(54) Title: ACTIVE KETONE INHIBITORS OF Tryptase

(57) Abstract: The present invention relates to certain active tetracyclic ketone inhibitors of tryptase, pharmaceutical composition comprising these compounds and methods of treating asthma, allergic rhinitis, and/or Chronic Obstructive Pulmonary Disease utilizing these compounds.
ACTIVE KETONE INHIBITORS OF TRYPHTASE

BACKGROUND OF THE INVENTION

Cross-Reference

[001] The Applicants claim priority under 35 U.S.C. 119(e) to copending Provisional Application No. 60/613,016 filed on September 24, 2004, the disclosure of which is incorporated herein by reference in its entirety.

Field of the Invention

[002] This invention relates to novel methods and compositions for the treatment of diseases associated with tryptase activity by administration of novel tryptase inhibitors.

State of the Art

[003] Tryptase, the predominant protease secreted from human mast cells, is thought to be involved in neuropeptide processing and tissue inflammation. Elevated levels of tryptase have been detected in a number of diseases, including asthma, allergic conjunctivitis, allergic rhinitis, rheumatoid arthritis, multiple sclerosis, interstitial cititis (Drugs of the Future 1996, 21, 811), and Chronic Obstructive Pulmonary Disease (COPD). In particular, tryptase concentrations are elevated in the bloodstream for several hours following anaphylaxis (Schwartz et al. N. Eng. J. Med. 1987, 316, 1622-1626) (Shalit, et al. J. Allergy & Clin. Immunol. 1990, 86, 117-125.), are increased in nasal and lung lavage fluid from atopic subjects following specific antigen challenge (Castells et al. J. Allerg. Clin. Immunol. 1988, 141, 563-568), and are elevated in lung lavage fluid of atopic asthmatics after endobronchial allergen challenge. Smokers often have striking elevations of bronchoalveolar lavage fluid tryptase levels, a finding that provides some support for the hypothesis that release of proteinase from activated mast cells could contribute to lung destruction in smoker's emphysema. (Celenteron et al. Chest 1988, 94, 119-123). Animal studies have shown microvascular leakage subsequent to injection of tryptase (He, et al. Eur J. Pharmacol. 1997, 328, 89-97). In addition, tryptase has been shown to be a potent mitogen for fibroblasts, suggesting that it is involved in pulmonary fibrosis and interstitial lung disease (Ross et al. (1991) J. Clin. Invest. 88:493-499).

[004] Asthma is becoming increasingly prevalent, especially in the pediatric population (GINA Workshop Report, Global Strategy for Asthma Management and Prevention –updated April 2002. (Scientific information and recommendations for asthma programs. NIH Publication No. 02-
3659)). It is recognized as an inflammatory disorder (Hood et al., Immunology, Benjamin-Cummings, ed., 2nd ed., 1984) and frequently is characterized by progressive development of hyperresponsiveness of the trachea and bronchi to both immunospecific allergens and generalized chemical or physical stimuli. The disease involves multiple biochemical mediators in both its acute and chronic stages. The hyperresponsiveness of asthmatic bronchiolar tissue is believed to be the result of chronic inflammatory reactions, involving a variety of cells and inflammatory mediators (Busse & Lemanske (2001) N Engl. J. Med. 344:350-362) which irritate and damage the epithelium lining the airway wall and promote pathological thickening of the underlying tissue. Bronchial biopsies in patients with only mild asthma have features of inflammation in the airway wall.

[005] Allergic responses to inhaled allergens can initiate the inflammatory sequence. For example, allergens can activate mast cells and basophils, which are present in the epithelium and underlying smooth muscle tissue by binding IgE located on the cell surface. Activated mast cells release a number of preformed or primary chemical mediators (e.g., histamine) of the inflammatory response and generate numerous other secondary mediators of inflammation (e.g., superoxide, lipid derived mediators, etc.) in situ. In addition, several large molecules (e.g., proteoglycans, tryptase, chymase, etc.) are released by degranulation of mast cells.

[006] The release of these preformed mediators from mast cells probably accounts for the early bronchiolar constriction in the asthmatic reaction to airborne allergens. The early phase of the asthmatic reaction peaks approximately fifteen minutes after exposure to allergen and is generally followed by recovery over the ensuing one to two hours. Twenty five to thirty five percent of the patient population experience a further decline in respiratory function which maximizes six to twelve hours after exposure. This late reaction phase is accompanied by a marked increase in the number of inflammatory cells (e.g., eosinophils, neutrophils, lymphocytes, etc.) infiltrating the bronchiolar tissue. The infiltrating cells are attracted to the site by release of mast cell derived chemotactic agents and then become activated during the late reaction phase. The late asthmatic response is believed to be a secondary inflammatory reaction mediated in part by the secretory activity of granulocytes.

These findings suggest that tryptase may increase bronchoconstriction in asthma by destroying bronchodilating peptides. Tryptase activates prostromelysin (pro-MMP-3) and procollagenase (pro-MMP-1) via MMP-3, which suggests that tryptase is involved in tissue inflammation and remodeling and joint destruction in rheumatoid arthritis. Tryptase was also shown to activate PAR-2 (Molino, et al. J. Biol. Chem. 1997, 272, 4043-4049), a tethered ligand G-protein-coupled receptor that is believed to mediate some of the inflammation and hyperreactivity seen in asthma (Schmidlin, et al J. Immunol. 2002, 169, 5315-5321). Further, administration of tryptase inhibitor protects against development of the late and airway hyperresponsive phases in allergen challenged sheep (Clark et al. Am. J. Respir. Crit. Care Med. 1995, 152, 2076-2083) and inhibits the immediate cutaneous response to intradermal injection of allergen in allergic sheep (Molinari et al. Amer. Physiol. Soc. 1995, 79(6), 1966-1970). Tryptase inhibitor was also found to reduce the acute airway response to allergen in pigs (Dahlback, et al. Clin. & Exp. Allergy 2002, 32, 967-971). Most relevant are results from a clinical trial showing that a tryptase inhibitor reduced allergen-induced late asthmatic response in mild atopic asthmatics (Krishna, et al. J. Allergy Clin. Immunol. 2001, 107, 1039-1045). All of the above-described findings clearly indicate the applicability of tryptase inhibitors as therapeutic agents in treating asthma and other disorders associated with inflammation of the respiratory tract.

Tryptase has been observed to cleave gelatinase and fibronectin (J. Cell. Biochem. 1992, 50, 337) which suggests that it may function in the normal regulation of extracellular matrix turnover through a direct proteolytic mechanism. Such activity is important for tissue growth and remodeling, cell migration and wound healing, and probably metastasis as well. Tryptase may also have a role in other pathological conditions where pro-matrix metalloproteinase 3 (MMP-3) is implicated because of tryptase’s role in activation of MMP-3. Once activated, MMP-3 can degrade proteoglycans, fibronectin, laminin, and type IV and type IX collagen. Such conditions include cartilage degradation as well as collagen deposits in such diseases as arthritis, chronic periodontitis, rheumatoid synovium and sclerosis.

Diseases or conditions that may be mediated by tryptase activity include: metastasis of tumor cells, anaphylaxis, mastocytosis, scleroderma, urticaria, atopic dermatitis, bullous pemphigoid, psoriasis, pulmonary fibrosis, interstitial pneumonia, nephritis, hepatic fibrosis, hepatitis, hepatic cirrhosis, Crohn’s disease, ulcerative colitis, allergic rhinitis, peptic ulcers, gastric disease induced by non-steroidal inflammatory agents, cardiac infarction, disseminated intravascular coagulation, pancreatitis, multi-organ failure, interstitial lung diseases, gingivitis,
peridontitis, viral infections, breast cancer, ocular allergy, bladder cancer, fibrotic lung disease, artherosclerosis, cardiomyopathic disorders, rheumatoid arthritis, and Chronic Obstructive Pulmonary Disease (COPD).

[010] The disclosures of these and other documents referred to throughout this application are incorporated herein by reference.

**SUMMARY OF THE INVENTION**

[011] A Compound of Formula I

![Chemical Structure](image)

\[ \text{where} \]

[012] \( \text{Ar}^1 \) is activating heteroarylene or activating phenylene;

[013] \( W \) is \(-A^1-D-A^2-\); where \( D \) is \(-O-, -NR^4-\), \(-C(O)-\), \(-C(O)O-\), \(-OC(O)-\), \(-C(O)NR^4-\), \(-NR^4C(O)-\), \(-S(O)_n-\) (where \( n \) is 0, 1, or 2), \(-NR^4S(O)_2-\), \(-S(O)_2NR^4-\), \(-NR^4C(O)O-\), \(-OC(O)NR^4-\), \(-NR^4C(O)NR^5-\), \(-CR^R'-R''-\) (where \( R' \) and \( R'' \) together with the carbon to which they are attached form cycloalkylene), or a bond and where \( R^4 \) and \( R^5 \) are independently hydrogen, alkyl, alkenylcarbonyl, or haloalkylcarbonyl; where \( A^1 \) and \( A^2 \) are independently a bond, alkylene, alkenyleny, alkynylene, haloalkylene, haloalkenylen, or haloalkynylene; and where at least one of \( A^1, D, \) or \( A^2 \) is not a bond;

[014] \( R^1 \) is hydrogen, alkyl, or substituted alkyl;

[015] \( R^2 \) is heteroaralkyl, alkylaminomethyloxyalkyl, dialkylaminoalkyloxyalkyl, heterocycloalkylalkyl, \( R^aR^bNC(=NH)NH-S(O)alkyl \), \( R^aR^bNC(=NH)NH-C(O)alkyl \), \( R^aR^bNC(=NH)NH-Oalkyl \), \( R^aR^bNC(=NH)NHalkyl \), \( R^aR^bNC(=NH)alkyl \), alkoxyalkyl, alkyl-S(O)alkyl, aminocarbonylalkyl, alkylaminocarbonylalkyl, dialkylaminocarbonylalkyl, alkoxyalkylalkyl, alkoxyalkylalkylen, alkoxyalkylalkyl, aminocarbonyloxyalkyl, alkyl-NR^a-carbonyloxyalkyl, hydroxyalkyl, alkoxyaminolamino, alkyl-NR^a-sulfonylealkyl, heteroaryl, heteroaralkyl, heteroaralkenyl, heteroaralkylaminocarbonylalkyl, heteroaralkylxocarbonylalkyl, heteroaralkylxenyl, aryl, alkenyl, aralkyl, aralkenyl, alkyl-NR^a-xocarbonylalkyl, heteroaryl-NR^a-sulfonylealkyl, heterocycloalkylalkyl, heteroaralkylalkyl,
wherein R\(^6\) and R\(^7\) are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, aryl, acyl, aminoalkylcarbonyl, alkylaminoalkylcarbonyl, dialkylaminoalkylcarbonyl, alkylcarbonylalkenyl, alkyldcioalkoxyalkylcarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, aminocarbonyl, alkoxy carbonyl, alkylsulfon yl, heteroaralkyl-NR\(^8\)-carbonyl, heteroaryl, heteroarylcarbonyl, heteroaralkyl, heteroar alkylcarbonyl, heteroaralkyloxycarbonyl, heteroarylcarbonyl, heterocycloalkylcarbonyl, hetero clycotalkylalkylcarbonyl, heterocycloalkyloxycarbonyl, and heterocycloalkylsulfon yl, 

wherein n is 0, 1, or 2 and wherein R\(^8\) and R\(^9\) are independently hydrogen or alkyl;

R\(^3\) is hydroxy or -OSiR\(^{24a}\)R\(^{24b}\)R\(^{24c}\) (where R\(^{24a}\), R\(^{24b}\), and R\(^{24c}\) are independently alkyl or aryl) and R\(^{3a}\) is hydrogen, hydroxy, or -OSiR\(^{24a}\)R\(^{24b}\)R\(^{24c}\) (where R\(^{24a}\), R\(^{24b}\), and R\(^{24c}\) are independently alkyl or aryl); or R\(^3\) and R\(^{3a}\) together with the carbon to which they are attached form carbonyl;

Q is

i) -OR\(^8\) wherein R\(^8\) is hydrogen, alkyl, substituted alkyl, acyl, aralkyl, alkenyl, heteroaralkyl, aryl, heteroaryl, or -C(O)NR\(^9\)R\(^10\) (wherein R\(^9\) and R\(^10\) are independently hydrogen, alkyl, aryl, heteroaryl, aralkyl, alkenyl, heterocycloalkyl, heterocycloalkylalkyl, or heteroaralkyl);

ii) -S(O)\(^r\)R\(^{11}\) where r is 0, 1, or 2 and R\(^{11}\) is alkyl, substituted alkyl, aryl, heteroaryl, heteroaralkyl, aralkyl, or alkenyl; or -S(O)\(^r\)R\(^{11}\) where r is 2 and R\(^{11}\) is -N\(^{12}\)R\(^{13}\) (wherein R\(^{12}\) and R\(^{13}\) are alkyl, substituted alkyl, aryl, heteroaryl, heteroaralkyl, aralkyl, or alkenyl);

iii) -NR\(^{14}\)R\(^{15}\) wherein each R\(^{14}\) and R\(^{15}\) are independently hydrogen, alkyl, substituted alkyl, alkyldcarbonyl, cyanoalkylcarbonyl, haloalkylcarbonyl, alkoxy carbonyl, and alkoxycarbonyl, and alkoxycarbonyl,
alkoxyalkyloxycarbonyl, alkoxy carbonylaminocarbonyl, cycloalkyl carbonyl, cycloalkylalkyloxycarbonyl, aryl carbonyl, aralkyl carbonyl, heteroaryl carbonyl, heterocycloalkyloxycarbonyl, heterocycloalkyl carbonyl, aralkenoxy carbonyl, aralkenyl oxycarbonyl, heterocycloalkylcarbonyl amino, heterocycloalkylcarbonyl amino, aryl, aralkyl, aralkenyl, heteroaryl, heteroaralkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, \( R^{16} \text{R}^{17} \text{N} = \text{R}^{16} \)C- (wherein \( R^{16}, \text{R}^{17}, \text{and} \text{R}^{18} \text{are independently hydrogen, alkyl, or substituted alkyl}, \text{R}^{19} \text{R}^{20} \text{NC(O)O}-, \text{R}^{21} \text{S(O)O}_{2}-, \text{or} \text{R}^{19} \text{R}^{20} \text{NS(O)}_{2}-\text{, wherein} \text{R}^{19}, \text{R}^{20}, \text{and} \text{R}^{21} \text{are independently hydrogen, alkyl, substituted alkyl, alkenyl, aryl, heteroaryl, heterocycloalkyl, cycloalkyl, aralkyl, aralkenyl, heterocycloalkylalkyl, heteroaralkyl, cycloalkylalkyl, or heteroaralkenyl, or \text{R}^{14} \text{and} \text{R}^{15} \text{together with the nitrogen to which they are attached form} \text{heterocycloalkyl or heteroaryl;}\)

iv) heterocycloalkylalkylcarbonylamino;

v) fused-heterocycloalkylalkylcarbonylamino;

vi) heteroaralkylcarbonylamino; or

vii) hydrogen; and

\[ \text{Ar}^{2} \text{is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl where} \text{Ar}^{2} \text{is further substituted with} \]

