AVITGACRDVQCAGTCCAISSLWRGLRMCTPLGREGEECHPGSHKVFP
FRKRKHHTCPCLPNLLCSRFPDGRYRCMSDLKNINF
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

```
AVITGACERDVQCGAGTCCAISLWRGLRMCTPLGREGEECHPGSHKVPF
FRKRKHHTCPCLPNLLCSRFPGDRYRCMDLK
```

Calculated Avg. Molecular Mass= 9178.8.

No other related proteaceous 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% CO₂. 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/ Ca²⁺ and Mg²⁺ 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% CO₂ 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 EC₅₀ 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 IC₅₀ 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. IC₅₀ 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**
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* 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 LLLLLPLLLTPRAGDADYKDDDDKAVI TGACDKDSQC GGGMCCAVSI WVKSIRICTPMGKLGDSCP LTRKVPFFGRMMHHTCPCLPGLACLRTSFNRFICLAQK) 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):

\[
\begin{align*}
&\text{L}_1\text{N} - \text{W} - \text{L}_2\text{Q} \\
&\text{A}_1
\end{align*}
\]

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, di\((C_{1-6}\)alkyl)aminocarbonyl, \(C_{1-6}\)alkylaminocarbonyl, \(C_{1-6}\)alkoxycarbonylamino, \(C_{1-6}\)alkylcarbonyl, \(C_{1-6}\)alkylthiocarbonyl, formyl, \(C_{1-6}\)alkylsulfonyl, \(C_{1-6}\)alkylsulfonylamino, aminosulfonyl, \(C_{1-6}\)alkylaminosulfonyle, and di\((C_{1-6}\)alkyl)aminosulfonyle;
- \(L_1\) is \(=\)\((CH_2)_r\) – or \(-\)CH\(_2\)CH\(_2\)X(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;
- \(s\) is an integer of 1 to 3;
- \(X\) is O or S;
D is $-\text{P-A}_2$; wherein when $\text{A}_2$ is hydrogen, $\text{P}$ is $-(\text{CH}_2)_4$ or $-(\text{CH}_2)_1 \text{H}$, and when $\text{A}_2$ is other than hydrogen, $\text{P}$ is $-(\text{CH}_2)_1 \text{H}$ or $-\text{CH}_2 \text{CH}=$; $\text{A}_2$ is hydrogen; benzodioxalyl; heteroaryl other than unsubstituted pyridin-2-yl; $\text{C}_3$-cycloalkyl; or phenyl optionally substituted at the meta and para positions with one to three substituents independently selected from the group consisting of $\text{C}_1$-alkyl, $\text{C}_1$-alkoxy, halogen, halogenated $\text{C}_1$-alkyl, halogenated $\text{C}_1$-alkoxy, aryl($\text{C}_1$-$\text{C}_6$)-alkoxy, phenyl, $\text{C}_1$-alkylthio, $\text{C}_1$-alkoxycarbonyl, amino, $\text{C}_1$-alkylamino, di($\text{C}_1$-alkyl)amino, cyano, hydroxy, nitro, $\text{C}_1$-alkylcarbonyl, $\text{C}_1$-alkylthiocarbonyl, aminocarbonyl, $\text{C}_1$-alkylaminocarbonyl, di($\text{C}_1$-alkyl)aminocarbonyl, $\text{C}_1$-alkylcarbonylamino, and a non fused $\text{C}_3$-cycloalkoxy; wherein benzodioxalyl, heteroaryl, and $\text{C}_3$-cycloalkyl are optionally substituted with one to three substituents independently selected from the group consisting of $\text{C}_1$-alkyl, $\text{C}_1$-alkoxy, halogen, halogenated $\text{C}_1$-alkyl, halogenated $\text{C}_1$-alkoxy, aryl($\text{C}_1$-$\text{C}_6$)-alkoxy, phenyl, $\text{C}_1$-alkylthio, $\text{C}_1$-alkoxycarbonyl, amino, $\text{C}_1$-alkylamino, di($\text{C}_1$-alkyl)amino, cyano, hydroxy, nitro, $\text{C}_1$-alkylcarbonyl, $\text{C}_1$-alkylthiocarbonyl, aminocarbonyl, $\text{C}_1$-alkylaminocarbonyl, di($\text{C}_1$-alkyl)aminocarbonyl, $\text{C}_1$-alkylcarbonylamino, and a non fused $\text{C}_3$-cycloalkoxy;

provided that no more than two substituents on $\text{A}_2$ are aryl($\text{C}_1$-$\text{C}_6$)-alkoxy, phenyl, or a non fused $\text{C}_3$-cycloalkoxy;

provided that when $\text{A}_1$ is unsubstituted phenyl and $\text{L}_2$ is $-\text{X}_1\text{CH}(\text{R}^\text{a})(\text{CR}^\text{b} \text{R}^\text{c})$- wherein $\text{X}_1$ is NH, and $\text{R}^\text{a}$, $\text{R}^\text{b}$, and $\text{R}^\text{c}$ are each hydrogen, $\text{A}_2$ is other than unsubstituted phenyl; phenyl substituted with aryl($\text{C}_1$-$\text{C}_6$)-alkoxy or phenyl; or phenyl substituted at the meta position with cyano;

and, further provided that when $\text{A}_1$ is unsubstituted phenyl and $\text{L}_2$ is $-\text{X}_1\text{CH}(\text{R}^\text{a})(\text{CR}^\text{b} \text{R}^\text{c})_2$- wherein $\text{X}_1$ is NH and $\text{R}^\text{a}$, $\text{R}^\text{b}$, and $\text{R}^\text{c}$ are each hydrogen, $\text{A}_2$ is other than phenyl substituted with methoxy;
and, provided that when \( A_1 \) is 3,4-dichloro-phenyl and \( P \) is \(-\text{CH}_2\), \( A_2 \) 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 \(-\text{(CH}_2\text{)}_2\text{-}\), \( A_2 \) 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 \(-\text{(CH}_2\text{)}_{0-2}\text{-}\);

\(-\text{NH-C}_5\text{-cycloalkyl-}-(\text{CH}_2\text{)}_{0-2}\text{-}\); provided that when \( C_5\text{-cycloalkyl \ is cyclohexyl,} \)
\( \text{O} \) is attached at either the 2- or cis-4-position relative to the position of \(-\text{NH-}\);

\(-\text{X}_1\text{-C}_2\text{-alkyl-}\);

\(-\text{X}_1\text{-}(\text{CH}_2\text{)}_{u}\text{-X}_2\text{-}(\text{CH}_2\text{)}_{v}\text{-}\); 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;

\(-\text{X}_2\text{-}(\text{CH}_2\text{)}_{0-4}\text{-}\);

\(-\text{X}_1\text{-}(\text{CH}_2\text{)}_{2-3}\text{-X}_3\text{-}(\text{CH}_2\text{)}_{2-3}\text{-}\);

\(-\text{NH}(\text{CH}_2\text{)}_{1-4}\text{-C(=O)-}\); provided that at least one of \( R^b \), \( R^c \), or \( R^d \) is other than hydrogen and \( m \) is 0;

\(-\text{NHC(=O)}-(\text{CH}_2\text{)}_{1-4}\text{-}\);

\(-\text{C(=O)NH(CR}^b\text{R}^3\text{)}_{2-5}\text{-}\);

and

\(-\text{X}_1\text{-CH}(R^4)\text{-}(\text{CR}^b\text{R}^3)_{1-5}\text{-}\); such that when \( X_1 \) is a direct bond and \( W \) is C(R\( W \)), then \( R^5 \) is hydrogen;

wherein \( X_1 \) is \(-\text{NH-}, \text{O, S, or a direct bond, such that X} \)
\( \text{is other than O when} \)
\( W \) is N;

\( X_2 \) is \(-\text{CH=CH-}\);
\(X_3\) is O, S, NH, or C=O;
\(R^k, R^l, \) and \(R^2\) are independently H or C-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 \(-C(=O)NH(CR^2R^6)_{2-5}-\),
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-alkyl, C-alkenyl, or C-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-alkoxy, fluoro, amino, C-alkylamino,
diC-alkylamino, and C-alkylcarbonyl; or \(R^a\) and \(R^d\) 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-alkyl, C-alkenyl, C-alkynyl, C-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-alkyl, C-alkenyl, C-alkynyl, C-cycloalkyl,
adamantyl, amino, C-alkylamino, di(C-alkyl)amino, C-alkylcarbonyl,
C-alkoxycarbonyl, arylcarbonyl, heteroarylcarbonyl, heterocyclylcarbonyl,
aryl, heteroaryl, or heterocycl; wherein C-alkyl, C-alkenyl, and C-alkynyl are optionally substituted with one to three substituents
independently selected from the group consisting of hydroxy, C-alkoxy,
trifluoromethyl, aryl, heteroaryl, and heterocycl; and wherein any aryl- or
eheteroaryl-containing substituents of \(R^c\) are optionally substituted with one
to three substituents independently selected from the group consisting of
C-alkyl, C-alkoxy, halogen, fluorinated C-alkyl, fluorinated C-alkoxy,
C-alkylcarbonyl, C-alkoxycarbonyl, aminocarbonyl, C-alkyl.
alkylaminocarbonyl, di(C₁₆alkyl)aminocarbonyl, C₁₆alkoxy carbonylamino, formyl, C₁₆alkylsulfonyl, C₁₆alkylsulfonylamino, aminosulfonyl, C₁₆alkylaminosulfonyl, and di(C₁₆alkyl)aminosulfonyl, nitro, methylthio, hydroxy, and cyano; or, R² and R³ 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 R⁷ and R⁸, R⁹ and R¹⁰, or R¹¹ and R¹².