E where E is selected from the group consisting of

i) \(-Y^{1}-X^{1}-Y^{2}-Z^{1}-Y^{3}-\text{Ar}^{3}\), wherein \( X^{1} \) and \( Z^{1} \) are independently \(-\text{O}-, \text{NR}^{22}-, \text{-C(O)}-, \text{-C(O)O}-, \text{-OC(O)}-, \text{-C(O)NR}^{22}-, \text{-NR}^{22} \text{C(O)O}-, \text{-NR}^{22} \text{C(O)}-, \text{-OC(O)NR}^{22}-, \text{or} \text{-NR}^{22} \text{C(O)NR}^{23}-; \text{and} \text{Y}^{1}, \text{Y}^{2}, \text{Y}^{3}, \text{and} \text{Ar}^{3} \text{are as defined below;}

ii) \(-X^{1}-Z^{2}-Y^{3}-\text{Ar}^{3}\), wherein \( X^{1} \) is \(-\text{O}-, \text{-NR}^{22}-, \text{-C(O)}-, \text{-C(O)O}-, \text{-OC(O)}-, \text{-C(O)NR}^{22}-, \text{-NR}^{22} \text{C(O)O}-, \text{-NR}^{22} \text{C(O)}-, \text{-OC(O)NR}^{22}-, \text{-NR}^{22} \text{C(O)NR}^{23}-, \text{or} \text{-NR}^{22} \text{C(O)NR}^{23}-; \text{Z}^{2} \text{is cycloalkyleno or heterocycloalkyleno; and} \text{Y}^{2} \text{and} \text{Ar}^{3} \text{are as defined below;}

iii) \(-X^{1}-Y^{2}-\text{Ar}^{3}\), wherein \( X^{1} \) is \(-\text{O}-, \text{-NR}^{22}-, \text{-C(O)}-, \text{-C(O)O}-, \text{-OC(O)}-, \text{-C(O)NR}^{22}-, \text{-NR}^{22} \text{C(O)O}-, \text{-NR}^{22} \text{C(O)O}-, \text{-NR}^{22} \text{C(O)O}-, \text{-OC(O)NR}^{22}-, \text{or} \text{-NR}^{22} \text{C(O)NR}^{23}-; \text{and} \text{Y}^{2} \text{and} \text{Ar}^{3} \text{are as defined below;}

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iv) $-X^2$-$Ar^3$, wherein $X^2$ is -O-, -C(O)NR$^{22}$-, or -NR$^{22}$C(O)-; and $Ar^3$ is substituted aryl, heteroaryl, cycloalkyl, or heterocycloalkyl;

v) $-X^3$-$Ar^3$, wherein $X^3$ is -NR$^{22}$-, -C(O)-, -C(O)O-, -OC(O)-, -S(O)$_n$- (where n is 0, 1, or 2), -NR$^{22}$S(O)$_2$-, -S(O)$_2$NR$^{22}$-, -NR$^{22}$C(O)O-, -OC(O)NR$^{22}$-, or -NR$^{22}$C(O)NR$^{23}$; and $Ar^3$ is as defined below;

vi) $-X^1$-$Y^2$-$Z^1$-$Ar^3$, wherein $X^1$ and $Z^1$ are independently -O-, -NR$^{22}$-, -C(O)-, -C(O)O-, -OC(O)-, -C(O)NR$^{22}$-, -NR$^{22}$C(O)-, -S(O)$_n$- (where n is 0, 1, or 2), -NR$^{22}$S(O)$_2$-, -S(O)$_2$NR$^{22}$-, -NR$^{22}$C(O)O-, -OC(O)NR$^{22}$-, or -NR$^{22}$C(O)NR$^{23}$; and $Y^2$ and $Ar^3$ are as defined below;

vii) $-Y^1$-$Ar^3$ where $Y^1$ and $Ar^3$ are as defined below;

viii) $-Y^1$-$X^1$-$Y^2$-$Ar^3$, wherein $X^1$ is -O-, -NR$^{22}$-, -C(O)-, -C(O)O-, -OC(O)-, -C(O)NR$^{22}$-, -NR$^{22}$C(O)-, -S(O)$_n$- (where n is 0, 1, or 2), -NR$^{22}$S(O)$_2$-, -S(O)$_2$NR$^{22}$-, -NR$^{22}$C(O)O-, -OC(O)NR$^{22}$-, or -NR$^{22}$C(O)NR$^{23}$; and $Y^1$, $Y^2$, and $Ar^3$ are as defined below;

ix) $-Y^1$-$X^1$-$Ar^3$, wherein $X^1$ is -O-, -NR$^{22}$-, -C(O)-, -C(O)O-, -OC(O)-, -C(O)NR$^{22}$-, -NR$^{22}$C(O)-, -S(O)$_n$- (where n is 0, 1, or 2), -NR$^{22}$S(O)$_2$-, -S(O)$_2$NR$^{22}$-, -NR$^{22}$C(O)O-, -OC(O)NR$^{22}$-, or -NR$^{22}$C(O)NR$^{23}$; and $Y^1$ and $Ar^3$ are as defined below;

xi) $-Y^1$-$X^1$-$Y^2$-$Z^1$-$Ar^3$, wherein $X^1$ and $Z^1$ are independently -O-, -NR$^{22}$-, -C(O)-, -C(O)O-, -OC(O)-, -C(O)NR$^{22}$-, -NR$^{22}$C(O)-, -S(O)$_n$- (where n is 0, 1, or 2), -NR$^{22}$S(O)$_2$-, -S(O)$_2$NR$^{22}$-, -NR$^{22}$C(O)O-, -OC(O)NR$^{22}$-, or -NR$^{22}$C(O)NR$^{23}$; and $Y^1$, $Y^2$, and $Ar^3$ are as defined below; and

wherein $R^{22}$ and $R^{23}$ are independently hydrogen, alkyl, substituted alkyl, or acyl; wherein $Y^1$, $Y^2$, and $Y^3$ are independently alkylene, alkenylene, alkyne, haloalkene, halocarboxy, or cycloalkylene, or -CR$^6$R$^d$ (where $R^e$ and $R^d$ together attach the carbon to which they are attached cycloalkylene); and wherein $Ar^3$ is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl; or

[021] a pharmaceutically acceptable salt thereof.
[022] In second aspect, this invention is directed to a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula I and a pharmaceutically acceptable excipient.

[023] In a third aspect, this invention is directed to a method of treating a disease, disorder, or syndrome responsive to the inhibition of tryptase in an animal suffering said disease, disorder, or syndrome, comprising administering to said animal a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula I.

[024] In a fourth aspect, this invention is directed to a method of treating an immunomediated respiratory disease independently selected from the group consisting of asthma, COPD, and allergic rhinitis, preferably asthma, in an animal which method comprises administering to said animal a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula I and a pharmaceutically acceptable excipient in combination with one or more compound(s) independently selected from the group consisting of a β-2 adrenoreceptor agonist, corticosteroid, leukotriene antagonist, phosphodiesterase 4 inhibitor, and antihistamine. Preferably, the compound of Formula I and the pharmaceutically acceptable excipient is administered in combination with one or more compound(s) independently selected from salmeterol, fluticasone, budesonide, montelukast, levalbuterol, and roflumilast.

[025] In a fifth aspect, this invention is directed to a method of treating an immunomediated disease independently selected from the group consisting of rheumatoid arthritis, inflammatory bowel disease (IBD) (comprising Crohn’s Disease and Ulcerative Colitis), and systemic lupus erythematosus (SLE) in an animal which method comprises administering to said animal a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula I and a pharmaceutically acceptable excipient in combination with one or more anti-inflammatory compound(s). Preferably, the compound of Formula I and the pharmaceutically acceptable excipient is administered in combination with one or more compound(s) independently selected from azathioprine, plaquenil, prednisone, sulfasalazine, methotrexate, Arava, Remicade, and Enbrel.
[026] In a sixth aspect, this invention is directed to an intermediate of formula 7:

where PG¹ is a N-protecting group, such as tert-butoxycarbonyl (Boc) or 9-fluorenlymethoxycarbonyl (Fmoc), and the like; PG² is N-protecting group, such as benzyloxycarbonyl (CBz), and the like; and W and Ar² are as defined above for a compound of Formula I, including preferred embodiments;

[027] an intermediate of formula 16:

where PG¹ is a N-protecting group, such as tert-butoxycarbonyl (Boc) or 9-fluorenlymethoxycarbonyl (Fmoc), and the like; PG² is N-protecting group, such as benzyloxycarbonyl (CBz), and the like; and W and Ar² are as defined above for a compound of Formula I, including preferred embodiments, and LG is –OH or a leaving group under acylating reaction conditions;

[028] an intermediate of formula 27:

where PG¹ is a N-protecting group, such as tert-butoxycarbonyl (Boc) or 9-fluorenlymethoxycarbonyl (Fmoc), and the like; PG³ is an O-protecting group, such as tert-butyldimethylsilyl (TBDMS), and the like; and Y² and Ar³ are as defined above for a compound of
Formula I, including preferred embodiments;

[029] an intermediate of Formula 30:

where PG¹ is a N-protecting group, such as tert-butoxycarbonyl (Boc) or 9-fluorenylmethoxycarbonyl (Fmoc), and the like, and PG² is N-protecting group, such as benzyloxy carbonyl (CBz), and the like; or

[030] an intermediate of Formula 36:

where PG¹ is a N-protecting group, such as tert-butoxycarbonyl (Boc) or 9-fluorenylmethoxycarbonyl (Fmoc), and the like, and PG² is N-protecting group, such as benzyloxy carbonyl (CBz), and the like.

[031] In a seventh aspect, this invention is directed to a process of preparing a compound of Formula I comprising:

[a] reacting an intermediate of Formula 7:

where PG¹ is a N-protecting group, such as tert-butoxycarbonyl (Boc) or 9-fluorenylmethoxycarbonyl (Fmoc), and the like; PG² is N-protecting group, such as benzyloxy carbonyl (CBz), and the like; and W and Ar² are as defined above for a compound of
Formula I, including preferred embodiments; with an alcohol of the formula \( \text{Ar}^3\cdot \text{Y}^2\cdot \text{OH} \) or an isocyanate of formula \( \text{Ar}^3\cdot \text{Y}^2\cdot \text{NCO} \) where \( \text{Y}^2 \) and \( \text{Ar}^3 \) are as defined above, including preferred embodiments; optionally oxidizing the hydroxy; optionally removing the protecting group(s); and optionally further modifying the deprotected amine(s) to yield a compound of Formula I;

(b) reacting an intermediate of formula 16:

![Formula 16](image)

where \( \text{PG}^1 \) is a N-protecting group, such as tert-butoxycarbonyl (Boc) or 9-fluorenylmethoxycarbonyl (Fmoc), and the like; \( \text{PG}^2 \) is N-protecting group, such as benzyloxycarbonyl (CBz), and the like; and \( \text{W} \) and \( \text{Ar}^2 \) are as defined above for a compound of Formula I, including preferred embodiments; and \( \text{LG} \) is a leaving group under acylating conditions, e.g., \( \text{LG} \) is \( \cdot \text{OH} \) in the presence of a coupling agent or \( \text{LG} \) is halo; with an amine of formula \( \text{Ar}^3\cdot \text{Y}^2\cdot \text{NHR}^{22} \), where \( \text{Y}^2 \), \( \text{R}^{22} \), and \( \text{Ar}^3 \) are as defined above, including preferred embodiments; optionally oxidizing the hydroxy; optionally removing the protecting group(s); and optionally further modifying the deprotected amine(s) to yield a compound of Formula I;

(c) reacting an intermediate of formula 27:

![Formula 27](image)

where \( \text{PG}^1 \) is a N-protecting group, such as tert-butoxycarbonyl (Boc) or 9-fluorenylmethoxycarbonyl (Fmoc), and the like; \( \text{PG}^3 \) is an O-protecting group, such as tert-butyldimethylsilyl (TBDMS), and the like; and \( \text{Y}^2 \) and \( \text{Ar}^3 \) are as defined above for a compound of Formula I, including preferred embodiments; with

\( (1) \) an intermediate of formula \( \text{R}^{14}\cdot \text{X} \) where \( \text{X} \) is halo and \( \text{R}^{14} \) is alkyl, substituted alkyl, aryl, aralkyl, aralkenyl, heteroaryl, heteroaralkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, or heterocycloalkylalkyl; optionally removing the O-protecting
group; optionally oxidizing the deprotected hydroxy; optionally removing the N-
protecting group; and optionally further modifying the deprotected amine to yield a
compound of Formula I;

(2) an intermediate of formula RC(O)LG where LG is a leaving group under acylating
conditions, e.g., -OH in the presence of a coupling agent or halo, and R is alkyl,
cyanoalkyl, haloalkyl, haloalkoxy, alkenyloxy, alkoxy, alkoxyalkyl, alkoxyalkyloxy,
alkoxy carbonylamino, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl,
heterocycloalkyl, aryloxy, heteroaryloxy, cycloalkylloxy, heterocycloalkylloxy,
aralkyloxy, aralkenyloxy, heterocycloalkylalkyloxy, heteroaralkyloxy, or
heteroaralkenyloxy; optionally removing the O-protecting group; optionally
oxidizing the deprotected hydroxy; optionally removing the N-protecting group; and
optionally further modifying the deprotected amine to yield a compound of Formula I;

(3) an intermediate of formula $R^{21}S(O)_{2}LG$ where LG is a leaving group under
sulfonylating reaction conditions; optionally removing the O-protecting group;
optionally oxidizing the deprotected hydroxy; optionally removing the N-protecting
group; and optionally further modifying the deprotected amine to yield a compound
of Formula I;

(4) an intermediate of formula $R^{19}R^{20}NC(O)LG$ where LG a leaving group under
acylating reaction conditions; optionally removing the O-protecting group; optionally
oxidizing the deprotected hydroxy; optionally removing the N-protecting group; and
optionally further modifying the deprotected amine to yield a compound of Formula I; or

(5) an intermediate of formula $R^{19}R^{20}NS(O)_{2}LG$ where LG is a leaving group under
sulfonylating reaction conditions; optionally removing the O-protecting group;
optionally oxidizing the deprotected hydroxy; optionally removing the N-protecting
group; and optionally further modifying the deprotected amine to yield a compound
of Formula I;
(d) reacting an intermediate of formula 30:

where PG\textsuperscript{1} is a N-protecting group, such as tert-butoxycarbonyl (Boc) or 9-fluorenylmethoxycarbonyl (Fmoc), and the like, and PG\textsuperscript{2} is N-protecting group, such as benzyloxycarbonyl (CBz), and the like; with an amine of formula 31:

where E is as defined above for a compound of Formula I, including preferred embodiments; optionally oxidizing the hydroxy; optionally removing the protecting group(s); and optionally further modifying the deprotected amine(s) to yield a compound of Formula I;