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 A₁ is phenyl, L is -CH₂-, D is -CH₂-(4-methoxy-phenyl), W is N, L₂ is -NH(CH₂)₂-, and Q is -NHC(=NH)NH₂.

3. The compound according to claim 1 wherein A₁ is hydrogen; aryl; heteroaryl; or C₆₋₅cycloalkyl; wherein substituents of A₁ other than hydrogen are optionally substituted with one to three substituents independently selected from the group consisting of C₁₆alkyl, hydroxy(C₁₆alkyl), C₁₆alkoxy, halogen, nitro, halogenated C₁₆alkyl, halogenated C₁₆alkoxy, C₁₆alkylthio, C₁₆alkoxy carbonyl, amino, C₁₆alkylamino, di(C₁₆alkyl)amino, cyano, hydroxy, aminocarbonyl, C₁₆alkylaminocarbonyl, di(C₁₆alkyl)aminocarbonyl, C₁₆alkoxycarbonylamino, C₁₆alkylicarbonyl, C₁₆alkylthiocarbonyl, formyl, C₁₆alkylsulfonyl, C₁₆alkylsulfonylamino, aminosulfonyl, C₁₆alkylaminosulfonyl, and di(C₁₆alkyl)aminosulfonyl.
4. The compound according to claim 1 wherein $A_1$ is hydrogen; aryl; heteroaryl; 
$C_{5-6}$cycloalkyl; or heterocycl; 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; 
$C_{5-6}$cycloalkyl; or heterocycl 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 $C_{1-6}$alkyl, $C_{1-6}$alkoxy, halogen, nitro, halogenated $C_{1-6}$alkyl, 
halogenated $C_{1-6}$alkoxy, methylthio, $C_{1-6}$alkoxycarbonyl, amino, cyano, 
hydroxy, aminocarbonyl, and $C_{1-6}$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 C₁-
₄alkyl, C₁₋₄alkoxy, halogen, nitro, halogenated C₁₋₄alkyl, halogenated C₁-
₄alkoxy, methylthio, amino, cyano, and C₁₋₄alkylcarbonyl.

8. The compound according to claim 1 wherein A₁ 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 L₁ is –(CH₂)ᵣ–, optionally
substituted with one to three substituents independently selected from the
group consisting of C₁₋₄alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, and halogen; provided
that when A₁ is hydrogen, r is greater than or equal to 4.

10. The compound according to claim 1 wherein L₁ is –(CH₂)ᵣ–, optionally
substituted with a substituent selected from the group consisting of C₁₋₄alkyl,
C₂₋₆alkenyl, and C₂₋₆alkynyl; provided that r is 1 to 3 when A₁ is other than
hydrogen; or r is greater than or equal to 4 when A₁ is hydrogen.

11. The compound according to claim 1 wherein L₁ is –(CH₂)ᵣ– optionally
substituted with a substituent selected from the group consisting of methyl
and allyl; provided that r is 1 to 3 when A₁ is other than hydrogen.

12. The compound according to claim 1 wherein L₁ is –CH₂– optionally substituted
with methyl or allyl.

13. The compound according to claim 1 wherein A₂ is hydrogen, heteroaryl other
than unsubstituted pyridin-2-yl, C₃₋₆cycloalkyl, or phenyl optionally substituted
at the meta and para positions with one to three substituents independently
selected from the group consisting of C₁₋₆-alkyl, C₁₋₆-alkoxy, halogen, halogenated C₁₋₆-alkyl, halogenated C₁₋₆-alkoxy, aryl(C₁₋₆)alkoxy, phenyl, C₁₋₆-alkythio, C₁₋₆-alkoxycarbonyl, amino, cyano, hydroxy, nitro, aminocarbonyl, C₁₋₆-alkylcarbonylamino, and a non fused C₃₋₆-cycloalkyloxy; wherein heteroaryl other than unsubstituted pyridin-2-yl and C₃₋₆-cycloalkyl are optionally substituted with one to three substituents independently selected from the group consisting of C₁₋₆-alkyl, C₁₋₆-alkoxy, halogen, halogenated C₁₋₆-alkyl, halogenated C₁₋₆-alkoxy, aryl(C₁₋₆)alkoxy, phenyl, C₁₋₆-alkythio, C₁₋₆-alkoxycarbonyl, amino, cyano, hydroxy, nitro, aminocarbonyl, C₁₋₆-alkylcarbonylamino, and a non fused C₃₋₆-cycloalkyloxy; provided that no more than two substituents on A₂ are aryl(C₁₋₆)alkoxy, phenyl, or a non fused C₃₋₆-cycloalkyloxy; provided that when A₁ is unsubstituted phenyl and L₂ is -X₁-CH(R¹)-(CR²R³)₂- wherein X₁ is NH and R¹, R², and R³ are each hydrogen, A₂ is other than unsubstituted phenyl; phenyl substituted with aryl(C₁₋₆)alkoxy or phenyl; or phenyl substituted at the meta position with cyano; and, further provided that when A₁ is unsubstituted phenyl and L₂ is -X₁-CH(R¹)-(CR²R³)₂- wherein X₁ is NH and R¹, R², and R³ are each hydrogen, A₂ is other than phenyl substituted with methoxy; and, provided that when A₁ is 3,4-dichloro-phenyl and P is -CH₂-, A₂ is other than phenyl substituted at the meta position with trifluoromethyl or trifluoromethoxy and, further provided that when A₁ is 3,4-dichloro-phenyl and P is −(CH₂)₂−, A₂ is other than 4-methoxy-phenyl; and in addition, when A₂ is hydrogen, P is -(CH₂)₄₋₆−, and when A₂ is other than hydrogen, P is -(CH₂)₁₋₂− or −CH₂CH=CH−. The compound according to claim 1 wherein A₂ is is a heteroaryl other than unsubstituted pyridin-2-yl, a non fused C₃₋₆-cycloalkyl, or phenyl optionally
substituted at the meta and para positions with one to three substituents independently selected from the group consisting of C₁₋₆alkyl, C₁₋₆alkoxy, halogen, halogenated C₁₋₆alkyl, halogenated C₁₋₆alkoxy, C₁₋₆alkylthio, C₁₋₆alkoxycarbonyl, amino, hydroxy, nitro, aminocarbonyl, C₁₋₆alkylcarbonylamino, and a non fused C₃₋₆cycloalkoxy; wherein heteroaryl other than unsubstituted pyridin-2-yl and a non fused C₈cycloalkyl are optionally substituted with one to three substituents independently selected from the group consisting of C₁₋₆alkyl, C₁₋₆alkoxy, halogen, halogenated C₁₋₆alkyl, halogenated C₁₋₆alkoxy, C₁₋₆alkylthio, C₁₋₆alkoxycarbonyl, amino, hydroxy, nitro, aminocarbonyl, C₁₋₆alkylcarbonylamino, and a non fused C₃₋₆cycloalkoxy; provided that no more than two substituents on A₂ are non fused C₃₋₆cycloalkoxy; provided that when A₁ is unsubstituted phenyl and L₂ is -X₁-CH(R¹)_(N)·-(CR³R⁴)_2· wherein X₁ is NH and R¹, R³, and R⁴ are each hydrogen, A₂ is other than unsubstituted phenyl; and, further provided that when A₁ is unsubstituted phenyl and L₂ is -X₁-CH(R¹)_(N)·-(CR³R⁴)_2· wherein X₁ is NH and R¹, R³, and R⁴ are each hydrogen, A₂ is other than phenyl substituted with methoxy; and, provided that when A₁ is 3,4-dichloro-phenyl, A₂ is other than phenyl substituted at the meta position with trifluoromethyl or trifluoromethoxy; and, further provided that when A₁ is 3,4-dichloro-phenyl and P is -(CH₂)_2-, A₂ is other than 4-methoxy-phenyl.

The compound according to claim 1 wherein A₂ 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 C₁₋₄alkyl, C₁₋₄alkoxy, halogen, halogenated C₁₋₄alkoxy, C₁₋₄alkylthio, hydroxy, amino, aminocarbonyl, C₁₋₄alkylcarbonylamino, and a non fused C₃₋₆cycloalkoxy;
cycloalkylxy; 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 C1-alkyl, C1-alkoxy, halogen, halogenated C1-alkoxy, C1-alkylthio, hydroxy, amino, aminocarbonyl, C1-alkylcarboxylamino, and a non fused C3-6cycloalkylxy; provided that no more than two substituents on A2 are non fused C3-6cycloalkylxy;
provided that when A1 is unsubstituted phenyl and L2 is -X1-CH(R’)-(CR’R’)- wherein X1 is NH and R’, R”, and R” are each hydrogen, A2 is other than unsubstituted phenyl;
and, further provided that when A1 is unsubstituted phenyl and L2 is -X1-CH(R’)-(CR’R’)- wherein X1 is NH and R’, R”, and R” are each hydrogen, A2 is other than phenyl substituted with methoxy;
and, provided that when A1 is 3,4-dichloro-phenyl, A2 is other than phenyl substituted in the meta position with trifluoromethoxy.

16. The compound according to claim 1 wherein A2 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, isopropylxy, trifluoromethoxy, difluoromethoxy, hydroxy, aminocarbonyl, and methylcarboxylamino; 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, isopropylxy, trifluoromethoxy, difluoromethoxy, hydroxy, aminocarbonyl, and methylcarboxylamino;
provided that when A1 is unsubstituted phenyl and L2 is -X1-CH(R’)-(CR’R’)- wherein X1 is NH and R’, R”, and R” are each hydrogen, A2 is other than unsubstituted phenyl;
and, further provided that when A1 is unsubstituted phenyl and L2 is
-X₁-CH(R¹⁺)-(CR⁴⁺R³)₂ - wherein X₁ is NH and R⁵, R⁶, and R² are each hydrogen, A₂ is other than phenyl substituted with methoxy; and, further provided that when A₁ is 3,4-dichloro-phenyl, A₂ is other than phenyl substituted at the meta position with trifluoromethoxy

17. The compound according to claim 1 wherein A₂ is phenyl substituted at the para position with a substituent selected from the group consisting of methoxy, ethoxy, isopropylxy, difluoromethoxy, hydroxy, and aminocarbonyl; or A₂ is pyridin-3-yl or pyridin-4-yl substituted with methoxy.

18. The compound according to claim 1 wherein P is –CH₂⁻.

19. The compound according to claim 1 wherein W is N or C(R₆) wherein R₆ is H.

20. The compound according to claim 1 wherein L₂ is a bivalent radical selected from the group consisting of
- NH-C₅₋₇ cycloalkyl-(CH₂)₀⁻²⁻; such that when C₅₋₇ cycloalkyl is cyclohexyl, Q is attached at either the 2- or cis-4-position relative to the position of –NH⁻;
- X₂⁻(CH₂)₀⁻⁴⁻;
- X₁⁻(CH₂)₂⁻³⁻ X₁⁻(CH₂)₂⁻³⁻;
- NH(CH₂)₁⁻⁴⁻ C(=O)⁻ provided that at least one of R⁵⁻, R⁶⁻, or R₇⁻ is other than hydrogen and m is 0;
- NH-C(=O)-(CH₂)₁⁻⁴⁻;
- C(=O)NH(CR⁴⁺R³)₂⁻⁶⁻;

and
- X₁⁻CH(R¹⁺)-(CR⁴⁺R³)₁⁻⁵⁻; such that when X₁ is a direct bond and W is C(R₆), then R⁵⁻ of CH(R⁶) 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$_1$-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.

10 21. The compound according to claim 1 wherein $L_2$ is a bivalent radical selected from the group consisting of -NH-C$_5$-cycloalkyl–($CH_2$)$_{0-2}$ - provided that when C$_5$-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.

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

$-X_1$-($R,R$-$CH(R^x)$)$CR^y(R^z)$ – 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\(^n\))(CR\(^z\)/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\(^n\))(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\(_{1-6}\)-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.
27. The compound according to claim 1 wherein R\textsuperscript{a} and R\textsuperscript{d} are independently hydrogen, methyl or ethyl; or R\textsuperscript{a} and R\textsuperscript{c} are taken together with the atoms to which they are attached to form a 5-8 membered monocyclic ring optionally substituted with oxo.

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

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

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

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31. The compound according to claim 1 wherein R\textsuperscript{b} is hydrogen.

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

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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, $C_{2-5}$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, $C_{2-5}$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 C₁₄-alkyl is optionally substituted with one to two substituents independently selected from the group consisting of C₁₃-alkoxy, phenyl, pyridinyl, furanyl, and tetrahydrofuranyl; and wherein any phenyl- or heteroaryl-containing substituents of R² are optionally substituted with one to two substituents independently selected from the group consisting of C₁₃-alkyl, C₁₃-alkoxy, chloro, fluoro, bromo, fluorinated C₁₃-alkoxy, nitro, methylthio, hydroxy, and cyano; or, R² and R³ 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 R⁶ is hydrogen, C₁₃-alkyl, C₂₄-alkenyl, cyclohexyl, phenylcarbonyl, phenyl, pyrimidinyl, furanyl, benzo[1,3]dioxolyl, or pyridinyl; wherein C₁₃-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 R² are optionally substituted with one to two substituents independently selected from the group consisting of C₁₃-alkyl, C₁₃-alkoxy, chloro, fluoro, bromo, trifluoromethoxy, nitro, hydroxy, and cyano; or, R² and R³ are taken together with the atoms to which they are attached to form a 5-6 membered monocyclic ring.

37. A compound of Formula (la):

![Formula (la)]

wherein:
$A_1$ is hydrogen; aryl; heteroaryl; $C_{5-8}$cycloalkyl; or heterocyclyl provided that $A_1$
5 is other than piperidin-4-yl, $N$-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 $C_1$-$C_4$alkyl, hydroxy($C_1$-$C_4$)alkyl, $C_1$
6alkoxy, halogen, nitro, halogenated $C_1$-$C_4$alkyl, halogenated $C_1$-$C_4$alkoxy, $C_1$
6alkylthio, $C_1$-$C_4$alkoxycarbonyl, amino, cyano, hydroxy, aminocarbonyl, $C_1$
6alkylaminocarbonyl, di($C_1$-$C_4$alkyl)aminocarbonyl, and $C_1$-$C_4$alkylocarbonyl;
$L_1$ is $-(CH_2)_r-$ optionally substituted with one to three substituents
10 independently selected from the group consisting of $C_1$-$C_4$alkyl, $C_2$-$C_5$alkenyl,
$C_2$-$C_5$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 $-CH_2CH=CH-$
15 when $A_2$ is other than hydrogen;
$A_2$ is hydrogen, heteroaryl other than unsubstituted pyridin-2-yl, $C_3$-$C_8$cycloalkyl,
or phenyl optionally substituted at the meta and para positions with one to
three substituents independently selected from the group consisting of $C_1$
6alkyl, $C_1$-$C_4$alkoxy, halogen, halogenated $C_1$-$C_4$alkyl, halogenated $C_1$-$C_4$alkoxy,
aryl($C_1$-$C_4$)alkoxy, phenyl, $C_1$-$C_4$alkylthio, $C_1$-$C_4$alkoxycarbonyl, amino, cyano,
hydroxy, nitro, aminocarbonyl, $C_1$-$C_4$alkylocarbonylamino, and a non fused
$C_3$-$C_8$cycloalkyloxy; wherein heteroaryl other than unsubstituted pyridin-2-yl
20 and $C_3$-$C_8$cycloalkyl are optionally substituted with one to three substituents
independently selected from the group consisting of $C_1$-$C_4$alkyl, $C_1$-$C_4$alkoxy,
halogen, halogenated $C_1$-$C_4$alkyl, halogenated $C_1$-$C_4$alkoxy, aryl($C_1$-$C_4$)alkoxy,
phenyl, $C_1$-$C_4$alkylthio, $C_1$-$C_4$alkoxycarbonyl, amino, cyano, hydroxy, nitro,
aminocarbonyl, $C_1$-$C_4$alkylocarbonylamino, and a non fused $C_3$
6cycloalkyloxy;
provided that no more than two substituents on A₂ are aryl(C₁₋₆)alkoxy, phenyl, or a non-fused C₃₋₆cycloalkyloxy; provided that when A₁ is unsubstituted phenyl and L₂ is \(-X₁-\text{CH}(R^3)\)-(CR²R¹²)- wherein X₁ is NH and R⁸, R⁹, and R¹² are each hydrogen, A₂ is other than unsubstituted phenyl; phenyl substituted with aryl(C₁₋₆)alkoxy or phenyl; or phenyl substituted at the meta position with cyano;

and, further provided that when A₁ is unsubstituted phenyl and L₂ is \(-X₁-\text{CH}(R^3)\)-(CR²R¹²)- wherein X₁ is NH and R⁸, R⁹, and R¹² are each hydrogen, A₂ is other than phenyl substituted with methoxy;

and, provided that when A₁ is 3,4-dichloro-phenyl and P is \(-\text{CH}_₂\), A₂ is other than phenyl substituted at the meta position with trifluoromethyl or trifluoromethoxy;

and, further provided that when A₁ is 3,4-dichloro-phenyl and P is \(-\text{CH}_₂\), A₂ is other than 4-methoxy-phenyl;

W is N or CH;

L₂ is a bivalent radical selected from the group consisting of

\(-\text{NH}-\text{C}_₅₋₇\text{cycloalkyl}-(\text{CH}_₂)₀₋₂-\); provided that when C₅₋₇cycloalkyl is cyclohexyl, Q is attached at either the 2- or cis-4-position relative to the position of \(-\text{NH}-\);

\(-X₂-(\text{CH}_₂)₀₋₄-\);

\(-X₁-(\text{CH}_₂)₂₋₃-X₃-(\text{CH}_₂)₂₋₃-\);

\(-\text{NH}(\text{CH}_₂)₁₋₄\text{C}(=\text{O})-\); provided that at least one of R⁸, R⁹, or R¹² is other than hydrogen and m is 0;

\(-\text{NH}(\text{C}(=\text{O}))-(\text{CH}_₂)₁₋₄-\);

\(-\text{C}(=\text{O})\text{NH}(\text{CR}³\text{R}⁷)₂₋₅-\);

and

\(-X₁-\text{CH}(R^³)\)-(CR²R¹²)-; such that when X₁ is a direct bond and W is C(R₆), then R⁸ of CH(R⁹) is hydrogen;
wherein $X_1$ is $-\text{NH}_2$, O, S, or a direct bond; such that $X_1$ is other than O
when W is N;
$X_2$ is $-\text{CH}=\text{CH}_2$;
$X_3$ is O, S, NH, or C=O;

5
$R^x$, $R^y$, 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 $-X_2-(\text{CH}_2)_{0-4}-$ or $-\text{C}(=\text{O})\text{NH}(\text{CR}^y\text{R}^z)_{2-5}-$,
then $R_w$ is hydrogen;