(e) reacting an intermediate of formula 36:

where PG\textsuperscript{1} is a N-protecting group, such as tert-butoxycarbonyl (Boc) or 9-fluorenylmethoxycarbonyl (Fmoc), and the like, and PG\textsuperscript{2} is N-protecting group, such as benzyloxycarbonyl (CBz), and the like; with a halide of formula halo-Y\textsuperscript{2}-Ar\textsuperscript{3} and Y\textsuperscript{2} and Ar\textsuperscript{3} are as defined above for a compound of Formula I, including preferred embodiments; optionally oxidizing the hydroxy; optionally removing the protecting group(s); and optionally further modifying the deprotected amine(s) to yield a compound of Formula I;

(f) optionally modifying any of the R\textsuperscript{1}, R\textsuperscript{2}, W, Ar\textsuperscript{1}, Ar\textsuperscript{2}, and Ar\textsuperscript{3} groups in the product(s) from Methods (a)-(e); or

(g) optionally separating individual isomers yielded in Methods (a)-(f).
Definitions:

[039] Unless otherwise stated, the following terms used in the specification and claims are defined for the purposes of this Application and have the following meanings:

[040] “Activating heteroarylene” means a five- or six-membered, monocyclic, divalent, aromatic radical containing one, two, three, or four heteroatoms independently selected from N, O, and S, the remaining ring atoms being C, e.g., 1,2,4-oxadiazol-3,5-diyl, 1,3,4-oxadiazol-2,5-diyl, isoxazol-diyl (including 3,4-diyl, 3,5-diyl, and 4,5-diyl), 1,3-thiazolyl (including 2,4-diyl, 2,5-diyl, and 4,5-diyl), thien-diyl (including all permissible valencies, e.g. thien-2,5-diyl and the like), or 1,3-oxazolyl (including 2,4-diyl, 2,5-diyl, and 4,5-diyl), and the like. Any ring member may be optionally substituted with one, two, or three substituents independently selected from the group consisting of alkyl, alkoxy, alkylthio, haloalkyl, haloalkoxy, halo, hydroxy, amino, alkylamino, dialkylamino, nitro, alkylcarbonyl, alkylcarbonylamino, alkoxy carbonyl, alkoxyalkyl, aminoalkyl, aminocarbonyl, alkyaminocarbonyl, dialkylaminocarbonyl, carboxy, cyano, hydroxyalkyl, optionally substituted phenyl, and heteroaryl.

[041] “Acyl” means a \(-\text{C(O)R}\) radical where R is alkyl, cyanoalkyl, haloalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, heteroarylalkyl, or heterocycloalkylalkyl, as defined herein, e.g., acetyl, benzoyl, and the like.

[042] “Acyloxyalkyl” means an alkyl radical, as defined herein, substituted with at least one, preferably one or two, \(-\text{OR}\) group(s) where R is acyl, as defined herein, e.g., acetyloxymethyl, benzoyloxyethyl, and the like.

[043] “Administration” and variants thereof (e.g., “administering” a compound) in reference to a compound of the invention means introducing the compound or a prodrug of the compound into the system of the animal in need of treatment. When a compound of the invention or prodrug thereof is provided in combination with one or more other active agents (e.g., \(\beta\)-2 adrenoceptor agonists, corticosteroids, leukotriene antagonists, and/or phosphodiesterase 4 inhibitors, etc.), “administration” and its variants are each understood to include concurrent and sequential
introduction of the compound or prodrug thereof and other agents.

“Alkenyl” means a linear monovalent hydrocarbon radical of two to six carbon atoms or a branched monovalent hydrocarbon radical of three to six carbon atoms containing one or two double bonds e.g., ethenyl, propenyl (including all isomeric forms), 1-methylpropenyl, butenyl (including all isomeric forms), or pentenyl (including all isomeric forms), and the like.

“Alkenylene” means a linear divalent hydrocarbon radical of two to six carbon atoms or a branched divalent hydrocarbon radical of three to six carbon atoms containing at least one, preferably one or two, double bonds e.g., ethen-1,2-diyl, propen-3,3-diyl, propen-1,3-diyl, or 2-methyl-but-2-en-1,4-diyl, and the like.

“Alkenyloxy” means an –OR radical where R is alkenyl as defined herein, e.g., allyloxy, and the like.

“Alkenyloxy carbonyl” means a radical –C(O)R where R is alkenyloxy as defined herein, e.g., allyloxy carbonyl, and the like.

“Alkoxy” means a radical –OR where R is alkyl as defined herein, e.g., methoxy, ethoxy, propoxy, or 2-propoxy, n-, iso-, or tert-butoxy, and the like.

“Alkoxyalkyl” means an alkyl radical, as defined herein, substituted with at least one, preferably one or two, alkoxy group(s), as defined herein, e.g., 2-methoxyethyl, 1-, 2-, or 3-methoxypropyl, 2-ethoxyethyl, or 3,4-dimethoxybutyl, and the like.

“Alkoxyalkyl carbonyl” means a –C(O)R radical where R is alkoxyalkyl as defined herein.

“Alkoxyalkyl oxycarbonyl” means a –C(O)OR radical where R is alkoxyalkyl as defined herein.

“Alkoxycarbonyl” means a radical –C(O)OR where R is alkyl as defined herein, e.g., methoxycarbonyl, ethoxycarbonyl, n-propoxycarbonyl, or 2-propoxycarbonyl, n-, iso-, or tert-butoxycarbonyl, and the like.

“Alkoxycarbonylalkyl” means an alkyl radical, as defined herein, substituted with at least one, preferably one or two, alkoxycarbonyl group(s), as defined herein, e.g., methoxycarbonylmethyl or methoxycarbonylethyl, and the like.

“Alkoxycarbonylalkoxy” means an –OR radical where R is alkoxycarbonylalkyl as defined above, e.g. methoxycarbonylmethoxy, and the like.

“Alkoxycarbonylamino” means a –NRC(O)OR’ radical where R is hydrogen or alkyl, as defined herein, and R’ is alkyl, as defined herein, e.g., methoxycarbonylamino, methoxycarbonyl-N-methylamino or isopropoxycarbonylamino, and the like.
“Alkoxy carbonylaminoalkyl” means an alkyl radical as defined herein substituted with at least one, preferably one or two, alkoxy carbonylamino as defined herein, e.g., 2-(methoxycarbonylamino)ethyl, methoxycarbonyl-N-methy laminomethyl or 2-(isopropoxycarbonylamino)propyl, and the like.

“Alkoxy carbonylamino carbonyl” means a -C(O)R where R is alkoxy carbonylamino as defined herein.

“Alkyl” means a linear saturated monovalent hydrocarbon radical of one to six carbon atoms or a branched saturated monovalent hydrocarbon radical of three to six carbon atoms, e.g., methyl, ethyl, propyl, 2-propyl, butyl (including all isomeric forms), or pentyl (including all isomeric forms), and the like.

“Alkylamino” means a radical –NHR where R is alkyl as defined herein, or an N-oxide derivative, or a protected derivative thereof, e.g., methylamino, ethylamino, n-, iso-propylamino, n-, iso-, tert-buty lamino, or methylamino-N-oxide, and the like.

“Alkylaminoalkyl” means an alkyl radical, as defined herein, substituted with at least one, preferably one or two, alkylamino group(s) as defined herein, e.g., methylaminoethyl, 2-ethylamino-2-methylethyl, and the like.

“Alkylaminoalkyl carbonyl” means a –C(O)R radical where R is alkylaminoalkyl as defined herein, e.g., methylaminoethylcarbonyl or isopropylaminomethylcarbonyl, and the like.

“Alkylaminoalkyloxy” means a –OR radical where R is alkylaminoalkyl group as defined herein.

“Alkylaminoalkyloxyalkyl” means an alkyl radical substituted with at least one, preferably one or two, alkylaminoalkyloxy group(s) as defined herein, e.g., N-methylaminoethoxyethyl, 2-ethylamino-2-methyl ethoxypropyl, and the like.

“Alkylaminocarbonyl” means a –C(O)R radical where R is alkylamino as defined herein e.g., methylaminocarbonyl or ethylaminocarbonyl, and the like.

“Alkylaminocarbonylalkyl” means an alkyl radical as defined herein substituted with at least one, preferably one or two, alkylaminocarbonyl group(s) as defined herein, e.g., methylaminocarbonylethyl or n-propylaminocarbonylmethyl, and the like.

“Alkylaminocarbonylamino” means a –NHR radical where R is alkylaminocarbonyl as defined herein, e.g., methylaminocarbonylamino or ethylaminocarbonylamino, and the like.

“Alkylaminocarbonylaminoalkyl” means an alkyl radical as defined herein substituted with at least one, preferably one or two, alkylaminocarbonylamino group(s) as defined herein.
“Alkylaminocarbonyloxy” means a –OC(O)R radical where R is alkylamino as defined herein.

“Alkylaminocarbonyloxyalkyl” means an alkyl radical, as defined herein, substituted with at least one, preferably one or two, alkylaminocarbonyloxy group(s) as defined herein, e.g., methylaminocarbonyloxypropyl, ethylaminocarbonyloxyethyl, or n-propylaminocarbonyl-oxymethyl, and the like.

“Alkylcarbonyl” means a –C(O)R radical where R is alkyl as defined herein, e.g., methylcarbonyl, ethylcarbonyl, or 2-propylcarbonyl, and the like.

“Alkylcarbonylalkenyl” means an alkenyl radical, as defined herein, substituted with at least one, preferably one or two, alkylcarbonyl group(s) as defined herein, e.g., methylcarbonylprop-2-enyl or methylcarbonyl-1-methylprop-2-enyl, and the like.

“Alkylcarbonylalkyl” means an alkyl radical, as defined herein, substituted with at least one, preferably one or two, alkylcarbonyl group(s) as defined herein, e.g., methylcarbonylethyl, n-butylcarbonylmethyl, or isopropylcarbonylmethyl, and the like.

“Alkylcarbonylamino” means a –NRR’ radical, where R is hydrogen or alkyl, as defined herein, and R’ is alkylcarbonyl as defined herein, e.g., methylcarbonylamino or ethylcarbonylamino, and the like.

“Alkylcarbonylaminoalkyl” means an alkyl radical, as defined herein, substituted with at least one, preferably one or two, alkylcarbonylamino group(s) as defined herein.

“Alkylcarbonyloxy” means an –OR radical where R is alkylcarbonyl, as defined herein, e.g., methylcarbonyloxy, ethylcarbonyloxy, or n-propylcarbonyloxy, and the like.

“Alkylcarbonyloxyalkyl” means an alkyl radical, as defined herein, substituted with at least one, preferably one or two, alkylcarbonyloxy group(s) as defined herein, e.g., methylcarbonyloxyethyl, ethylcarbonyloxyethyl, or n-propylcarbonyloxyethyl, and the like.

“Alkylcarbonyloxyalkyloxyalkyl” means a –C(O)OR radical where R is alkylcarbonyloxyalkyl as defined herein, e.g., methylcarbonyloxyethylcarbonyl, ethylcarbonyloxyethylcarbonyl, or n-propylcarbonyloxyethylcarbonyl, and the like.

“Alkylene” means a linear saturated divalent hydrocarbon radical of one to six carbon atoms or a branched saturated divalent hydrocarbon radical of three to six carbon atoms e.g., methylene, 1,1-dimethylmethylene, eth-1,2-diyl, prop-1,3-diyl, 1-methylprop-1,3-diyl, 2-methylprop-1,3-diyl, but-1,4-diyl (including all isomers), or pent-1,5-diyl (including all isomers), and the like.
“Alkyl-\(\text{NR}^a\)-carbonyloxyalkyl” means an alkyl radical, as defined herein, substituted with at least one, preferably one or two, alkyl-\(\text{NR}^a\)-C(\(\text{O}\))O– group(s) where \(\text{R}^a\) is hydrogen or alkyl, e.g., methylaminocarboxyethyl- or dimethylaminocarbonyl oxyethyl-, and the like.

“Alkyl-\(\text{NR}^a\)-sulfonylalkyl” means an alkyl radical, as defined herein, substituted with at least one, preferably one or two, alkyl-\(\text{NR}^a\)-sulfonyl group(s) where \(\text{R}^a\) is hydrogen or alkyl, e.g., methylaminosulfonylethyl, and the like.

“Alkylsulfinyly” means a \(-\text{S(O)}\text{R}\) radical where \(\text{R}\) is alkyl as defined herein, e.g., methylsulfinyl, ethylsulfinyl, or propylsulfinyl, and the like.

“Alkylsulfinylalkyl” means an alkyl radical, as defined herein, substituted with at least one, preferably one or two, alkylsulfinyl group(s) as defined herein, e.g., methylsulfinylethyl, butylsulfinylethyl, or propylsulfinylmethyl, and the like.

“Alkylsulfonyl” means a \(-\text{SO}_2\text{R}\) radical where \(\text{R}\) is alkyl as defined herein, e.g., methylsulfonyl or ethylsulfonyl, and the like.

“Alkylsulfonylalkyl” means an alkyl radical, as defined herein, substituted with at least one, preferably one or two, alkylsulfonyl group(s) as defined herein, e.g., methylsulfonylethyl-, butylsulfonylethyl-, and propylsulfonyl-, and the like.

“Alkylthio” means an \(-\text{SR}\) radical where \(\text{R}\) is alkyl as defined herein, e.g., methylthio, ethylthio, propylthio, or butylthio, and the like.

“Alkylthioalkyl” means an alkyl radical, as defined herein, substituted with at least one, preferably one or two, alkylthio group(s) as defined herein, e.g., methylthioethyl-, ethylthiomethyl-, propylthiomethyl-, or butylthioethyl-, and the like.

“Alkynyl” means a linear monovalent hydrocarbon radical of two to six carbon atoms or a branched monovalent hydrocarbon radical of three to six carbon atoms containing at least one, preferably one or two, triple bond(s), e.g., ethynyl, propynyl (and all isomeric forms) and butynyl (and all isomeric forms), and the like.

“Alkynylene” means a linear divalent hydrocarbon radical of two to six carbon atoms or a branched divalent hydrocarbon radical of three to six carbon atoms containing at least one, preferably one or two, triple bond(s), e.g., ethyn-di-yl or butyn-di-yl, and the like.

“Amino” means a \(-\text{NH}_2\) radical or an N-oxide derivative, or a protected derivative thereof such as \(-\text{NH}\rightarrow\text{O}, -\text{NHBoc},\) or \(-\text{NHChz},\) and the like.

“Aminoalkyl” means an alkyl radical, as defined herein, substituted with at least one, preferably one or two, \(-\text{NH}_2\) group(s), e.g., aminomethyl, aminooethyl, or 1,4-diamino-2-methyl-
pentyl, and the like.

[092] “Aminoalkycarbonyl” means a –C(O)R radical where R is aminoalkyl as defined herein, e.g., aminomethylcarbonyl or aminoethylcarbonyl, and the like.

[093] “Aminocarbonyl” means a –CONH₂ radical, or an N-oxide derivative, or a protected derivative thereof.

[094] “Aminocarboxyalkyl” means an alkyl radical, as defined herein, substituted with at least one, preferably one or two, aminocarboxyl group(s) as defined herein, e.g., aminocarboxylethyl, aminocarboxylisopropyl, or aminocarboxy-1-butyl, and the like.

[095] “Aminocarboxyloxyalkyl” means an alkyl radical, as defined herein, substituted with at least one, preferably one or two, -OR radical(s) where R is aminocarboxyl as defined herein, e.g., aminocarboxyloxyethyl or aminocarboxyloxyethyl, and the like.

[096] “Alkenyl” means an alkenyl radical, as defined herein, substituted with at least one, preferably one or two, aryl group(s) as defined herein, e.g., phenylprop-2-en-1-yl and the like.

[097] “Alkenyloxycarbonyl” means a –C(O)OR radical where R is aralkenyl as defined herein.

[098] “Aralkyl” means an alkyl radical, as defined herein, substituted with at least one, preferably one or two, aryl group(s) as defined herein, e.g., benzyl or phenethyl, and the like.

[099] “Aralkylcarbonyl” means a –C(O)R radical where R is aralkyl as defined herein, e.g.,

[100] “Aralkyloxy” means an –OR radical where R is aralkyl as defined above, e.g., benzyloxy, and the like.

[101] “Aralkyloxyalkyl” means an alkyl radical, as defined herein, substituted with at least one, preferably one or two, aralkyloxy group(s) as defined herein.

[102] “Aralkyloxycarbonyl” means a –C(O)R radical where R is aralkyloxy as defined herein.

[103] “Aryl” means a monovalent, monocyclic or fused bicyclic hydrocarbon radical of 6 to 12 ring atoms, wherein the ring comprising a monocyclic radical ring is aromatic and wherein at least one of the fused rings comprising a bicyclic radical is aromatic. Unless otherwise stated, the valency of the group may be located on any atom of any ring within the radical, valency rules permitting. More specifically the term aryl includes, but is not limited to, phenyl, naphthyl, indanyl (including, for example, indan-5-yl, or indan-2-yl, and the like) or tetrahydronaphthyl (including, for example, tetrahydronaphth-1-yl, or tetrahydronaphth-2-yl, and the like), and the like.

Aryl may be optionally substituted on any of the rings with one, two, or three substituents independently selected from the group consisting of acyl, alkyl, alkoxy, alkylthio, haloalkyl, haloalkoxy, halo, hydroxy, amino, alkylamino, dialkylamino, nitro, alkylcarbonylamino,
alkoxycarbonyl, alkoxycarbonylaminoalkyl, alkoxalkyl, aminocarbonyl,
aminocarboxyl, alkylaminocarbonyl, dialkylaminocarbonyl, carboxy, cyano,
hydroxyalkyl, alkylsulfonfyl, alkylsulfinyl, -P(O)OR’R” (where R’ and R” are independently hydrogen, alkyl, substituted alkyl,
alkenyl, substituted alkyl, alkyne, substituted alkynyl, aryl, aralkyl, heteroaryl, heteroaralkyl,
cycloalkyl, cycloalkylalkyl, heterocycloalkyl, or heterocycloalkylalkyl), -P(O)R’R” (where R’ and R” are independently hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl,
substituted alkynyl, aryl, aralkyl, heteroaryl, heteroaralkyl, cycloalkyl, cycloalkylalkyl,
heterocycloalkyl, or heterocycloalkylalkyl; or R’ and R” together with the phosphorous to which they are attached form heterocycloalkyl as defined herein), optionally substituted phenyl, and
heteroaryl; or when two substituents are adjacent to each other they can combine to form
methylenedioxy group or aryl is pentafluorophenyl.

[0104] “Arlycarbonyl” means a –C(O)R radical where R is aryl as defined herein.
[0105] “Aryloxy” means a –OR where R is aryl as defined herein.
[0106] “Aryloxycarbonyl” means a –C(O)R radical where R is arylxy as defined herein.
[0107] “Aryloxyalkyl” means an alkyl radical, as defined herein, substituted with at least one,
preferably one or two, aryloxy group(s) as defined herein.
[0108] “Carboxy” means a –C(O)OH radical.
[0109] “Carboxyalkenyl” means an alkenyl radical, as defined herein, substituted with at least one,
preferably one or two, -C(O)OH group(s), e.g., carboxyethenyl, 1-, 2-, or 3-carboxypropenyl, and
the like.
[0110] “Carboxyalkylcarbonylamino” means a –NRC(O)R’ radical, where R is hydrogen or alkyl
as defined herein, and R’ is carboxyalkyl as defined herein, e.g., 2-carboxyethylcarbonylamino,
and the like.
[0112] “Carboxyalkylene” means an alkylene radical, as defined herein, substituted with at least
one, preferably one or two, -C(O)OH, e.g., CHC(O)OH or CHCH2C(O)OH, and the like.
[0113] “Chronic bronchitis” clinically means a daily cough with production of sputum for 3
months, two years in a row. In chronic bronchitis, the lining of the airways becomes inflamed and
swells leading to narrowing and obstruction of the airways. The inflammation stimulates
production of mucous (sputum), which can cause further obstruction of the airways. Obstruction of
the airways, especially with mucus, increases the likelihood of bacterial lung infections.

Chronic Obstructive Pulmonary Disease” or “COPD” is a disease comprising primarily chronic bronchitis and/or emphysema and is characterized by chronic obstruction of the flow of air through the airways and out of the lungs. The obstruction generally is permanent and progressive over time, limiting the ability to exhale. Chronic asthma may also develop into COPD where the lungs have become irreversibly damaged and scarred from repeated, untreated asthma flares. There is frequent overlap among COPD patients. Thus, patients with emphysema may have some of the characteristics of chronic bronchitis. Similarly, patients with chronic bronchitis also may have some of the characteristics of emphysema.

“Composition” is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

“Cyanoalkyl” means an alkyl radical, as defined herein, substituted with at least one, preferably one or two, cyano group(s), e.g., cyanomethyl, 2-cyanoethyl, or 2-cyanopropyl, and the like.

“Cyanoalkylcarboxyl” means a –C(O)R radical where R is cyanoalkyl as defined herein.

“Cycloalkyl” means a monocyclic or fused bicyclic, saturated or partially unsaturated, monovalent hydrocarbon radical of three to ten carbon ring atoms. Unless otherwise stated, the valency of the group may be located on any atom of any ring within the radical, valency rules permitting. More specifically, the term cycloalkyl includes, but is not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, decahydronaphthyl (including, but not limited to, decahydronaphth-1-yl or decahydronaphth-2-yl, and the like), or cyclohexenyl and the like. The cycloalkyl ring may be optionally substituted with one, two, or three substituents independently selected from the group consisting of alkyl, alkoxy, alkylthio, haloalkyl, haloalkoxy, halo, hydroxy, amino, alkylamino, dialkylamino, nitro, alkylcarbonyl, alkylcarbonylamino, alkoxycarbonyl, alkoxyalkyl, aminoaalkyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, carboxy, cyano, hydroxalkyl, oxo, thioxo, imino, and optionally substituted phenyl.

“Cycloalkylalkylcarbonyl” means an alkyl radical, as defined herein, substituted with at least one, preferably one or two, cycloalkyl group(s) as defined above, e.g., cyclopropylmethyl, cyclobutylmethyl, cyclopentylethyl, or cyclohexylmethyl, and the like.

“Cycloalkylalkylcarbonyl” means a –C(O)R radical where R is cycloalkylalkyl as defined
“Cycloalkylcarbonyl” means a –C(O)R radical where R is cycloalkyl as defined herein.

“Cycloalkylcarbonyloxy” means a –OC(O)R, where R is cycloalkyl, as defined above, e.g., cyclohexylcarbonyloxy, and the like.

“Cycloalkylene” means a monocyclic or fused bicyclic, saturated or partially unsaturated, divalent hydrocarbon radical of three to ten carbon ring atoms. Unless otherwise stated, the valencies of the group may be located on any atom of any ring within the radical, valency rules permitting. More specifically, the term cycloalkylene includes, but is not limited to, cycloprop-1,1-diyl, cyclobut-1,3-diyl, cyclopent-1,4-diyl, cyclohex-1,3-diyl, cyclohex-1,4-diyl, or cyclohex-3-en-1,2-diyl, and the like. The cycloalkylene ring may be optionally substituted with one, two, or three substituents independently selected from the group consisting of alkyl, alkoxy, alkylthio, haloalkyl, haloalkoxy, halo, hydroxy, amino, alkylamino, dialkylamino, nitro, alkylcarbonyl, alkylcarbonylamino, alkoxy carbonyl, alkoxyalkyl, aminoalkyl, aminocarbonyl, aminocarbonylamino, dialkylaminocarbonyl, carboxy, cyano, hydroxyalkyl, oxo, thioxo, imino, and optionally substituted phenyl.

“Cycloalkyloxycarbonyl” means a –C(O)OR radical where R is cycloalkyl as defined herein.

“Dialkylamino” means a radical –NRR’ where R and R’ are independently alkyl as defined herein, or an N-oxide derivative, or a protected derivative thereof, e.g., dimethylamino, diethylamino, N,N-methylpropylamino or N,N-methylethylamino, and the like.

“Dialkylaminoalkyl” means an alkyl radical, as defined herein, substituted with at least one, preferably one or two, dialkylamino group(s) as defined above e.g., dimethylaminomethyl, diethylaminoethyl, and the like.

“Dialkylaminocarbonyl” means a –C(O)R radical where R is a dialkylaminoalkyl group, as defined herein, e.g., diethylaminomethylcarbonyl or N-ethyl-N-methylaminoethylcarbonyl, and the like.

“Dialkylaminocarbonyloxy” means a –OR radical where R is dialkylaminoalkyl, as defined herein.

“Dialkylaminocarboxyalkyl” means an alkyl radical, as defined herein, substituted with at least one, preferably one or two, dialkylaminocarboxyloxy as defined herein, e.g., 1-(dimethylaminomethyloxyl)-ethyl, diethylaminoethylxymethyl, and the like.

“Dialkylaminocarboxy” means a –C(O)R radical where R is dialkylamino as defined
herein, e.g., dimethylaminocarbonyl or methylethylaminocarbonyl, and the like.

[0131] "Dialkylaminocarbonylalkyl" means an alkyl radical, as defined herein, substituted with at least one, preferably one or two, dialkylaminocarbonyl group(s) as defined herein, e.g., dimethylaminocarbonylthylethyl or N-methyl-N-ethylaminocarbonylthylethyl, and the like.

[0132] "Dialkylaminocarboxylamino" means a –NRC(O)NR’R" radical where R is hydrogen or alkyl as defined herein and R’ and R” are alkyl, as defiend herein.

[0133] "Dialkylaminocarbonylalkyl" means an alkyl radical, as defined herein, substituted with at least one, preferably one or two, dialkylaminocarbonylamino as defined herein, e.g., dimethylaminocarbonylaminomethyl, and the like.

[0134] "Dialkylaminocarboxylaminoxy" means a –OR radical where R is dialkylaminocarbonyl as defined herein.

[0135] "Emphysema" means a lung condition featuring an abnormal accumulation of air in the lung’s alveoli, leading to their enlargement and resulting breakage or damage or formation of scar tissue. Emphysema is associated with smoking cigarettes and also with or worsened by repeated infection of the lungs, such as is seen in chronic bronchitis.

[0136] "Further substituted" is defined below in the definition for “substituted”.

[0137] "Fused-heterocycloalkylalkylcarboxylicamino" means a –NRC(O)R’ radical where R is hydrogen or alkyl and where R’ is an alkyl radical, as defined herein, substituted with at least one, preferably one or two, fused-heterocycloalkyl groups where fused-heterocycloalkyl in the term “fused-heterocycloalkylalkylcarboxylicamino” means exclusively a saturated or partially unsaturated, monovalent, fused bicyclic group of 5 to 12 ring atoms in which one, two, three, four, or five ring atoms are heteroatoms independently selected from N, O, P(O)ₘ (where the phosphorous atom is optionally further substituted with alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, aralkyl, heteroaryl, heteroaralkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, or heterocycloalkylalkyl; when the phosphorous atom is not further substituted, it is the point of valency), Si (where Si is substituted with alkyl and one additional group selected from the group consisting of alkyl, alkenyl, cycloalkylalkyl, aryl, aralkyl, heteroaralkyl, and heterocycloalkylalkyl), and S(O)ₘ, where m is 1 or 2 and n is 0, 1, or 2, the remaining ring atoms being C. One or two ring carbon atoms can optionally be replaced by a -C(O)-, -C(S)-, or -C(=NH)- group. Unless otherwise stated, the valency of the group may be located on any atom of any ring within the radical, valency rules permitting. More specifically the term fused-heterocycloalkyl includes, but is not limited to, 2-oxo-hexahydro-thieno[3,4-
d)imidazol-4-yl, decahydro-quinoxalanyl, 2-oxo-decahydro-quinoxalanyl, and octahydro-
pyrrolo[3,2-b]pyridin-5-yl, and the like, and the derivatives thereof and N-oxide or a protected
derivative thereof. Unless stated otherwise, the fused-heterocycloalkyl ring is optionally
substituted, on any ring, with one, two, or three substituents independently selected from the group
consisting of alkyl, alkoxy, alkoxyalkyl, alkylthio, haloalkyl, haloalkoxy, halo, hydroxy, amino,
akylamino, dialkylamino, nitro, alky carbonylamino, carboxy, alkoxy carbonyl, amino alkyl,
amino carbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, cyano, cyclo alkyl, cycloalkylalkyl,
cyclo alkyl carbonyloxy, optionally substituted phenyl, heteroaryl, optionally substituted
phenyl alkyl, heteroaryl alkyl, and hydroxy alkyl.

[0138] “Halo” means fluoro, chloro, bromo, and iodo, preferably fluoro or chloro.

[0139] “Haloalkoxy” means a radical –OR where R is haloalkyl as defined herein, e.g.,
trifluoromethoxy or 2,2,2-trifluoroethoxy, and the like.

[0140] “Haloalkoxycarbonyl” means a –C(O)R radical where R is haloalkoxy as defined herein.

[0141] “Haloalkyl” means an alkyl radical, as defined herein, substituted with at least one,
preferably one to five halogen atoms, preferably fluorine or chlorine, including those substituted
with different halogens, e.g., -CH₂Cl, -CF₃, -CHF₂, -CF₂CF₃, -CF(CH₃)₃, or -CHFCl, and the like.

[0142] “Haloalkylcarbonyl” means a –C(O)R radical where R is haloalkyl as defined herein.