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$m$ is 0 or 1;
$G$ is $-\text{C}(=\text{NR}^b)\text{NR}^c\text{R}^d$;
$R^a$ 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, di$C_{1-4}$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;

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$R^b$ 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;

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$R^c$ 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

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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)](image)

wherein:

$A_1$ is hydrogen; aryl; heteroaryl; C$_6$-$\text{cycloalkyl}$; or heterocycl 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$_1$-$\text{alkyl}$, hydroxy(C$_1$-$\text{alkyl}$), C$_1$-$\text{alkoxy}$, halogen, nitro, halogenated C$_1$-$\text{alkyl}$, halogenated C$_1$-$\text{alkoxy}$, C$_1$-$\text{alkylthio}$, C$_1$-$\text{alkoxycarbonyl}$, amino, cyano, hydroxy, aminocarbonyl, C$_1$-$\text{alkylaminocarbonyl}$, di(C$_1$-$\text{alkyl}$)aminocarbonyl, and C$_1$-$\text{alkylcarbonyl}$;

$L_1$ is -(CH$_2$)$_r$ optionally substituted with a substituent selected from the group consisting of C$_1$-$\text{alkyl}$, C$_2$-$\text{alkenyl}$, and C$_2$-$\text{alkynyl}$; 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$_2$)$_r$;

$A_2$ is heteroaryl other than unsubstituted pyridin-2-yl, a non fused C$_8$-$\text{cycloalkyl}$, or phenyl optionally substituted at the meta and para positions with one to
three substituents independently selected from the group consisting of C₁-ealkyl, C₁,ealkoxy, halogen, halogenated C₁,ealkyl, halogenated C₁,ealkoxy, C₁-ealkythio, C₁,ealkoxycarbonyl, amino, hydroxy, nitro, aminocarbonyl, C₁-ealkylcarbonylamino, and a non fused C₃,e cycloalkyloxy; wherein heteroaryl other than unsubstituted pyridin-2-yl and a non fused C₃,e cycloalkyl are optionally substituted with one to three substituents independently selected from the group consisting of C₁-ealkyl, C₁,ealkoxy, halogen, halogenated C₁-ealkyl, halogenated C₁,ealkoxy, C₁,ealkythio, C₁,ealkoxycarbonyl, amino, hydroxy, nitro, aminocarbonyl, C₁,ealkylcarbonylamino, and a non fused C₃,e cycloalkyloxy;

provided that no more than two substituents on A₂ are non fused C₃,e cycloalkyloxy;

provided that when A₁ is unsubstituted phenyl and L₂ is -X₁-CH(R₁)(-CR₁R₂)-, wherein X₁ is -NH- or S and R₁, R', and R₂ are each hydrogen, A₂ is other than unsubstituted phenyl;

and, further provided that when A₁ is unsubstituted phenyl and L₂ is -X₁-CH(R₁)(-CR₁R₂)-, wherein X₁ is NH and R₁, R', and R₂ are each hydrogen, A₂ is other than phenyl substituted with methoxy;

and, further provided that when A₁ is 3,4-dichloro-phenyl, A₂ is other than phenyl substituted at the meta position with trifluoromethoxy;

W is N or CH;

L₂ is a bivalent radical selected from the group consisting of -NH-C₅,e cycloalkyl-(CH₂)₀-²⁻ ; provided that when C₅,e cycloalkyl is cyclohexyl, Q is attached at either the 2- or cis-4-position relative to the position of

- NH-;

-X₁-CH(R₁)(-CR₁R₂)-₁⁻, wherein X₁ is -NH-, O, or S; and R₁, R', and R₂ are each hydrogen; such that X₁ is other than O when W is N;

-C(=O)NH(CH₂)₂⁻;

and
-X₁-(R₁-R₂-CH(R³)CR⁴(R⁵))-; wherein X₁ is -NH-, and R⁴ and R⁵ are methyl, and
R⁴ is hydrogen;
provided that when L₂ is -C(=O)NH(CH₂)₂-, then R₇ is hydrogen;
and it is to be understood that when L₂ is -C(=O)NH(CH₂)₂-, then R₇ is hydrogen;
m is 0 or 1;
G is -C(=NR⁶)NR⁷R⁸;
R⁹ and R¹⁰ are independently hydrogen or C₁₋₃alkyl, wherein C₁₋₃alkyl is optionally
substituted with one to three substituents independently selected from the
the group consisting of hydroxy, C₁₋₃alkoxy, fluoro, amino, C₁₋₃alkylamino, diC₁₋₃alkylamino, and C₁₋₃alkylcarbonyl; or R⁹ and R¹⁰ are taken together with the
atoms to which they are attached to form a 5-8 membered monocyclic ring
optionally substituted with oxo;
R¹¹ is hydrogen or C₁₋₃alkyl; or, R¹¹ and R¹² are taken together with the atoms to
which they are attached to form a 5-8 membered monocyclic ring, optionally
substituted with oxo;
R¹³ is hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl, C₃₋₇cycloalkyl, adamantyl, heterocyclyl,
arylcarbonyl, phenyl, or heteroaryl; wherein C₁₋₆alkyl is optionally substituted
with one to two substituents independently selected from the group consisting
of C₁₋₃alkoxy, trifluoromethyl, phenyl, heteroaryl, and heterocyclyl; and
wherein any aryl-, phenyl-, or heteroaryl-containing substituents of R¹³ are
optionally substituted with one to three substituents independently selected
from the group consisting of C₁₋₆alkyl, C₁₋₆alkoxy, halogen, fluorinated C₁₋₆alkyl, fluorinated C₁₋₆alkoxy, C₁₋₆alkylcarbonyl, C₁₋₆alkoxycarbonyl, nitro,
methylthio, hydroxy, and cyano; or, R¹³ and R¹⁰ 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 R⁹
and R¹¹, R¹¹ and R¹², or R¹³ and R¹⁰;
and enantiomers, diastereomers, tautomers, solvates, and pharmaceutically acceptable salts thereof.

39. A compound of Formula (Ia)

\[
\begin{align*}
&\text{O} \\
&\text{A}_1 \text{L}_1 \text{N} \text{W} \\
&\text{O} \text{N} \text{P} \text{A}_2 \\
&\text{L}_2 \text{(O)}_m \text{N} \text{G} \\
&\text{R}^a \\
\end{align*}
\]

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 \(\text{C}_1-\text{C}_4\)-alkyl, \(\text{C}_1-\text{C}_4\)-alkoxy, halogen, nitro, halogenated \(\text{C}_1-\text{C}_4\)-alkyl, halogenated \(\text{C}_1-\text{C}_4\)-alkoxy, methylthio, amino, cyano, and \(\text{C}_1-\text{C}_4\)-alkylcarbonyl;

- \(L_1\) is \(-(\text{CH}_2)_r\) optionally substituted with a substituent selected from the group consisting of methyl and allyl, and \(r\) is 1 to 3;

- \(P\) is \(-\text{CH}_2\); 

- \(A_2\) 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, isopropyl, 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, isopropyl, trifluoromethoxy, difluoromethoxy, hydroxy, aminocarbonyl, and
methylcarbonylamino; provided that when A₁ is 3,4-dichloro-phenyl, A₂ is other than phenyl substituted at the meta position with trifluoromethoxy; W is N or CH;
L₂ is a bivalent radical selected from the group consisting of
- NH-cyclohexyl-(CH₂)₀₋₂; and Q is attached at either the 2- or cis-4-
position relative to the position of –NH–;
- X₁-CH(R³⁻)⁻(CR³⁻R⁴⁻)₁⁻⁻; wherein X₁ is –NH- or S; and R³⁻, R⁴⁻, and R⁵⁻ are each hydrogen;
and
- X₁-(R,R-CH(R₃⁻)⁻CR⁻(R₅⁻)); wherein X₁ is –NH–, and R₃⁻ and R₅⁻ are methyl, and R⁴⁻ is hydrogen;
m is 0;
G is –C(=NR₄⁻)NR₅⁻R₆⁻;
R₈ and R₉ are independently hydrogen, methyl or ethyl; or R₄⁻ and R₅⁻ are
taken together with the atoms to which they are attached to form a 5-8
membered monocyclic ring optionally substituted with oxo;
R₉⁻ is hydrogen;
R₅⁻ is hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl, C₃₋₇cycloalkyl, heterocyclyl,
phenylcarbonyl, phenyl, or heteroaryl; wherein C₁₋₆alkyl is optionally
substituted with one to two substituents independently selected from the
group consisting of C₁₋₃alkoxy, phenyl, pyridinyl, furanyl, and
tetrahydrofuranyl; and wherein any phenyl- or heteroaryl-containing
substituents of R₅⁻ are optionally substituted with one to two substituents
independently selected from the group consisting of C₁₋₆alkyl, C₁₋₆alkoxy,
chloro, fluoro, bromo, fluorinated C₁₋₃alkoxy, nitro, methylthio, hydroxy,
and cyano; or, R₅⁻ and R₆⁻ 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)

\[
\begin{align*}
\text{A}_1 & \rightarrow N \\
\text{W} & \rightarrow \text{O} \\
\text{L}_2 \rightarrow \text{O}_m \\
\text{A}_2 & \rightarrow N \\
\text{R}^a & \rightarrow G
\end{align*}
\]

Formula (Ia)

wherein:

A\textsubscript{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\textsubscript{1} is \(-\text{CH}_2\)- optionally substituted with methyl or allyl; \(\text{P}\) is \(-\text{CH}_2\);  

A\textsubscript{2} is phenyl substituted at the para position with a substituent selected from the group consisting of methoxy, ethoxy, isopropyl, difluoromethoxy, hydroxy, and aminocarbonyl; or \(\text{A}_2\) is pyridin-3-yl or pyridin-4-yl substituted with methoxy;  

W is N or CH;  

L\textsubscript{2} is a bivalent radical selected from the group consisting of \(-\text{NH-}\text{cyclohexyl-}\text{-(CH}_2\text{)}_{0-2}\text{-- and Q is attached at either the 2- or cis-4-position relative to the position of }\text{NH-;}

\(-\text{X}_1\text{-(CH}_3\text{)}\text{-(CR}_1\text{R}_2\text{)}\text{--; wherein }\text{X}_1\text{ is }\text{NH- or S; and }\text{R}_1, \text{R}_2, \text{and }\text{R}_3\text{ are each hydrogen; and}

\(-\text{X}_1\text{-(R}_1\text{R}_2\text{-(CH}_3\text{)}\text{CR}_1\text{R}_2\text{)}\text{--; wherein }\text{X}_1\text{ is }\text{NH-}, \text{and }\text{R}_1\text{ and }\text{R}_2\text{ are methyl, and }\text{R}_3\text{ is hydrogen;}

\(m\) is 0;
G is \(-\text{C}(=\text{NR}^{\text{B}})\text{NR}^{\text{C}}\text{R}^{\text{d}}\);

\(\text{R}^{\text{B}}\) and \(\text{R}^{\text{d}}\) are independently hydrogen, methyl or ethyl;

\(\text{R}^{\text{C}}\) is hydrogen;

\(\text{R}^{\text{C}}\) is hydrogen, \(\text{C}_{1-4}\text{alkyl, C}_{2-4}\text{alkenyl, cyclohexyl, phenylcarbonyl, phenyl, pyrimidinyl, furanyl, benzo[1,3]dioxolyl, or pyridinyl; wherein C}_{1-4}\text{alkyl is}

optionally substituted with one to two substituents independently selected from the group consisting of \(\text{C}_{1-3}\text{alkoxy, phenyl, pyridinyl, furanyl, and tetrahydrofuranyl; and wherein any phenyl- or heteroaryl-containing substituents of R}^{\text{C}}\) are optionally substituted with one to two substituents independently selected from the group consisting of \(\text{C}_{1-4}\text{alkyl, C}_{1-4}\text{alkoxy, chloro, fluoro, bromo, fluorinated C}_{1-3}\text{alkoxy, nitro, methylthio, hydroxy, and cyano; or, R}^{\text{C}}\) and \(\text{R}^{\text{d}}\) 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 \(\text{A}_1\) is phenyl, \(\text{L}_1\) is \(-\text{CH}_2\)\,-, \(\text{D}\) is \(-\text{CH}_2\)\-(4-fluoro-phenyl), \(\text{W}\) is \(\text{N}\), \(\text{L}_2\) is \(-\text{NH}(\text{CH}_2)_2\)\,-, and \(\text{Q}\) is \(-\text{NHC}(=\text{NH})\text{NH}_2\);

a compound of Formula (I) wherein \(\text{A}_1\) is phenyl, \(\text{L}_1\) is \(-\text{CH}_2\)\,-, \(\text{D}\) is \(-\text{CH}_2\)\-(4-methoxy-phenyl), \(\text{W}\) is \(\text{N}\), \(\text{L}_2\) is \(-\text{NH}(\text{CH}_2)_2\)\,-, and \(\text{Q}\) is \(-\text{NHC}(=\text{NH})\text{NH}_2\);

a compound of Formula (I) wherein \(\text{A}_1\) is phenyl, \(\text{L}_1\) is \(-\text{CH}_2\)\,-, \(\text{D}\) is \(-\text{CH}_2\)\-(4-methylcarboxy-phenyl), \(\text{W}\) is \(\text{N}\), \(\text{L}_2\) is \(-\text{NH}(\text{CH}_2)_2\)\,-, and \(\text{Q}\) is \(-\text{NHC}(=\text{NH})\text{NH}_2\);

a compound of Formula (I) wherein \(\text{A}_1\) is phenyl, \(\text{L}_1\) is \(-\text{CH}_2\)\,-, \(\text{D}\) is \(-\text{CH}_2\)\-(4-methoxy-phenyl), \(\text{W}\) is \(\text{N}\), \(\text{L}_2\) is \(-\text{NH}(\text{CH}_2)_2\)\,-, and \(\text{Q}\) is \(-\text{NHC}(=\text{NH})\text{NH}_2\);

a compound of Formula (I) wherein \(\text{A}_1\) is H, \(\text{L}_1\) is \(-\text{(CH}_2)_4\)\,-, \(\text{D}\) is \(-\text{CH}_2\)\-(4-methoxy-phenyl), \(\text{W}\) is \(\text{N}\), \(\text{L}_2\) is \(-\text{NH}(\text{CH}_2)_2\)\,-, and \(\text{Q}\) is \(-\text{NHC}(=\text{NH})\text{NH}_2\);
a compound of Formula (I) wherein \( A_1 \) is furan-2-yl, \( L_1 \) is \(-\text{CH}_2\), \( D \) is \(-\text{CH}_2-(4\text{-methoxy-phenyl})\), \( W \) is \( N \), \( L_2 \) is \(-\text{NH}(-\text{CH}_2)_2\), and \( Q \) is \(-\text{NHC}(=\text{NH})\text{NH}_2\);

a compound of Formula (I) wherein \( A_1 \) is phenyl, \( L_1 \) is \(-\text{CH}_2\), \( D \) is \(-\text{CH}_2-(3\text{-trifluoromethyl-phenyl})\), \( W \) is \( N \), \( L_2 \) is \(-\text{NH}(-\text{CH}_2)_2\), and \( Q \) is \(-\text{NHC}(=\text{NH})\text{NH}_2\);

a compound of Formula (I) wherein \( A_1 \) is phenyl, \( L_1 \) is \(-\text{CH}_2\), \( D \) is \(-\text{CH}_2-(4\text{-butyl-phenyl})\), \( W \) is \( N \), \( L_2 \) is \(-\text{NH}(-\text{CH}_2)_2\), and \( Q \) is \(-\text{NHC}(=\text{NH})\text{NH}_2\);

a compound of Formula (I) wherein \( A_1 \) is phenyl, \( L_1 \) is \(-\text{CH}_2\), \( D \) is \(-\text{CH}_2-(4\text{-nitro-phenyl})\), \( W \) is \( N \), \( L_2 \) is \(-\text{NH}(-\text{CH}_2)_2\), and \( Q \) is \(-\text{NHC}(=\text{NH})\text{NH}_2\);

a compound of Formula (I) wherein \( A_1 \) is phenyl, \( L_1 \) is \(-\text{CH}_2\), \( D \) is \(-\text{CH}_2-(4\text{-methoxy-phenyl})\), \( W \) is \( N \), \( L_2 \) is \(-\text{NH}(-\text{CH}_2)_2\), and \( Q \) is \(-\text{ONHC}(=\text{NH})\text{NH}_2\);

a compound of Formula (I) wherein \( A_1 \) is phenyl, \( L_1 \) is \(-\text{CH}_2\), \( D \) is \(-\text{CH}_2-( pyridin-4-yl)\), \( W \) is \( N \), \( L_2 \) is \(-\text{NH}(-\text{CH}_2)_2\), and \( Q \) is \(-\text{NHC}(=\text{NH})\text{NH}_2\);

a compound of Formula (I) wherein \( A_1 \) is phenyl, \( L_1 \) is \(-\text{CH}_2\), \( D \) is \(-\text{CH}_2-(4\text{-ethoxy-phenyl})\), \( W \) is \( N \), \( L_2 \) is \(-\text{NH}(-\text{CH}_2)_2\), and \( Q \) is \(-\text{NHC}(=\text{NH})\text{NH}_2\);

a compound of Formula (I) wherein \( A_1 \) is phenyl, \( L_1 \) is \(-\text{CH}_2\), \( D \) is \(-\text{CH}_2-(4\text{-difluoromethoxy-phenyl})\), \( W \) is \( N \), \( L_2 \) is \(-\text{NH}(-\text{CH}_2)_2\), and \( Q \) is \(-\text{NHC}(=\text{NH})\text{NH}_2\);

a compound of Formula (I) wherein \( A_1 \) is phenyl, \( L_1 \) is \(-\text{CH}_2\), \( D \) is \(-\text{CH}_2-(4\text{-n-butyl-phenyl})\), \( W \) is \( N \), \( L_2 \) is \(-\text{NH}(-\text{CH}_2)_2\), and \( Q \) is \(-\text{NHC}(=\text{NH})\text{NH}_2\);

a compound of Formula (I) wherein \( A_1 \) is phenyl, \( L_1 \) is \(-\text{CH}_2\), \( D \) is \(-\text{CH}_2-(4\text{-trifluoromethyl-phenyl})\), \( W \) is \( N \), \( L_2 \) is \(-\text{NH}(-\text{CH}_2)_2\), and \( Q \) is \(-\text{NHC}(=\text{NH})\text{NH}_2\);