[0143] “Haloalkylene” means an alkylene radical, as defined herein, substituted with at
least one, preferably one to five, halogen atoms, preferably fluorine or chlorine, including those
substituted with different halogens, e.g., CHCH₂Cl, CHCF₃, CHF, or CF₂, and the like.

[0144] “Haloalkenylene” means an alkenylene radical, as defined herein, substituted with
at least one, preferably one to five, halogen atoms, preferably fluorine or chlorine, including those
substituted with different halogens.

[0145] “Heteroaralkenyln” means an alkyl radical, as defined herein, substituted with at least
one, preferably one or two, heteroaryl group(s) as defined herein.

[0147] “Heteroaralkenyloxycarbonyl” means a –C(O)OR radical where R is heteroarakenyl as
defined herein.

[0148] “Heteroaralkyl” means an alkyl radical, as defined herein, substituted with at least one,
preferably one or two, heteroaryl group(s) as defined herein, e.g., pyridinylmethyl, furanyl methyl,
or chloropyridinylmethyl, and the like.

[0149] “Heteroaralkylaminocarbonylalkyl” means an alkyl radical, as defined herein, substituted with at least one, preferably one or two, -C(O)NR’ group(s) where R is hydrogen or alkyl and R’ is heteroaralkyl as defined herein.

[0150] “Heteroaralkylcarbonyl” means a –C(O)R radical where R is heteroaralkyl as defined herein.

[0151] “Heteroaralkylcarbonylalkyl” means an alkyl radical, as defined herein, substituted with at least one, preferably one or two, heteroaryl groups where heteroaryl in the term “heteroaralkylcarbonylamino” means exclusively a monocyclic or fused bicyclic, monovalent radical of 5 to 12 ring atoms containing one or more, preferably one, two, three, or four ring heteroatoms independently selected from N, O, P(O)ₘₙ (where the phosphorous atom is optionally further substituted with alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, aralkyl, heteroaryl, heteroaralkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, or heterocycloalkylalkyl; when the phosphorous atom is not further substituted, it is the point of valency), Si (where Si is substituted with alkyl and one additional group selected from the group consisting of alkyl, alkenyl, cycloalkylalkyl, aryl, aralkyl, heteroaralkyl, and heterocycloalkylalkyl), and S(O)ₘₙ, where m is 1 or 2 and n is 0, 1, or 2, the remaining ring atoms being carbon, wherein the ring comprising a monocyclic radical is aromatic and wherein at least one of the fused rings comprising the bicyclic radical is aromatic. One or two ring carbon atoms can optionally be replaced by a -C(O)-, -C(S)-, or -C(=NH)- group. Unless otherwise stated, the valency may be located on any atom of any ring of the heteroaryl group, valency rules permitting. More specifically, the term heteroaryl includes, but is not limited to, pyridinyl, pyrrolyl, imidazolyl, thienyl, furanyl, indolyl, 2,3-dihydro-1H-indolyl (including, for example, 2,3-dihydro-1H-indol-2-yl or 2,3-dihydro-1H-indol-5-yl, and the like), pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, isooxazolyl, benzoxazolyl, quinolinyl, isoquinolinyl, tetrahydroisoquinolinyl (including, for example, tetrahydroisoquinolin-4-yl or tetrahydroisoquinolin-6-yl, and the like), pyrrolo[3,2-c]pyridinyl (including, for example, pyrrolo[3,2-c]pyridin-2-yl or pyrrolo[3,2-c]pyridin-7-yl, and the like), benzopyranyl, thiazolyl, methylenedioxyphenyl (including, for example, methylenedioxyphen-5-yl), and the derivatives thereof, or N-oxide or a protected derivative thereof. The heteroaryl ring may be optionally
substituted with one, two, or three substituents independently selected from the group consisting of alkyl, alkoxy, alkylthio, haloalkyl, haloalkoxy, halo, hydroxy, nitro, alkylcarbonyl, alkoxy carbonyl, alkoxyalkyl, aminoalkyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, carboxy, cyano, hydroxyalkyl, phenyl (optionally substituted with alkyl, halo, hydroxy, alkoxy, carboxy, amino, alkylamino, or dialkylamino), and heteroaryl (optionally substituted with alkyl, halo, hydroxy, alkoxy, carboxy, amino, alkylamino, or dialkylamino); or when two substituents are adjacent to each other they can combine to form methylenedioxy group.

[H0153] “Heteroarylalkylcarbonyloxyalkyl” means an alkyl radical, as defined herein, substituted with at least one, preferably one or two, -OR group(s) where R is heteroarylcarbonyl as defined herein.

[H0154] “Heteroarylalkyl-NR²-carbonyl” means a -C(O)NR²R’ radical where R² is hydrogen or alkyl and R’ is heteroarylalkyl as defined herein, e.g., N-(pyridinylmethyl)aminocarbonyl, and the like.

[H0155] “Heteroarylalkyl-NR²-carbonyloxyalkyl” means an alkyl radical, as defined herein, substituted with at least one, preferably one or two, -OR group(s) where R is heteroarylalkyl-NR²-carbonyl, as defined herein, e.g., N-(pyridinylmethyl)aminocarbonylmethyl, and the like.

[H0156] “Heteroarylalkyl-NR²-sulfonylalkyl” means an alkyl radical, as defined here, substituted with at least one, preferably one or two, heteroarylalkyl-NR²-sulfonyl group(s) where R² is hydrogen or alkyl.

[H0157] “Heteroarylalkyl-S(O)ₙ-alkyl” means an alkyl radical, as defined herein, substituted with at least one, preferably one or two, heteroarylalkyl-S(O)ₙ group(s) where n is 0, 1, or 2, e.g., pyridinylmethylthioethyl.

[H0158] “Heteroarylalkyloxy” means an -OR radical where R is heteroarylalkyl as defined herein e.g., furanyl methyl or pyridinylethoxy, and the like.

[H0159] “Heteroarylalkoxyalkyl” means an alkyl radical, as defined herein, substituted with at least one, preferably one or two, heteroarylalkoxy, as defined herein.

[H0160] “Heteroarylalkoxy carbonyl” means a -C(O)R radical where R is heteroarylalkoxy as defined herein.

[H0161] “Heteroarylalkoxy carbonylalkyl” means an alkyl radical, as defined herein, substituted with at least one, preferably one or two, heteroarylalkoxy carbonyl group(s) as defined herein.

[H0162] “Heteroarylalkylsulfonyl” means a -S(O)₂R radical where R is heteroarylalkyl as defined herein, e.g., benzy lsulfonyl, and the like.
“Heteroaryl” means a monocyclic or fused bicyclic, monovalent radical of 5 to 12 ring atoms containing one or more, preferably one, two, three, or four ring heteroatoms independently selected from the group consisting of N, O, P(O)ₘ (where the phosphorous atom is optionally further substituted with alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, aralkyl, heteroaryl, heteroaralkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, or heterocycloalkylalkyl; when the phosphorous atom is not further substituted, it is the point of valency), Si (where Si is substituted with alkyl and one additional group selected from alkyl, alkenyl, cycloalkylalkyl, aryl, aralkyl, heteroaralkyl, and heterocycloalkylalkyl), and S(O)ₙ, where m is 1 or 2 and n is 0, 1, or 2, the remaining ring atoms being carbon, wherein the ring comprising a monocyclic radical is aromatic and wherein at least one of the fused rings comprising the bicyclic radical is aromatic. One or two ring carbon atoms can optionally be replaced by a -C(O)-, -C(S)-, or -C(=NH)- group. Unless otherwise stated, the valency may be located on any atom of any ring of the heteroaryl group, valency rules permitting. More specifically, the term heteroaryl includes, but is not limited to, phthalimidyld, pyridinyl, pyrrolyl, imidazolyl, thienyl, furanyl, indolyl, 2,3-dihydro-1H-indolyl (including, for example, 2,3-dihydro-1H-indol-2-yl or 2,3-dihydro-1H-indol-5-yl, and the like), pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, isoxazolyl, benzoazolyl, quinolinyl, isoquinolinyl, tetrahydroisoquinolinyl (including, for example, tetrahydroisoquinolin-4-yl or tetrahydroisoquinolin-6-yl, and the like), pyrrolo[3,2-c]pyridinyl (including, for example, pyrrolo[3,2-c]pyridin-2-yl or pyrrolo[3,2-c]pyridin-7-yl, and the like), benzopyranyl, thiazolyl, methylenedioxyphenyl (including, for example, methylenedioxyphen-5-yl), and the derivatives thereof, or N-oxide or a protected derivative thereof. The heteroaryl ring may be optionally substituted with one, two, or three substituents independently selected from the group consisting of alkyl; alkoxy; alkylthio; haloalkyl; haloalkoxy; halo; hydroxy; amino; alkylamino; dialkylamino; nitro; alkylcarbonyl; alkylcarbonylamino; alkoxycarbonyl; alkoxycarbonyl; aminoalkyl; aminocarbonyl; alkylaminocarbonyl; dialkylaminocarbonyl; carboxy; cyano; hydroxalkyl; optionally substituted phenyl; and heteroaryl substituted with a group independently selected from hydrogen, alkyl, alkoxy, haloalkyl, haloalkoxy, halo, hydroxy, amino, alkylamino, dialkylamino, alkylcarbonyl, alkylcarbonylamino, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, carboxy, and cyano; or when two substituents are adjacent to each other they can combine to form methylenedioxy group.

“Heteroarylcarbonyl” means a –C(O)R radical where R is heteroaryl as defined herein.

“Heteroaryloxy” means an –OR radical where R is heteroaryl, as defined herein.
"Heteroaryloxyalkyl" means an alkyl radical, as defined herein, substituted with at least one, preferably one or two, heteroaryloxy group(s) as defined herein, e.g., furanyloxymethyl or pyridinloxyethyl, and the like.

"Heteroaryloxycarbonyl" means a \(-\text{C(O)R}\) radical where \(\text{R}\) is heteroaryloxy as defined herein.

"Heterocycloalkyl" means a saturated or partially unsaturated monovalent monocyclic group of 3 to 8 ring atoms or a saturated or partially unsaturated monovalent fused bicyclic group of 5 to 12 ring atoms in which one, two, or three ring atoms are heteroatoms independently selected from the group consisting of \(\text{N, O, P(O)}_m\) (where the phosphorous atom is optionally further substituted with alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, aralkyl, heteroaryl, heteroaralkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, or heterocycloalkylalkyl; when the phosphorous atom is not further substituted, it is the point of valency), \(\text{Si}\) (where \(\text{Si}\) is substituted with alkyl and one additional group selected from the group consisting of alkyl, alkenyl, cycloalkylalkyl, aryl, aralkyl, heteroaralkyl, and heterocycloalkylalkyl), and \(\text{S(O)}_n\) (where \(m\) is 1 or 2 and \(n\) is 0, 1, or 2, the remaining ring atoms being \(\text{C}\). One or two ring carbon atoms can optionally be replaced by a \(-\text{C(O)-}, \text{-C(S)-}, \text{or -C(=NH)-}\) group. Unless otherwise stated, the valency of the group may be located on any atom of any ring within the radical, valency rules permitting. More specifically the term heterocycloalkyl includes, but is not limited to, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, tetrahydropyranyl, 2-oxopiperidinyl, and thiomorpholinyl, and the derivatives thereof and \(\text{N-oxide}\) or a protected derivative thereof. Unless stated otherwise, the heterocycloalkyl ring is optionally substituted with one, two, or three substituents independently selected from \(-\text{C(=NH)(NH}_2\), \(-\text{NHC(=NH)(NH}_2\), alkyl, alkoxy, alkylcarboxyl, alkylcarbonylamino, alkoxy carbonyl, alkylthio, halo, haloalkyl, haloalkoxy, amino, alkylamino, dialkylamino, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, hydroxy, hydroxyalkyl, hydroxyalkoxy, hydroxyalkyloxy, alkoxycarbonylalkyl, optionally substituted phenyl, optionally substituted phenylalkyl, heteroaryl, cycloalkyl, cycloalkenyloxy, optionally substituted phenylcarbonylamino, heteroaralkyloxy, aminoalkyl, alkoxyalkyl, alkoxyalkyloxy, haloalkoxyalkyl, aryloxyalkyl, heteroaryloxyalkyl, heterocycloalkyloxyalkyl, heterocycloalkylalkoxy, heterocycloalkylalkyloxy, heterocycloalkylalkyloxy, \(-\text{alkylene-S(O)}_n\)-\(\text{R}^x\) (where \(n\) is 0 to 2 and \(R^x\) is alkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, optionally substituted phenyl, optionally substituted phenylalkyl, heteroaryl, or heteroaralkyl), \(-\text{alkylene-NHSO}_2\)-\(\text{R}^w\) (where \(R^w\)
is alkyl, haloalkyl, optionally substituted phenyl, optionally substituted phenylalkyl, heteroaryl, or heteroaralkyl), \(-\text{alkylene-}N\text{HCO-R}^8 \) (where \( R^8 \) is alkyl, haloalkyl, optionally substituted phenyl, optionally substituted phenylalkyl, heteroaryl, or heteroaralkyl), and \( -(\text{alkylene})_{n1}\text{-CONR}^5\text{R}^8 \) (where \( n1 \) is 0 or 1, \( R^5 \) is hydrogen, alkyl, or hydroxyalkyl and \( R^8 \) is hydrogen, alkyl, hydroxyalkyl, alkoxyalkyl, optionally substituted phenylalkyl, heteroaryl, heteroaralkyl, or heterocycloalkylalkyl, or \( R^5 \) and \( R^8 \) together with the nitrogen atom to which they are attached form heterocycloalkyl); and wherein the alkyl chain in haloalkoxyalkyl, optionally substituted phenyloxyalkyl, heteroaryloxyalkyl, or aminoalkyl is optionally substituted with one or two fluoro.

[0169] “Heterocycloalkylalkylcarbonyl” means an alkyl radical, as defined herein, substituted with at least one, preferably one or two, heterocycloalkylalkyl group(s) as defined herein, e.g., piperazinylmethyl or morpholinylethyl, and the like.

[0170] “Heterocycloalkylalkylcarbonylalkyl” means a \(-\text{C(O)R} \) radical where \( R \) is heterocycloalkylalkyl as defined herein.

[0171] “Heterocycloalkylalkylcarbonylaminoo” means an alkyl radical, as defined herein, substituted with at least one, preferably one or two, heterocycloalkylalkylcarbonyl group(s) as defined herein.