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

a compound of Formula (I) wherein \( A_1 \) is 4-fluoro-phenyl, \( L_1 \) is \(-\text{CH}_2\), \( D \) is \(-\text{CH}_2-(4\text{-methoxy-phenyl})\), \( W \) is \( N \), \( L_2 \) is \(-\text{NH}(-\text{CH}_2)_2\), and \( Q \) is \(-\text{NHC}(=\text{NH})\text{NH}_2\);
a compound of Formula (I) wherein A₁ is 3,4-dichloro-phenyl, L₁ is -CH₂⁻, D is -CH₂⁻(4-methoxy-phenyl), W is N, L₂ is -NH(CH₂)₂⁻, and Q is -NHC(=NH)NH₂;

a compound of Formula (I) wherein A₁ is phenyl, L₁ is -CH₂⁻, D is -CH₂⁻(4-trifluoromethoxy-phenyl), W is N, L₂ is -NH(CH₂)₂⁻, and Q is -NHC(=NH)NH₂;

a compound of Formula (I) wherein A₁ is 3-methoxy-phenyl, L₁ is -CH₂⁻, D is -CH₂⁻(4-methoxy-phenyl), W is N, L₂ is -NH(CH₂)₂⁻, and Q is -NHC(=NH)NH₂;

a compound of Formula (I) wherein A₁ is 2-methoxy-phenyl, L₁ is -CH₂⁻, D is -CH₂⁻(4-methoxy-phenyl), W is N, L₂ is -NH(CH₂)₂⁻, and Q is -NHC(=NH)NH₂;

a compound of Formula (I) wherein A₁ is phenyl, L₁ is -CH₂⁻, D is -CH₂⁻(4-aminocarbonyl-phenyl), W is N, L₂ is -NH(CH₂)₂⁻, and Q is -NHC(=NH)NH₂;

a compound of Formula (I) wherein A₁ is phenyl, L₁ is -CH₂⁻, D is -CH₂⁻(4-methylcarboxylamino-phenyl), W is N, L₂ is -NH(CH₂)₂⁻, and Q is -NHC(=NH)NH₂;

a compound of Formula (I) wherein A₁ is 4-fluoro-phenyl, L₁ is -CH₂⁻, D is -CH₂⁻(4-ethoxy-phenyl), W is N, L₂ is -NH(CH₂)₂⁻, and Q is -NHC(=NH)NH₂;

a compound of Formula (I) wherein A₁ is phenyl, L₁ is -(R,R−CH(CH₃)CH(CH₃))⁻, D is -CH₂⁻(4-methoxy-phenyl), W is N, L₂ is -NH(CH₂)₂⁻, and Q is -NHC(=NH)NH₂;

a compound of Formula (I) wherein A₁ is phenyl, L₁ is -(R,R−CH(CH₃)CH(CH₃))⁻, D is -CH₂⁻(4-methoxy-phenyl), W is N, L₂ is -NH(CH₂)₂⁻, and Q is -NHC(=NH)NH₂;

a compound of Formula (I) wherein A₁ is 3,4-dichloro-phenyl, L₁ is -CH₂⁻, D is -CH₂⁻(4-methoxy-phenyl), W is N, L₂ is -NH(CH₂)₂⁻, and Q is -ONHC(=NH)NH₂;
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\(_2\))\(_2\)-, 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 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-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-cyclopentylxyoxy-phenyl), \( W \) is N, \( L_2 \) is -NH(CH\(_2\))\(_2\)-, and \( Q \) is -NHC(=NH)NH\(_2\);

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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) 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 (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) wherein $A_1$ 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 A₁ is 3,4-dichloro-phenyl, L₁ is -CH₂-, D is -CH₂-(4-methoxy-phenyl), W is N, L₂ is trans(1R, 2R)-cyclohexyl-, and Q is -NHC(=NH)NH₂;
a compound of Formula (I) wherein A₁ is 3,4-dichloro-phenyl, L₁ is -CH₂-, D is -CH₂-(4-methoxy-phenyl), W is N, L₂ is -NH(CH₂)₂-, and Q is -NH(3,5-dihydro-imidazol-4-on-2-yl);
a compound of Formula (I) wherein A₁ is 3,4-dichloro-phenyl, L₁ is -CH₂-, D is -CH₂-(4-methylcarbonylamino-phenyl), W is N, L₂ is -NH(CH₂)₂-, and Q is -NHC(=NH)NH₂;
a compound of Formula (I) wherein A₁ is 3,4-dichloro-phenyl, L₁ is -CH₂-, D is -CH₂-(4-aminocarbonyl-phenyl), W is N, L₂ is -NH(CH₂)₂-, and Q is -NHC(=NH)NH₂;
a compound of Formula (I) wherein A₁ is 3,4-dichloro-phenyl, L₁ is -CH₂-, D is -CH₂-(3-ethoxy-phenyl), W is N, L₂ is -NH(CH₂)₂-, and Q is -NHC(=NH)NH₂;
a compound of Formula (I) wherein A₁ is 3,4-dichloro-phenyl, L₁ is -CH₂-, D is -CH₂-(4-ethoxy-phenyl), W is N, L₂ is -NH(CH₂)₂-, and Q is -NHC(=NH)NH-ethyl;
a compound of Formula (I) wherein A₁ is 3,4-dichloro-phenyl, L₁ is -CH₂-, D is -CH₂-(4-methoxy-phenyl), W is N, L₂ is -NH(CH₂)₂-, and Q is -NHC(=NH)NH-propyl;
a compound of Formula (I) wherein A₁ is 3,4-dichloro-phenyl, L₁ is -CH₂-, D is -CH₂-(4-methoxy-phenyl), W is N, L₂ is pyrrolindin-1-yl, and Q is 3-NHC(=NH)NH₂;
a compound of Formula (I) wherein \(A_1\) is 4-chloro-phenyl, \(L_1\) is \(-\text{CH}_2\), \(D\) is \(-\text{CH}_2\)-(4-methoxy-phenyl), \(W\) is \(N\), \(L_2\) is trans (1R, 2R)-cyclohexyl-, and \(Q\) is \(-\text{NHC}(=\text{NH})\text{NH}_2\);

a compound of Formula (I) wherein \(A_1\) is 3,4-dichloro-phenyl, \(L_1\) is \(-\text{CH}_2\), \(D\) is \(-\text{CH}_2\)-(3-difluoromethoxy-phenyl), \(W\) is \(N\), \(L_2\) is \(-\text{NH}({\text{CH}}_2)_2\), and \(Q\) is \(-\text{NHC}(=\text{NH})\text{NH}(\text{t}-\text{propyl})\);

a compound of Formula (I) wherein \(A_1\) is 3,4-dichloro-phenyl, \(L_1\) is \(-\text{CH}_2\), \(D\) is \(-\text{CH}_2\)-(4-methoxy-phenyl), \(W\) is \(N\), \(L_2\) is \(-\text{NH}({\text{CH}}_2)_2\), and \(Q\) is \(-\text{NHC}(=\text{NH})\text{NH}({\text{t}}\text{-propyl})\);

a compound of Formula (I) wherein \(A_1\) is 3,4-dichloro-phenyl, \(L_1\) is \(-\text{CH}_2\), \(D\) is \(-\text{CH}_2\)-(4-methoxy-phenyl), \(W\) is \(N\), \(L_2\) is \(-\text{NH}({\text{CH}}_2)_2\), and \(Q\) is \(-\text{N(ethyl)}\text{C}(=\text{NH})\text{NH}_2\);

a compound of Formula (I) wherein \(A_1\) is 3,4-dichloro-phenyl, \(L_1\) is \(-\text{CH}_2\), \(D\) is \(-\text{CH}_2\)-(4-methoxy-phenyl), \(W\) is \(N\), \(L_2\) is \(-\text{NH}({\text{CH}}_2)_2\), and \(Q\) is \(-\text{N(ethyl)}\text{C}(=\text{NH})\text{NH}_2\);

a compound of Formula (I) wherein \(A_1\) is 3,4-dichloro-phenyl, \(L_1\) is \(-\text{CH}_2\), \(D\) is \(-\text{CH}_2\)-(4-methoxy-phenyl), \(W\) is \(N\), \(L_2\) is \(-\text{NH}({\text{CH}}_2)_2\), and \(Q\) is \(-\text{N}(\text{ethyl})\text{C}(=\text{NH})\text{NH}_2\);