[0172] “Heterocycloalkylalkylcarbonylamino” means a \(-\text{NRC(O)R}^\prime \) radical where \( R \) is hydrogen or alkyl and where \( R^\prime \) is an alkyl radical, as defined herein, substituted with at least one, preferably one or two, heterocycloalkyl groups where heterocycloalkyl in the term “heterocycloalkylalkylcarbonylamino” means exclusively a saturated or partially unsaturated, monovalent, monocyclic group of 3 to 8 ring atoms in which

a) one ring atom is nitrogen and zero, one, two, or three additional ring atom(s) are independently selected from O, P(O)\(_m\) (where the phosphorous atom is optionally further substituted with alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, aralkyl, heteroaryl, heteroaralkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, or heterocycloalkylalkyl); when the phosphorous atom is not further substituted, it is the point of valency), Si (where Si is substituted with alkyl and one additional group selected from the group consisting of alkyl, alkenyl, cycloalkylalkyl, aryl, aralkyl, heteroaralkyl, and heterocycloalkylalkyl), and S(O)\(_n\) (where \( m \) is 1 or 2 and \( n \) is an integer from 0 to 2), the remaining ring atom(s) being C;

b) one, two, three, or four ring atom(s) are independently selected from O, P(O)\(_m\) (where
the phosphorous atom is optionally further substituted with alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, aralkyl, heteroaryl, heteroaralkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, or heterocycloalkylalkyl; when the phosphorous atom is not further substituted, it is the point of valency), and $S(O)_n$ (where $m$ is 1 or 2 and $n$ is an integer from 0 to 2), the remaining ring atom(s) being C;

c) three or more ring atoms are nitrogen and zero, one, or two additional ring atom(s) is independently selected from O, P(O)$_m$ (where the phosphorous atom is optionally further substituted with alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, aralkyl, heteroaryl, heteroaralkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, or heterocycloalkylalkyl; when the phosphorous atom is not further substituted, it is the point of valency), Si (where Si is substituted with alkyl and one additional group selected from the group consisting of alkyl, alkenyl, cycloalkylalkyl, aryl, aralkyl, heteroaralkyl, and heterocycloalkylalkyl), and $S(O)_n$ (where $m$ is 1 or 2 and $n$ is an integer from 0 to 2), the remaining ring atom(s) being C; or

d) two ring atoms are nitrogen and zero, one, two, or three additional ring atom(s) are independently selected from O, P(O)$_m$ (where the phosphorous atom is optionally further substituted with alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, aralkyl, heteroaryl, heteroaralkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, or heterocycloalkylalkyl; when the phosphorous atom is not further substituted, it is the point of valency), Si (where Si is substituted with alkyl and one additional group selected from the group consisting of alkyl, alkenyl, cycloalkylalkyl, aryl, aralkyl, heteroaralkyl, and heterocycloalkylalkyl), and $S(O)_n$ (where $m$ is 1 or 2 and $n$ is an integer from 0 to 2), the remaining ring atom(s) being C and the valency of the heterocycloalkyl ring being located on a carbon ring atom; and

where, unless otherwise stated above, the valency of the heterocycloalkyl ring may be located on any atom of any ring within the radical, valency rules permitting. One or two ring carbon atoms optionally may be replaced by a $-C(=O)-$, $-C(S)-$, or $-C(=\text{NH})-\text{group.}$ More specifically the term heterocycloalkyl includes, but is not limited to, pyrrolidinyl, piperidinyl, morpholinyl, piperazin-2-yl, tetrahydropyranyl, tetrahydrofuranyl, 2-oxopiperazin-3-yl, 2-oxopiperidinyl, and thiomorpholinyl, and the like, and the derivatives thereof and N-oxide or a protected derivative thereof. Unless stated otherwise, the heterocycloalkyl ring is optionally substituted, on any ring,
with one, two, or three substituents independently selected from the group consisting of alkyl, alkoxy, alkoxyalkyl, allylthio, haloalkyl, haloalkoxy, halo, hydroxy, amino, alkylamino, dialkylamino, nitro, alkylcarbonylamino, carboxy, alkoxycarbonyl, aminoalkyl, aminocarbonyl, alkelaminocarbonyl, dialkylaminocarbonyl, cyano, cycloalkyl, cycloalkylalkyl, cycloalkylcarbonyloxy, optionally substituted phenyl, heteroaryl, optionally substituted phenylalkyl, heteroaralkyl, and hydroxyalkyl.

[0173] “Heterocyloalkylalkylcarbonyloxyalkyl” means an alkyl radical, as defined herein, substituted with at least one, preferably one or two, heterocyloalkylalkylcarbonyl group(s) as defined herein.

[0174] “Heterocyloalkylalkyl-NR²-carbonyl” means a –C(O)NR²R’ radical where R² is hydrogen or alkyl and R’ is heterocyloalkylalkyl, as defined herein.

[0175] “Heterocyloalkylalkyl-NR²-carbonylalkyl” means an alkyl radical, as defined herein, substituted with at least one, preferably one or two, heterocyloalkylalkyl-NR²-carbonyl group(s), as defined herein.

[0176] “Heterocyloalkylalkylalkyl-NR²-carbonyloxyalkyl” means an alkyl radical, as defined herein, substituted with at least one, preferably one or two, -OR group(s) where R is heterocyloalkylalkyl-NR²-carbonyl, as defined herein.

[0177] “Heterocyloalkylalkylalkyl-NR²-sulfonylalkyl” means an alkyl radical, as defined herein, substituted with at least one, preferably one or two, heterocyloalkylalkylalkyl-NR²-sulfonyl group(s).

[0178] “Heterocyloalkylalkylalkyloxy” means an –OR radical where R is heterocyloalkylalkyl as defined herein, e.g., tetrahydropyranylalkoxy, and the like.

[0179] “Heterocyloalkylalkylalkyloxyalkyl” means an alkyl radical, as defined herein, substituted with at least one, preferably one or two, heterocyloalkylalkyloxy group(s) as defined herein.

[0180] “Heterocyloalkylalkylalkyloxyalkylalkyloxy” means a –C(O)R radical where R is heterocyloalkylalkyloxy as defined herein.

[0181] “Heterocyloalkylalkylalkyloxyalkylalkylalkyl” means an alkyl radical, as defined herein, substituted with at least one, preferably one or two, heterocyloalkylalkyloxyalkylalkyl as defined herein.

[0182] “Heterocyloalkylalkylalkyl-S(O)n-alkyl” means an alkyl radical, as defined herein, substituted with at least one, preferably one or two heterocyloalkylalkyl-S(O)n group(s).

[0183] “Heterocyloalkylalkylsulfonyl” means a –S(O)₂R radical where R is heterocyloalkylalkyl as defined herein.
“Heterocycloalkylcarbonyl” means a $-\text{C(O)}R$ radical where $R$ is heterocycloalkyl as defined herein, e.g. morpholin-4-ylcarbonyl, and the like.

“Heterocycloalkylene” means a saturated or partially unsaturated, divalent, monocyclic group of 3 to 8 ring atoms or a saturated or partially unsaturated, divalent, fused bicyclic group of 5 to 12 ring atoms in which one, two, or three ring atoms are heteroatoms independently selected from the group consisting of $\text{N}$, $\text{O}$, $\text{P(O)}_m$ (where the phosphorous atom is optionally further substituted with alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, aralkyl, heteroaryl, heteroaralkyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkyl, or heterocycloalkylalkyl); when the phosphorous atom is not further substituted, it is the point of valency), $\text{Si}$ (where $\text{Si}$ is substituted with alkyl and one additional group selected from the group consisting of alkyl, alkenyl, cycloalkylalkyl, aryl, aralkyl, heteroaralkyl, and heterocycloalkylalkyl), and $\text{S(O)}_n$, where $m$ is 1 or 2 and $n$ is 0, 1, or 2, the remaining ring atoms being $\text{C}$. One or two ring carbon atoms can optionally be replaced by a $-\text{C(O)-}$, $-\text{C(S)-}$, or $-\text{C(=NH)-}$ group. Unless otherwise stated, the valency of the group may be located on any atom of any ring within the radical, valency rules permitting. More specifically the term heterocycloalkylene includes, but is not limited to, pyrrolidin-diyl, piperidin-diyl, morpholin-diyl, piperazin-diyl, tetrahydropryan-diyl, 2-oxopiperidin-diyl, and thiomorpholin-diyl, and the derivatives thereof and $\text{N}$-oxide or a protected derivative thereof. Unless stated otherwise, the heterocycloalkylene ring is optionally substituted with one, two, or three substituents independently selected from $-\text{C(=NH)(NH$_2$)}$, $-\text{NHC(=NH)(NH$_2$)}$, alkyl, alkoxy, halo, haloalkyl, haloalkoxy, amino, alkylamino, dialkylamino, hydroxy, hydroxyalkyl, hydroxyalkyloxy, hydroxyalkyloxyalkyl, alkoxyalkyloxyalkyl, optionally substituted phenyl, optionally substituted phenylalkyl, heteroaryl, cycloalkyloxy, cycloalkenylxno, optionally substituted phenylcarbonylamino, heteroaralkyloxy, aminoalkyl, aminoalkoxy, alkoxyalkyl, alkoxyalkyloxy, methylenedioxy, haloalkoxyalkyl, optionally substituted phenylxno, heteroaralkoxyalkyl, heterocycloalkyloxyalkyl, heterocycloalkylalkyloxy, heterocycloalkylalkyl, heterocycloalkylalkyloxy, heterocycloalkyloxyalkyl, -alkylene-$\text{S(O)}_n$-$\text{R}^s$ (where $n$ is 0 to 2 and $\text{R}^x$ is alkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, optionally substituted phenyl, optionally substituted phenylalkyl, heteroaryl, or heteroaralkyl), -alkylene-$\text{HSO}_2$-$\text{R}^w$ (where $\text{R}^w$ is alkyl, haloalkyl, optionally substituted phenyl, optionally substituted phenylalkyl, heteroaryl, or heteroaralkyl), -alkylene-$\text{NHCO}$-$\text{R}^q$ (where $\text{R}^q$ is alkyl, haloalkyl, optionally substituted phenyl, optionally substituted phenylalkyl, heteroaryl, or heteroaralkyl), and -(alkylene)$_n$-$\text{CONR}^e$-$\text{R}^e$ (where $n$ is 0 or 1, $\text{R}^f$ is hydrogen, alkyl, or hydroxyalkyl and $\text{R}^e$ is hydrogen, alkyl,
hydroxyalkyl, alkoxyalkyl, optionally substituted phenyl, optionally substituted phenylalkyl,
heteryl, heteroaryl, heterocycloalkylalkyl, or R^f and R^g together with the nitrogen atom to
which they are attached form heterocycloalkyl); and wherein the alkyl chain in haloalkoxyalkyl,
only substituted phenyloxyalkyl, heteroarylxyalkyl, or aminoalkyl is optionally substituted
with one or two fluoro.

[0186] “Heterocycloalkyloxy” means a -OR radical where R is heterocycloalkyl as defined
herein.

[0187] “Heterocycloalkyloxyalkyl” means an alkyl radical, as defined herein, substituted with at
least one, preferably one or two, heterocycloalkyloxy group(s), as defined herein.

[0188] “Heterocycloalkyloxy carbonyl” means a -C(O)OR radical where R is heterocycloalkyl as
defined herein.

[0189] “Hydroxyalkyl” means an alkyl radical, as defined herein, substituted with at least one,
preferably one or two, hydroxy group(s), provided that if two hydroxy groups are present they are
not both on the same carbon atom. Representative examples include, but are not limited to,
hydroxymethyl, 2-hydroxyethyl, 2-hydroxypropyl, 3-hydroxypropyl, 1-(hydroxymethyl)-2-
ethylpropyl, 2-hydroxybutyl, 3-hydroxybutyl, 4-hydroxybutyl, 2,3-dihydroxypropyl,
1-(hydroxymethyl)-2-hydroxyethyl, 2,3-dihydroxybutyl, 3,4-dihydroxybutyl and
2-(hydroxymethyl)-3-hydroxypropyl, preferably 2-hydroxyethyl, 2,3-dihydroxypropyl, or
1-(hydroxymethyl)-2-hydroxyethyl, and the like.

[0190] “Hyperresponsiveness” means the late phase bronchoconstriction and airway
hyperreactivity associated with chronic asthma. Hyper-responsiveness of asthmatic bronchial
tissue is believed to result from chronic inflammation reactions, which irritate and damage the
epithelium lining the airway wall and promote pathological thickening of the underlying tissue.

[0191] “Immunomedi­ated inflammatory disorders” means those diseases associated with mast cell
mediator release and susceptible to treatment with a tryp­tase inhibitor [e.g., immunomedi­ated type
hersensitivity diseases such as asthma, allergic rhinitis, Chronic Obstructive Pulmonary Disease
(COPD), urticaria and angioedema, eczematosus anaphylaxis, dermatitis such as atopic dermatitis,
hyper proliferative skin disease, peptic ulcers, inflammatory bowel disorder, ocular and vernal
conjunctivitis, rheumatoid arthritis, SLE, Inflammatory Bowel Disease, including Crone’s Disease
and Ulcerative Colitis, or inflammatory skin conditions, and the like].

[0192] “Isomer” or “isomers” means compounds of Formula I having identical molecular
formulae but differ in the nature or sequence of bonding of their atoms or in the arrangement of
their atoms in space. Isomers that differ in the arrangement of their atoms in space are termed “stereoisomers”. Stereoisomers that are not mirror images of one another are termed “diastereomers” and stereoisomers that are nonsuperimposable mirror images are termed “enantiomers” or sometimes “optical isomers”. An atom bonded to four nonidentical substituents is termed a “chiral center”. A compound with one chiral center has two enantiomeric forms of opposite chirality; and a mixture of both enantiomeric forms in equal amounts is termed racemic. A compound that has one or more chiral centers has $2^n-1$ enantiomeric pair(s), where $n$ is the number of chiral centers, unless the compound is meso (i.e. the compound has 2 or more assymetric or chiral centers but which is achiral because it contains an internal plane of symmetry). Compounds with more than one chiral center may exist as ether an individual diastereomer or as a mixture of diastereomers, termed a “diastereomeric mixture”. When one chiral center is present a stereoisomer may be characterized by the absolute configuration of that chiral center. Absolute configuration refers to the arrangement in space of the substituents attached to the chiral center. Enantiomers are characterized by the absolute configuration of their chiral centers and described by the $R$- and $S$-sequencing rules of Cahn, Ingold and Prelog. Conventions for stereochemical nomenclature, methods for the determination of stereochemistry and the separation of stereoisomers are well known in the art (e.g., see “Advanced Organic Chemistry,” 4th edition, March, Jerry, John Wiley & Sons, New York, 1992). It is understood that the names and illustration used in this Application to describe compounds of Formula I are meant to be encompassed all possible stereoisomers and any mixture, racemic or otherwise, thereof.

[0193] “Methylenedioxy” means a radical –O-CH$_2$-O–.

[0194] “Optional” or “optionally” means that the subsequently described event or circumstance may but need not occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not. For example, “heterocycloalkyl group optionally mono- or di-substituted with an alkyl group” means that the alkyl may but need not be present, and the description includes situations where the heterocycloalkyl group is mono- or disubstituted with an alkyl group and situations where the heterocycloalkyl group is not substituted with the alkyl group.

[0195] “Optionally substituted phenyl” means a phenyl ring optionally substituted with one, two, or three substituents independently selected from alkyl, halo, alkoxy, alkylthio, haloalkyl, haloalkoxy, heteroaryl (optionally substituted with one or two substituents independently selected from alkyl, halo, hydroxy, alkoxy, carboxy, amino, alkylamino, and dialkylamino),
heterocycloalkyl (optionally substituted with one or two substituents independently selected from alkyl, halo, hydroxy, alkoxy, carboxy, amino, alkylamino, and dialkylamino), amino, alkylamino, dialkylamino, hydroxy, cyano, nitro, aminocarbonyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, and carboxy; or optionally substituted with five fluorine atoms.

[0196] “Optionally substituted phenylalkyl” means an alkyl radical, as defined herein, substituted with at least one, preferably one or two, optionally substituted phenyl as defined herein e.g., benzyl or phenylethyl, and the like.

[0197] “Optionally substituted phenylcarbonylamino” means a –NR\textsuperscript{R}C(O)R radical where R is optionally substituted phenyl, as defined herein, and R\textsuperscript{R} is hydrogen or alkyl.

[0198] “Optionally substituted phenoxyalkyl” means an alkyl radical, as defined herein, substituted with at least one, preferably one or two, -OR radical(s), where R is optionally substituted phenyl, as defined herein.

[0199] “Partially unsaturated” describes a group which contains at least one unsaturated bond but does not contain an aromatic ring. For example, partially unsaturated cycloalkylene includes cyclohexenyl group but not indanyl.

[0200] A “pharmaceutically acceptable carrier or excipient” means a carrier or an excipient that is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable, and includes a carrier or an excipient that is acceptable for veterinary use as well as human pharmaceutical use. “A pharmaceutically acceptable carrier/excipient” as used in the specification and claims includes both one and more than one such excipient.

[0201] “Substituted,” when modifying a particular group, means that the group the term modifies must be substituted. Where the term “substituted” is used to modify a particular group, this does not mean, unless otherwise stated, that any other groups not so modified cannot be substituted. Furthermore, where a group is defined as being substituted by one of a number of enumerated alternative substituents, it does not mean, unless otherwise stated, that the group cannot be substituted further with one or more substituents not enumerated. For example, the phrase “substituted alkyl” means that the alkyl group referred to must be substituted with one or more of the substituents set forth in the definitions for “substituted alkyl.” By further example, the phrase “Ar\textsuperscript{2} is further substituted with E”, where Ar\textsuperscript{1} is defined as aryl, heteroaryl, cycloalkyl or heterocycloalkyl and alternative E substituents i-xi are enumerated, means that Ar\textsuperscript{2} is substituted with one of the enumerated E alternative substituents and that Ar\textsuperscript{2} may be substituted further with
one or more of the optional substituents set forth in the definitions for “aryl”, “heteroaryl”, “cycloalkyl” and “heterocycloalkyl.”

[0202] “Substituted alkenyl” means an alkenyl radical, as defined herein, substituted with one or more substituent(s), preferably one, two, or three substituents, independently selected from halo, haloalkoxy, amino, alkylamino, dialkylamino, alkoxy, hydroxy, carboxy, aminocarbonyl, alkylcarbonyl, alkylcarbonylamino-, alkylcarbonyloxy-, alkylaminocarbonyl-, dialkylaminocarbonyl-, alkyl-S(O)\textsubscript{n}-, alkoxy carbonyl-, alkylamino-S(O)\textsubscript{n}-, dialkylamino-S(O)\textsubscript{n}-, alkyaminocarbonyloxy, dialkylaminocarbonyloxy, alkoxy carbonylamino, alkylaminocarbonylamino, and dialkylaminocarbonylamino-, and where n is 0, 1, or 2.

[0203] “Substituted alkyl” means an alkyl radical, as defined herein, substituted with one or more substituent(s), preferably one, two, or three substituents, independently selected from halo, haloalkoxy, haloalkylcarbonyl, haloalkoxy carbonyl, amino, alkylamino, dialkylamino, alkoxy, hydroxy, carboxy, aminocarbonyl, alkylcarbonyl, alkylcarbonylamino-, alkylcarbonyloxy-, alkylaminocarbonyl-, dialkylaminocarbonyl-, alkyl-S(O)\textsubscript{n}-, alkoxy carbonyl-, alkylamino-S(O)\textsubscript{n}-, dialkylamino-S(O)\textsubscript{n}-, dialkylaminocarbonyloxy, dialkylaminocarbonyloxy, alkoxy carbonylamino, alkylaminocarbonylamino, alkoxy alkyl oxyl, dialkylaminocarbonylamino-, and where n is 0, 1, or 2.

[0204] “Substituted aryl” means a monovalent, monocyclic or fused bicyclic hydrocarbon radical of 6 to 12 ring atoms, wherein the ring comprising a monocyclic radical is aromatic and wherein at least one of the fused rings comprising a bicyclic radical is aromatic. Unless otherwise stated, the valency of the group may be located on any atom of any ring within the radical, valency rules permitting. More specifically the term aryl includes, but is not limited to, indanyl (including, for example, indan-5-yl, or indan-2-yl, and the like), methylenedioxyphenyl (including, for example, methylenedioxyphen-5-yl), tetrahydroisoquinolinyl (including, for example, tetrahydroisoquinolin-4-yl or tetrahydroisoquinolin-6-yl, and the like), and the like. The aryl ring is substituted on any of the rings with one, two, or three substituents independently selected from the group consisting of alkyl, alkoxy, alkylthio, haloalkyl, haloalkoxy, halo, hydroxy, amino, alkylamino, dialkylamino, nitro, alkylcarbonyl, alkylcarbonylamino, alkoxy carbonyl, alkoxy alkyl, amino alkyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, carboxy, cyano, hydroxy alkyl, optionally substituted phenyl, and heteroaryl; or when two substituents are adjacent to each other they can combine to form methylenedioxy group or aryl is pentafluorophenyl.

[0205] “Sulfonylalkyl” means an alkyl radical, as defined herein, substituted with at least one,
preferably one or two sulfonyl group(s).

[0206] “Syncytial viral infection” means an infection by a virus, such as a respiratory syncytial virus, causing the formation of a cellular protoplasmic mass, i.e. syncytia, via infection.

[0207] “Treating” or “treatment” of a disease, disorder, or syndrome includes:

[0208] (1) preventing the disease, disorder, or syndrome, i.e. causing the clinical symptoms of the disease, disorder, or syndrome not to develop in an animal that may be exposed to or predisposed to the disease, disorder, or syndrome but does not yet experience or display symptoms of the disease, disorder, or syndrome;

[0209] (2) inhibiting the disease, disorder, or syndrome, i.e., arresting or reducing the development of the disease, disorder, or syndrome or its clinical symptoms; or

[0210] (3) relieving the disease, disorder, or syndrome, i.e., causing regression of the disease, disorder, or syndrome or its clinical symptoms.

[0211] A “therapeutically effective amount” means the amount of a compound of Formula I that, when administered to an animal for treating a disease, is sufficient to effect such treatment for the disease. The “therapeutically effective amount” will vary depending on the compound, the disease and its severity and the age, weight, etc., of the animal to be treated.

[0212] The present invention also includes the prodrugs of compounds of Formula I. The term prodrug is intended to represent covalently bonded carriers, which are capable of releasing the active ingredient of Formula I when the prodrug is administered to an animal subject. Release of the active ingredient occurs in vivo. Prodrugs can be prepared by techniques known to one skilled in the art. These techniques generally modify appropriate functional groups in a given compound. These modified functional groups however regenerate original functional groups by routine manipulation or in vivo. Prodrugs of compounds of Formula I include compounds wherein a hydroxy, amidino, guanidino, amino, carboxylic, or a similar group is modified. Examples of prodrugs include, but are not limited to esters (e.g., acetate, formate, and benzoate derivatives), carbamates (e.g., N,N-dimethylaminocarbonyl) of hydroxy or amino functional groups in compounds of Formula I, amides (e.g, trifluoroacetylamino, acetylamino, and the like), and the like. Prodrugs of compounds of Formula I are also within the scope of this invention.

[0213] The present invention also includes N-oxide derivatives and protected derivatives of compounds of Formula I. For example, when compounds of Formula I contain an oxidizable nitrogen atom, the nitrogen atom can be converted to an N-oxide by methods well known in the art. Also when compounds of Formula I contain groups such as hydroxy, carboxy, thiol or any
group containing a nitrogen atom(s), these groups can be protected with a suitable protecting groups. A comprehensive list of suitable protective groups can be found in T.W. Greene, *Protective Groups in Organic Synthesis*, John Wiley & Sons, Inc. 1991, the disclosure of which is incorporated herein by reference in its entirety. The protected derivatives of compounds of

Formula I can be prepared by methods well known in the art.

[0214] A “pharmacologically acceptable salt” of a compound means a salt that is pharmaceutically acceptable and that possesses the desired pharmacological activity of the parent compound. Such salts include:

[0215] acid addition salts, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 4-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, 4-toluenesulfonic acid, camphorsulfonic acid, glucoheptonic acid, 4,4'-methylenebis-(3-hydroxy-2-ene-1-carboxylic acid), 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid, and the like; or

[0216] salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, e.g., an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base such as ethanolamine, diethanolamine, triethanolamine, tromethamine, N-methylglucamine, and the like. It is understood that the pharmaceutically acceptable salts are non-toxic. Additional information on suitable pharmaceutically acceptable salts can be found in *Remington’s Pharmaceutical Sciences*, 17th ed., Mack Publishing Company, Easton, PA, 1985, which is incorporated herein by reference.

[0217] The compounds of the present invention may have asymmetric centers. Compounds of the present invention containing an asymmetrically substituted atom may be isolated in optically active or racemic forms. It is well known in the art how to prepare optically active forms, such as by resolution of materials. All chiral, diastereomeric, racemic forms are within the scope of this invention, unless the specific stereochemistry or isomeric form is specifically indicated.

[0218] Certain compounds of Formula I can exist as isomers. All possible isomers are within the
scope of this invention. Additionally, as used herein the terms alkyl includes all the possible isomeric forms of said alkyl group albeit only a few examples are set forth. Furthermore, when the cyclic groups such as aryl, heteroaryl, heterocycloalkyl are substituted, they include all the positional isomers albeit only a few examples are set forth.

Preferred Embodiments

[0219] While the broadest definition of this invention is set forth in the Summary of the Invention, certain compounds of Formula I are preferred. For example:

[0220] 1. One preferred group of compounds of Formula I:

\[ \text{I} \]

is that wherein:

[0221] Ar\textsuperscript{1} is activating heteroarylene or activating phenylene;

[0222] W is \(-\text{A}^1\text{-D-}\text{A}^2\); where D is \(-\text{O}\text{-}, \text{-NR}^4\text{-}, \text{-C(O)}\text{-}, \text{-C(O)O)}\text{-}, \text{-OC(O)}\text{-}, \text{-C(O)NR}^4\text{-}, \text{-NR}^4\text{C(O)}\text{-}, \text{-S(O)}\text{n}\text{-} (where n is 0, 1, or 2), \text{-NR}^4\text{S(O)}\text{2}\text{-}, \text{-S(O)}\text{2}\text{NR}^4\text{-}, \text{-NR}^4\text{C(O)O)}\text{-}, \text{-OC(O)NR}^4\text{-}, \text{-NR}^4\text{C(O)NR}^5\text{-}, \text{-CR’R”-} (where R’ and R” together with the carbon to which they are attached form cycloalkylene), or a bond and where R\textsuperscript{4} and R\textsuperscript{5} are independently hydrogen, alkyl, alkylcarbonyl, or haloalkylcarbonyl; where A\textsuperscript{1} and A\textsuperscript{2} are independently a bond, alkylene, alkenylene, alkynylene, haloalkylene, haloalkynylene, and where at least one of A\textsuperscript{1}, D, or A\textsuperscript{2} is not a bond;

[0223] R\textsuperscript{1} is hydrogen, alkyl, or substituted alkyl;

[0224] R\textsuperscript{2} is heteroaralkyl, alkylaminoalkyloxyalkyl, dialkylaminoalkyloxyalkyl, heterocycloalkylalkyl, R\textsuperscript{b}R\textsuperscript{b}NC(=NH)NH-S(O)\text{2}alkyl, R\textsuperscript{b}R\textsuperscript{b}NC(=NH)NH-C(O)alkyl, R\textsuperscript{b}R\textsuperscript{b}NC(=NH)NH-Oalkyl, R\textsuperscript{b}R\textsuperscript{b}NC(=NH)NHalkyl, R\textsuperscript{b}R\textsuperscript{b}NC(=NH)alkyl, alkoxyalkyl, alkyl-S(O)\text{2}alkyl, aminocarbonylalkyl, alkylaminocarbonylalkyl, dialkylaminocarbonylalkyl, alkylcarbonylalkyl, alkoxyalkyl, aminocarbonyloxyalkyl, alkyl-NR\textsuperscript{a}-carbonyloxyalkyl, hydroxyalkyl, alkoxyalkyloxyalkyl, alkyl-NR\textsuperscript{a}-sulfonylalkyl, heteroaryl, heteroaralkyl, heteroaralkenyl, heteroaralkylaminocarbonylalkyl, heteroaralkylcarbonylalkyl, heteroaralkylcarbonylalkyl, aryl, aralkyl, aralkenyl, aralkyloxyalkyl, alkoxyalkyl, heteroaryloxyalkyl, heteroaralkyl-NR\textsuperscript{a}-carbonyloxyalkyl, heteroaralkyl-NR\textsuperscript{a}-sulfonylalkyl,
heterocycloalkylalkyl, heterocycloalkylalkyloxyalkyl, heteroarylalkyloxyalkyl, heterocycloalkylalkyl-S(O)n-alkyl, heterocycloalkylalkylNR®-carbonylalkyl, heteroarylalkyl-S(O)n-alkyl, heterocycloalkylalkyl-NR®-carbonylalkyl, heterocycloalkylalkylalkyloxyalkyl, heteroarylalkylalkyloxyalkyl, heterocycloalkylalkyl-NR®-carbonylalkyl, heteroarylalkylalkylalkyloxyalkyl, heterocycloalkylalkyl-NR®-sulfonylalkyl, R®R®Nalkyl (where alkyl is optionally substituted with halo), or R®R®Nalkenyl (where alkenyl is optionally substituted with halo),

[0225] wherein R® and R® are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, aryl, acyl, aminoalkylcarboxyl, alkyaminocarbonyl, dialkylaminocarbonylcarbonyl, alkylcarbonylalkenyl, alkylcarbonyloxyalkyloxyalkyl, alkylaminocarbonyl, dialkylaminocarbonyl, aminocarbonyl, alkoxycarbonyl, alkylsulfonil, heteroarylalkyl-NR®-carbonyl, heteroaryl, heteroarylcarbonyl, heteroaryalkyl, heteroarylalkyloxyalkyl, heteroarylalkylsulfonil, heterocycloalkylalkyl, heterocycloalkylalkyloxyalkyl, heterocycloalkylalkylalkyloxyalkyl, and heterocycloalkylalkylalkyloxyalkylsulfonil,