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

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

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

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

a compound of Formula (I) wherein \(A_1\) is 3,4-dichloro-phenyl, \(L_1\) is \(-\text{CH}_2\), \(D\) is \(-\text{CH}_2\)-(4-methoxy-phenyl), \(W\) is \(N\), \(L_2\) is \(-\text{NH}({\text{CH}}_2)_2\), and \(Q\) is \(-\text{NHC}(=\text{NH})\text{NH}({\text{tetrahydrofuran-2-ylmethyl}})\);
a compound of Formula (I) wherein \( A_1 \) is 3,4-dichloro-phenyl, \( L_1 \) is \(-\text{CH}_2^2\), \( D \) is 
\(-\text{CH}_2^2(4\text{-methoxy-phenyl}), W \) is \( N \), \( L_2 \) is \(-\text{NH}(\text{CH}_2)^2\), and \( Q \) is 
\(-\text{NHC}(=\text{NH})\text{NH}(\text{phenylethyl})
); a compound of Formula (I) wherein \( A_1 \) is 3,4-dichloro-phenyl, \( L_1 \) is \(-\text{CH}_2^2\), \( D \) is 
\(-\text{CH}_2^2(4\text{-methoxy-phenyl}), W \) is \( N \), \( L_2 \) is \(-\text{NH}(\text{CH}_2)^2\), and \( Q \) is 
\(-\text{NHC}(=\text{NH})\text{NH}(\text{furan-2-ylmethyl})
); a compound of Formula (I) wherein \( A_1 \) is 3,4-dichloro-phenyl, \( L_1 \) is \(-\text{CH}_2^2\), \( D \) is 
\(-\text{CH}_2^2(4\text{-methoxy-phenyl}), W \) is \( N \), \( L_2 \) is \(-\text{NH}(\text{CH}_2)^2\), and \( Q \) is 
\(-\text{NHC}(=\text{NH})\text{NH}(2\text{-methoxy-ethyl})
); a compound of Formula (I) wherein \( A_1 \) is 3,4-dichloro-phenyl, \( L_1 \) is \(-\text{CH}_2^2\), \( D \) is 
\(-\text{CH}_2^2(4\text{-methoxy-phenyl}), W \) is \( N \), \( L_2 \) is \(-\text{NH}(\text{CH}_2)^2\), and \( Q \) is 
\(-\text{NHC}(=\text{NH})\text{NH}_2
); a compound of Formula (I) wherein \( A_1 \) is 3,4-dichloro-phenyl, \( L_1 \) is \(-\text{CH}_2^2\), \( D \) is 
\(-(\text{CH}_2)^6\text{-H}, W \) is \( N \), \( L_2 \) is \(-\text{NH}(\text{CH}_2)^2\), and \( Q \) is 
\(-\text{NHC}(=\text{NH})\text{NH}_2
); a compound of Formula (I) wherein \( A_1 \) is 3,4-dichloro-phenyl, \( L_1 \) is \(-\text{CH}_2^2\), \( D \) is 
\(-\text{CH}_2^2(4\text{-methoxy-phenyl}), W \) is \( N \), \( L_2 \) is \(-\text{NH}(\text{CH}_2)^2\), and \( Q \) is 
\(-\text{NHC}(=\text{NH})\text{NH}(\text{allyl})
); a compound of Formula (I) wherein \( A_1 \) is 3,4-dichloro-phenyl, \( L_1 \) is \(-\text{CH}_2^2\), \( D \) is 
\(-\text{CH}_2^2(4\text{-methoxy-phenyl}), W \) is \( N \), \( L_2 \) is \(-\text{NH}(\text{CH}_2)^2\), and \( Q \) is 
\(-\text{NHC}(=\text{NH})\text{NH}(\text{phenyl})
); a compound of Formula (I) wherein \( A_1 \) is 3,4-dichloro-phenyl, \( L_1 \) is \(-\text{CH}_2^2\), \( D \) is 
\(-\text{CH}_2^2(4\text{-methoxy-phenyl}), W \) is \( N \), \( L_2 \) is \(-\text{NH}(\text{CH}_2)^2\), and \( Q \) is 
\(-\text{NHC}(=\text{NH})\text{NH}(4\text{-methoxy-phenyl})
); a compound of Formula (I) wherein \( A_1 \) is 3,4-dichloro-phenyl, \( L_1 \) is \(-\text{CH}_2^2\), \( D \) is 
\(-\text{CH}_2^2(4\text{-methoxy-phenyl}), W \) is \( N \), \( L_2 \) is \(-\text{NH}(\text{CH}_2)^2\), and \( Q \) is 
\(-\text{NHC}(=\text{NH})\text{NH}(4\text{-chloro-phenyl})
); a compound of Formula (I) wherein \( A_1 \) is 3,4-dichloro-phenyl, \( L_1 \) is \(-\text{CH}_2^2\), \( D \) is 
\(-\text{CH}_2^2(4\text{-methoxy-phenyl}), W \) is \( N \), \( L_2 \) is \(-\text{NH}(\text{CH}_2)^2\), and \( Q \) is 
\(-\text{NHC}(=\text{NH})\text{NH}(4\text{-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$_3$)$_2$-, $D$ 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-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 A₁ is 4-nitro-phenyl, L₁ is -CH₂-, D is -CH₂-(4-methoxy-phenyl), W is N, L₂ is -NH(CH₂)₂-, and Q is -NHC(=NH)NH₂;

a compound of Formula (I) wherein A₁ is 3-amino-phenyl, L₁ is -CH₂-, D is -CH₂-(4-methoxy-phenyl), W is N, L₂ is -NH(CH₂)₂-, and Q is -NHC(=NH)NH₂;

a compound of Formula (I) wherein A₁ is 4-cyano-phenyl, L₁ is -CH₂-, D is -CH₂-(4-methoxy-phenyl), W is N, L₂ is v-NH(CH₂)₂-, and Q is -NHC(=NH)NH₂;

a compound of Formula (I) wherein A₁ is 3-cyano-phenyl, L₁ is -CH₂-, D is -CH₂-(4-methoxy-phenyl), W is N, L₂ is -NH(CH₂)₂-, and Q is -NHC(=NH)NH₂;

a compound of Formula (I) wherein A₁ is 4-methoxycarbonyl-phenyl, L₁ is -CH₂-, D is -CH₂-(4-methoxy-phenyl), W is N, L₂ is -NH(CH₂)₂-, and Q is -NHC(=NH)NH₂;

a compound of Formula (I) wherein A₁ is 3-methoxycarbonyl-phenyl, L₁ is -CH₂-, D is -CH₂-(4-methoxy-phenyl), W is N, L₂ is -NH(CH₂)₂-, and Q is -NHC(=NH)NH₂;

a compound of Formula (I) wherein A₁ is 4-carboxy-phenyl, L₁ is -CH₂-, D is -CH₂-(4-methoxy-phenyl), W is N, L₂ is -NH(CH₂)₂-, and Q is -NHC(=NH)NH₂;

a compound of Formula (I) wherein A₁ is 3,4-dichloro-phenyl, L₁ is -CH₂-, D is -CH₂-(4-methoxy-phenyl), W is N, L₂ is -NH(CH₂)C(Me)₂-, and Q is -NHC(=NH)NH₂;

a compound of Formula (I) wherein A₁ is 4-fluoro-phenyl, L₁ is -CH₂-, D is -CH₂-(4-methoxy-phenyl), W is N, L₂ is -NH(CH₂)₂-, and Q is -NHC(=NH)NH(4-bromo-phenyl);

a compound of Formula (I) wherein A₁ is 4-fluoro-phenyl, L₁ is -CH₂-, D is -CH₂-(4-methoxy-phenyl), W is N, L₂ is -NH(CH₂)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 \(-\text{CH}_2\), \( D \) is \(-\text{CH}_2\)-(4-methoxy-phenyl), \( W \) is \( N \), \( L_2 \) is \(-\text{NH}(\text{CH}_2)_2\), and \( Q \) is \(-\text{NHC}(=\text{NH})\text{NH}(\text{pyridin-2-yl-ethyl})\);

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

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

a compound of Formula (I) wherein \( A_1 \) is 4-fluoro-phenyl, \( L_1 \) is \(-\text{CH}_2\), \( D \) is \(-\text{CH}_2\)-(4-methoxy-phenyl), \( W \) is \( N \), \( L_2 \) is \(-\text{NH}(\text{CH}_2)_2\), and \( Q \) is \(-\text{NHC}(=\text{NH})\text{NH}(n\text{-decanyl})\);

a compound of Formula (I) wherein \( A_1 \) is 4-t-butoxy-phenyl, \( L_1 \) is \(-\text{CH}_2\), \( D \) is \(-\text{CH}_2\)-(4-methoxy-phenyl), \( W \) is \( N \), \( L_2 \) is \(-\text{NH}(\text{CH}_2)_2\), and \( Q \) is \(-\text{NHC}(=\text{NH})\text{NH}_2\);

a compound of Formula (I) wherein \( A_1 \) is 4-hydroxy-phenyl, \( L_1 \) is \(-\text{CH}_2\), \( D \) is \(-\text{CH}_2\)-(4-methoxy-phenyl), \( W \) is \( N \), \( L_2 \) is \(-\text{NH}(\text{CH}_2)_2\), and \( Q \) is \(-\text{NHC}(=\text{NH})\text{NH}_2\);

a compound of Formula (I) wherein \( A_1 \) is 2-chloro-thiazol-4-yl, \( L_1 \) is \(-\text{CH}_2\), \( D \) is \(-\text{CH}_2\)-(4-methoxy-phenyl), \( W \) is \( N \), \( L_2 \) is \(-\text{NH}(\text{CH}_2)_2\), and \( Q \) is \(-\text{NHC}(=\text{NH})\text{NH}_2\);

a compound of Formula (I) wherein \( A_1 \) is benzofuran-2-yl, \( L_1 \) is \(-\text{CH}_2\), \( D \) is \(-\text{CH}_2\)-(4-methoxy-phenyl), \( W \) is \( N \), \( L_2 \) is \(-\text{NH}(\text{CH}_2)_2\), and \( Q \) is \(-\text{NHC}(=\text{NH})\text{NH}_2\);

a compound of Formula (I) wherein \( A_1 \) is 3,4-dichloro-phenyl, \( L_1 \) is \(-\text{CH}_2\), \( D \) is \(-\text{CH}_2\)-(4-methoxy-phenyl), \( W \) is \( N \), \( L_2 \) is \(-\text{NH}(\text{CH}_2)_2\), and \( Q \) is \(-\text{N}(\text{Me})\text{C}(=\text{NH})\text{NH}_2\);
a compound of Formula (I) wherein A₁ is 4-fluoro-phenyl, L₁ is -CH₂⁻, D is -
CH₂-(4-methoxy-phenyl), W is N, L₂ is -NH(CH₂)₂⁻, and Q is -
NHC(=NH)NH(CH₂CF₃);
a compound of Formula (I) wherein A₁ is 4-fluoro-phenyl, L₁ is -CH₂⁻, D is -
CH₂-(4-methoxy-phenyl), W is N, L₂ is -NH(CH₂)₂⁻, and Q is -
NHC(=NH)NH(3-methoxypropyl);
a compound of Formula (I) wherein A₁ is 4-fluoro-phenyl, L₁ is -CH₂⁻, D is -
CH₂-(4-methoxy-phenyl), W is N, L₂ is -NH(CH₂)₂⁻, and Q is -
NHC(=NH)piperidin-1-yl;
a compound of Formula (I) wherein A₁ is 4-fluoro-phenyl, L₁ is -CH₂⁻, D is -
CH₂-(4-methoxy-phenyl), W is N, L₂ is -NH(CH₂)₂⁻, and Q is -
NHC(=NH)N(Me)phenyl;
a compound of Formula (I) wherein A₁ is 4-fluoro-phenyl, L₁ is -CH₂⁻, D is -
CH₂-(4-methoxy-phenyl), W is N, L₂ is -NH(CH₂)₂⁻, and Q is -
NHC(=NH)NH(2-fluoro-phenyl);
a compound of Formula (I) wherein A₁ is 4-fluoro-phenyl, L₁ is -CH₂⁻, D is -
CH₂-(4-methoxy-phenyl), W is N, L₂ is -NH(CH₂)₂⁻, and Q is -
NHC(=NH)NH(4-fluoro-phenyl);
a compound of Formula (I) wherein A₁ is 4-fluoro-phenyl, L₁ is -CH₂⁻, D is -
CH₂-(4-methoxy-phenyl), W is N, L₂ is -NH(CH₂)₂⁻, and Q is -
NHC(=NH)NH(4-methyl-phenyl);
a compound of Formula (I) wherein A₁ is 4-fluoro-phenyl, L₁ is -CH₂⁻, D is -
CH₂-(4-methoxy-phenyl), W is N, L₂ is -NH(CH₂)₂⁻, and Q is -
NHC(=NH)NH(t-buty1);
a compound of Formula (I) wherein A₁ is 4-chloro-phenyl, L₁ is -CH₂⁻, D is -
CH₂-(4-amino-phenyl), W is N, L₂ is -NH(CH₂)₂⁻, and Q is -NHC(=NH)NH₂;
a compound of Formula (I) wherein A₁ is t-buty1, L₁ is -CH₂⁻, D is -CH₂-(4-
methoxy-phenyl), W is N, L₂ is -NH(CH₂)₂⁻, and Q is -NHC(=NH)NH₂;
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 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$_2$C(=O)$_2^-$, 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 \( A \) is 4-fluoro-phenyl, \( L_1 = \text{-CH}_2\), \( D = \text{-CH}_2(4\text{-methoxy-phenyl}) \), \( W = \text{N} \), \( L_2 = \text{-NH(\text{CH}_2)_2} \), and \( Q = \text{-NHC(=NH)NH(C(=O)phenyl)} \);

a compound of Formula (I) wherein \( A \) is 4-fluoro-phenyl, \( L_1 = \text{-CH}_2\), \( D = \text{-CH}_2(4\text{-methoxy-phenyl}) \), \( W = \text{N} \), \( L_2 = \text{-NH(\text{CH}_2)_2} \), and \( Q = \text{-NHC(=NH)NH(pyrimidin-2-yl)} \);

a compound of Formula (I) wherein \( A \) is 4-fluoro-phenyl, \( L_1 = \text{-CH}_2\), \( D = \text{-CH}_2(4\text{-methoxy-phenyl}) \), \( W = \text{N} \), \( L_2 = \text{-NH(\text{(S)-CHMe})_2} \), and \( Q = \text{-NHC(=NH)NH}_2 \);

a compound of Formula (I) wherein \( A \) is 4-fluoro-phenyl, \( L_1 = \text{-CH}_2\), \( D = \text{-CH}_2(4\text{-methoxy-phenyl}) \), \( W = \text{N} \), \( L_2 = \text{-NH(\text{(R)-CHMe})_2} \), and \( Q = \text{-NHC(=NH)NH}_2 \);

a compound of Formula (I) wherein \( A \) is 4-fluoro-phenyl, \( L_1 = \text{-CH}_2\), \( D = \text{-CH}_2(4\text{-methoxy-phenyl}) \), \( W = \text{N} \), \( L_2 = \text{-NH(\text{trifluoromethyl-5,6,7,8-tetrahydro-quinazolin-2-yl})} \);

a compound of Formula (I) wherein \( A \) is 4-fluoro-phenyl, \( L_1 = \text{-CH}_2\), \( D = \text{-CH}_2(4\text{-methoxy-phenyl}) \), \( W = \text{N} \), \( L_2 = \text{-NH(\text{5-methyl-pyridin-2-yl})} \);

a compound of Formula (I) wherein \( A \) is 4-fluoro-phenyl, \( L_1 = \text{-CH}_2\), \( D = \text{-CH}_2(4\text{-methoxy-phenyl}) \), \( W = \text{N} \), \( L_2 = \text{-NH(\text{morpholin-4-yl})} \);

a compound of Formula (I) wherein \( A \) is 4-chloro-phenyl, \( L_1 = \text{-CH}_2\), \( D = \text{-CH}_2(4\text{-furan-2-yl}) \), \( W = \text{N} \), \( L_2 = \text{-NH(\text{CH}_2)_2} \), and \( Q = \text{-NHC(=NH)NH}_2 \);

a compound of Formula (I) wherein \( A \) is 4-chloro-phenyl, \( L_1 = \text{-CH}_2\), \( D = \text{-CH}_2(4\text{-methoxy-phenyl}) \), \( W = \text{N} \), \( L_2 = \text{-NH(\text{CH}_2)_2} \), and \( Q = \text{-NHC(=NH)NH}_2 \);

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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 A₁ is 4-fluoro-phenyl, L₁ is -CH₂-, D is -
CH₂-(4-methoxy-phenyl), W is N, L₂ is -NH(CH₂)₂-, and Q is
-NHC(=NH)NH(ethyl);

a compound of Formula (I) wherein A₁ is 4-fluoro-phenyl, L₁ is -CH₂-, D is -
CH₂-(4-methoxy-phenyl), W is N, L₂ is -NH(CH₂)₂-, and Q is
-NHC(=NH)NH(methyl);

a compound of Formula (I) wherein A₁ is 4-methoxy-phenyl, L₁ is -CH₂-, D is -
CH₂-(4-methoxy-phenyl), W is CH, L₂ is -C(=O)NH(CH₂)₂-, and Q is
-NHC(=NH)NH₂;

a compound of Formula (I) wherein A₁ is 4-methoxy-phenyl, L₁ is -CH₂-, D is -
CH₂-(4-methoxy-phenyl), W is CH, L₂ is -O(CH₂)₂-, and Q is
-NHC(=NH)NH₂;

a compound of Formula (I) wherein A₁ is 4-methoxy-phenyl, L₁ is -CH₂-, D is -
CH₂-(4-methoxy-phenyl), W is CH, L₂ is -S(CH₂)₂-, and Q is
-NHC(=NH)NH₂; and

a compound of Formula (I) wherein A₁ is 4-methoxy-phenyl, L₁ is -CH₂-, D is -
CH₂-(4-methoxy-phenyl), W is CH, L₂ is -(CH₂)₃-, and Q is
-NHC(=NH)NH₂.

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 veterinarianly 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.

5. 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.

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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.

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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.

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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.

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49. The method of claim 45 wherein said therapeutically effective amount comprises a dose range of from about 50 mg to about 1000 mg.

30

50. The method of claim 45 wherein said therapeutically effective amount comprises a dose range of from about 100 mg to about 1000 mg.
FIG. 1

Matrix Assisted Laser Desorption (MALDI) mass spectrum of protein mixture.
**INTERNATIONAL SEARCH REPORT**

**INTERNATIONAL APPLICATION No**
PCT/US2006/009607

### A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D239/54 C07D403/12 C07D405/12 C07D401/12 C07D405/06
C07D409/06 C07D417/06 A61K31/495 A61P29/00

According to International Patent Classification (IPC) or to both national classification and IPC

### B. FIELDS SEARCHED

**Minimum documentation searched** (classification system followed by classification symbols)
C07D A61K

**Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched**

**Electronic data base consulted during the International search (name of data base and, where practical, search terms used)**
EPO-Internal, WPI Data, CHEM ABS Data

### C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<th>Category*</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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<td>A</td>
<td>US 6 218 376 B1 (KINDON NICHOLAS ET AL) 17 April 2001 (2001-04-17) the whole document</td>
<td>1-50</td>
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<td>A</td>
<td>WO 2004/014868 A (WARNER-LAMBERT COMPANY LLC; HICKS, JAMES, LESTER; ROARK, WILLIAM, HOWA) 19 February 2004 (2004-02-19) the whole document</td>
<td>1-50</td>
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</tbody>
</table>

* Special categories of cited documents:
  * "A" document defining the general state of the art which is not considered to be of particular relevance
  * "E" earlier document but published on or after the international filing date
  * "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
  * "O" document referring to an oral disclosure, use, exhibition or other means
  * "P" document published prior to the international filing date but later than the priority date claimed
  * "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
  * "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone or in combination with one or more of the documents cited in the earlier search report or with the search report or the international preliminary examination report or, if the said documents are not in a language which you understand, a translation into a language which you understand.
  * "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
  * "&" document member of the same patent family

**Date of the actual completion of the International search**
21 June 2006

**Date of mailing of the International search report**
05/07/2006

**Name and mailing address of the ISA/**
European Patent Office, P.B. 5818 Patentlaan 2 NL-2390 HV Rijswijk
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**Authorized officer**
Fritz, M
### Box II  Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. **X** Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
   
   Although claims 44-50 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2.  
   Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3.  
   Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

### Box III  Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1.  
   As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2.  
   As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3.  
   As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4.  
   No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- **X** The additional search fees were accompanied by the applicant's protest.
-  
  No protest accompanied the payment of additional search fees.
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