[0226] wherein n is 0, 1, or 2 and wherein R® and R® are independently selected from hydrogen and alkyl;

[0227] R® is hydroxy and R® is hydrogen or hydroxy; or R® and R® together with the carbon to which they are attached form carbonyl;

[0228] Q is

i) -OR® wherein R® is hydrogen, alkyl, substituted alkyl, acyl, aralkyl, aralkenyl, heteroarylalkyl, aryl, heteroaryl, or -C(O)NR®R® (wherein R® and R® are independently hydrogen, alkyl, aryl, heteroaryl, aralkyl, aralkenyl, heterocycloalkyl, heterocycloalkylalkyl, or heteroarylalkyl);

ii) -S(O)rR® where r is 0, 1, or 2 and R® is alkyl, substituted alkyl, aryl, heteroaryl, heteroarylalkyl, aralkyl, or aralkenyl; or -S(O)rR® where r is 2 and R® is -N R®R® (wherein R® and R® are alkyl, substituted alkyl, aryl, heteroaryl, heteroarylalkyl, aralkyl, or aralkenyl);

iii) -NR®R® wherein each R® and R® are independently hydrogen, alkyl, substituted alkyl, alkylcarbonyl, cyanoalkylcarbonyl, haloalkylcarbonyl, haloalkoxycarbonyl, alkenyloxycarbonyl, alkoxycarbonyl, alkoxyalkylcarbonyl, alkoxyalkyloxyalkyloxyalkyl, alkoxyalkylaminocarbonyl, cycloalkylcarbonyl,
cycloalkylalkylcarbonyl, arylcarbonyl, aralkylcarbonyl, heteroarylcarbonyl, 
heterocycloalkylcarbonyl, aryloxycarbonyl, heteroaryloxy carbonyl, 
cycloalkyloxycarbonyl, heterocycloalkyloxycarbonyl, aralkyloxycarbonyl, 
aralkenylloxycarbonyl, heterocycloalkyloxalkyloxycarbonyl, 
heteroaralkyloxycarbonyl, heteroaralkenyloxycarbonyl, aryl, aralkyl, aralkenyl, 
heteroaryl, heteroaralkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, 
heterocycloalkylalkyl, (R^{17}R^{18}N=)(R^{16}C- (wherein R^{16}, R^{17}, and R^{18} are 
individually hydrogen, alkyl, or substituted alkyl), R^{19}R^{20}NC(O)-, R^{21}S(O)_{2}-, or 
R^{19}R^{20}NS(O)_{2}-, wherein R^{19}, R^{20}, and R^{21} are individually hydrogen, alkyl, 
substituted alkyl, alkenyl, aryl, heteroaryl, heterocycloalkyl, cycloalkyl, aralkyl, 
aralkenyl, heterocycloalkylalkyl, heteroaralkyl, cycloalkylalkyl, or heteroaralkenyl, 
or R^{14} and R^{15} together with the nitrogen to which they are attached form 
heterocycloalkyl or heteroaryl; 

iv) heteroaralkylcarbonylamino; or 

v) hydrogen; and 

[0229] Ar^{2} is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl where Ar^{2} is further substituted with 
E where E is selected from the group consisting of 

\[
-Y^{1}-X^{1}-Y^{2}-Z^{1}-Y^{3}-Ar^{3}, \text{ wherein X}^{1} \text{ and Z}^{1} \text{ are independently } -O-, -NR^{22}-, -C(O)-, 
-C(O)O-, -OC(O)-, -C(O)NR^{22}-, -NR^{22}C(O), -S(O)_{n}- (where n is 0, 1, or 2), 
-NR^{22}S(O)_{2}-, -S(O)_{2}NR^{22}-, -NR^{22}C(O)O_{2}-, -OC(O)NR^{22}-, or -NR^{22}C(O)NR^{23}-; and 
Y^{1}, Y^{2}, Y^{3}, and Ar^{3} are as defined below; 
\]

\[
-X^{1}-Z^{2}-Y^{3}-Ar^{3}, \text{ wherein X}^{1} \text{ is } -O-, -NR^{22}-, -C(O)-, -C(O)O-, -OC(O)-, -C(O)NR^{22}-, 
-NR^{22}C(O), -S(O)_{n}- (where n is 0, 1, or 2), -NR^{22}S(O)_{2}-, -S(O)_{2}NR^{22}-, 
-NR^{22}C(O)O_{2}-, -OC(O)NR^{22}-, or -NR^{22}C(O)NR^{23}-; \text{ Z}^{2} \text{ is cycloalkylene or } 
\text{heterocycloalkylene; and Y}^{3} \text{ and Ar}^{3} \text{ are as defined below; } 
\]

\[
-X^{1}-Y^{2}-Ar^{3}, \text{ wherein X}^{1} \text{ is } -O-, -NR^{22}-, -C(O)-, -C(O)O-, -OC(O)-, -C(O)NR^{22}-, 
-NR^{22}C(O), -S(O)_{n}- (where n is 0, 1, or 2), -NR^{22}S(O)_{2}-, -S(O)_{2}NR^{22}-, 
-NR^{22}C(O)O_{2}-, -OC(O)NR^{22}-, or -NR^{22}C(O)NR^{23}-; \text{ and Y}^{2} \text{ and Ar}^{3} \text{ are as defined below; } 
\]
v) \(-X^1\cdot Y^2\cdot Z^1\cdot Ar^3\), wherein \(X^1\) and \(Z^1\) are independently \(-O-, -NR^{22}, -C(O)-, -C(O)O-, -OC(O)-, -C(O)NR^{22}, -NR^{22}C(O)-, -S(O)\_n-\) (where \(n\) is 0, 1, or 2), -NR^{22}S(O)\_2-, -S(O)\_2NR^{22}, -NR^{22}C(O)O-, -OC(O)NR^{22}, or -NR^{22}C(O)NR^{23}; and \(Y^2\) and \(Ar^3\) are as defined below;

vi) \(-Y^1\cdot Ar^3\) where \(Y^1\) and \(Ar^3\) are as defined below;

vii) \(-Y^1\cdot X^1\cdot Y^2\cdot Ar^3\), wherein \(X^1\) is \(-O-, -NR^{22}, -C(O)-, -C(O)O-, -OC(O)-, -C(O)NR^{22}, -NR^{22}C(O)-, -S(O)\_n-\) (where \(n\) is 0, 1, or 2), -NR^{22}S(O)\_2-, -S(O)\_2NR^{22}, -NR^{22}C(O)O-, -OC(O)NR^{22}, or -NR^{22}C(O)NR^{23}; and \(Y^1\), \(Y^2\), and \(Ar^3\) are as defined below;

viii) \(-Y^1\cdot X^1\cdot Ar^3\), wherein \(X^1\) is \(-O-, -NR^{22}, -C(O)-, -C(O)O-, -OC(O)-, -C(O)NR^{22}, -NR^{22}C(O)-, -S(O)\_n-\) (where \(n\) is 0, 1, or 2), -NR^{22}S(O)\_2-, -S(O)\_2NR^{22}, -NR^{22}C(O)O-, -OC(O)NR^{22}, or -NR^{22}C(O)NR^{23}; and \(Y^1\) and \(Ar^3\) are as defined below;

ix) \(-X^1\cdot Y^2\cdot Y^3\cdot Ar^3\), wherein \(X^1\) is \(-O-, -NR^{22}, -C(O)-, -C(O)O-, -OC(O)-, -C(O)NR^{22}, -NR^{22}C(O)-, -S(O)\_n-\) (where \(n\) is 0, 1, or 2), -NR^{22}S(O)\_2-, -S(O)\_2NR^{22}, -NR^{22}C(O)O-, -OC(O)NR^{22}, or -NR^{22}C(O)NR^{23}; and \(Y^1\), \(Y^2\), \(Y^3\), and \(Ar^3\) are as defined below; and

x) \(-Y^1\cdot X^1\cdot Y^2\cdot Z^1\cdot Ar^3\), wherein \(X^1\) and \(Z^1\) are independently \(-O-, -NR^{22}, -C(O)-, -C(O)O-, -OC(O)-, -C(O)NR^{22}, -NR^{22}C(O)-, -S(O)\_n-\) (where \(n\) is 0, 1, or 2), -NR^{22}S(O)\_2-, -S(O)\_2NR^{22}, -NR^{22}C(O)O-, -OC(O)NR^{22}, or -NR^{22}C(O)NR^{23}; and \(Y^1\), \(Y^2\), and \(Ar^3\) are as defined below; and

wherein \(R^{22}\) and \(R^{23}\) are independently hydrogen, alkyl, substituted alkyl, or acyl; wherein \(Y^1\), \(Y^2\), and \(Y^3\) are independently alkylene, alkenylene, alkynylene, haloalkylene, haloalkenylenne, haloalkynylene, carboxyalkylene, or \(-CR^c\_R^d\) (where \(R^c\) and \(R^d\) together with the carbon to which they are attached form cycloalkylene); and wherein \(Ar^3\) is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl; or

[0230] a pharmaceutically acceptable salt thereof.

[0231] 2. A compound of Formula I:

\[
\begin{array}{c}
\text{Ar}^1 \\
\text{Ar}^2 \\
\text{Q} \\
\text{R}^5 \\
\text{R}^3 \\
\text{R}^4 \\
\end{array}
\]

30
[0232] wherein

[0233] Ar¹ is activating heteroarylene;

[0234] W is \(-A¹-D-A²\); where D is \(-\text{C}(\text{O})\)-, \(-\text{CR } \text{R}''\)- (where \text{R'} and \text{R''} together with the carbon to which they are attached form cycloalkylene), or a bond; where \text{A¹} and \text{A²} are independently a bond or alkylene; and where at least one of \text{A¹}, \text{D}, or \text{A²} is not a bond;

[0235] R¹ is hydrogen;

[0236] R² is heteroaralkyl, \text{R}³\text{R}⁴\text{N}_(\text{C})\text{H}-\text{C}(\text{O})-alkyl, aralkyl, \text{R}⁶\text{R}⁷\text{N}alkyl (where alkyl is optionally substituted with halo), or \text{R}⁶\text{R}⁷\text{N}alkenyl (where alkenyl is optionally substituted with halo), wherein \text{R}⁶ and \text{R}⁷ are independently hydrogen or alkoxy-carbonyl, wherein \text{R}⁸ and \text{R}⁹ are independently selected from hydrogen and alkyl;

[0237] R³ is hydroxy or \(-\text{OSiR}^{2₄}\text{R}^{2₅}\text{R}^{2₆}\) (where \text{R}²₄, \text{R}²₅, and \text{R}²₆ are independently alkyl or aryl) and \text{R}³₈ is hydrogen; or \text{R}³ and \text{R}³₈ together with the carbon to which they are attached form carbonyl;

[0238] Q is fused-heterocycloalkylalkylcarbonylamino; hydrogen; or \(-\text{NR}^{1₄}\text{R}^{1₅}\) wherein each \text{R}¹₄ and \text{R}¹₅ are independently hydrogen, alkyl, substituted alkyl, alkylcarbonyl, haloalkylcarbonyl, haloalkoxy-carbonyl, alkenyloxy-carbonyl, alkoxy-carbonyl, alkoxyalkylcarbonyl, alkoxyalkyloxy-carbonyl, alkoxycarbonylamino-carbonyl, cycloalkylcarbonyl, arylcarbonyl, heteroarylcarbonyl, heterocycloalkylcarbonyl, aralkyloxycarbonyl, heterocycloalkylalkyloxy-carbonyl, heteroaralkyloxycarbonyl, \text{R}¹⁹\text{R}²₀\text{N}⁷\text{C}⁴\text{(O)}\text{⁻}, \text{R}²¹\text{S}⁴\text{(O)}₂⁻, \text{R}²¹\text{R}²²\text{N}₅\text{S}⁶\text{(O)}₂⁻, wherein \text{R}¹₉, \text{R}²₀, and \text{R}²¹ are independently hydrogen, alkyl, aryl, heteroaryl, heterocycloalkyl, aralkyl, or heteroaralkyl; or \text{R}¹₄ and \text{R}¹₅ together with the nitrogen to which they are attached form heterocycloalkyl or heteroaryl; and

[0239] Ar² is aryl or heterocycloalkyl where \text{Ar}² is further substituted with \text{E} where \text{E} is selected from the group consisting of

i) \(-X¹⁻Y²⁻\text{Ar}³\), where \text{X}¹ is \(-\text{C}(\text{O})\); \text{Z}² is heterocycloalkylene; \text{Y}² is alkylene; and \text{Ar}³ is aryl;

ii) \(-X¹⁻Y²⁻\text{Ar}³\), where \text{X}¹ is \(-\text{O}-\), \(-\text{NR}^{2₂}⁻\), \(-\text{C}(\text{O})⁻\), \(-\text{C}(\text{O})\text{O}-\), \(-\text{OC}(\text{O})⁻\), \(-\text{C}(\text{O})\text{NR}^{2₂}⁻\), \(-\text{NR}^{2₂}\text{C}(\text{O})⁻\), \(-\text{S}(\text{O})₂⁻\) (where \text{n} is \(0, 1, \) or \(2\)), \(-\text{NR}^{2₂}\text{S}(\text{O})₂⁻\), \(-\text{S}(\text{O})₂\text{NR}^{2₂}⁻\), \(-\text{NR}^{2₂}\text{C}(\text{O})\text{O}⁻\), \(-\text{OC}(\text{O})\text{NR}^{2₂}⁻\), or \(-\text{NR}^{2₂}\text{C}(\text{O})\text{NR}^{2₃}⁻\); \text{Y}² is alkylene, alkynylene, or carboxyalkylene; and \text{Ar}³ is aryl, heteroaryl, or cycloalkyl;

iii) \(-X¹⁻\text{Ar}³\), where \text{X}¹ is \(-\text{OC}(\text{O})\text{NR}^{2₂}⁻\), \(-\text{S}(\text{O})₂⁻\), or \(-\text{C}(\text{O})⁻\); and \text{Ar}³ is aryl;

iv) \(-X¹⁻\text{L}⁻\text{Z}¹⁻\text{Ar}³\), where \text{X}¹ is \(-\text{O}-\) or \(-\text{C}(\text{O})\text{NR}^{2₂}⁻\); \text{Y}² is alkylene; \text{Z}¹ is \(-\text{O}-\) or
v)  $-\text{Y}^1\text{-Ar}^3$ where $\text{Y}^1$ is alkylene and $\text{Ar}^3$ is aryl;

vi)  $-\text{Y}^1\text{-X}^1\text{-Ar}^3$, where $\text{Y}^1$ is alkylene; $\text{X}^1$ is $-\text{C}(\text{O})-$; and $\text{Ar}^3$ is heterocycloalkyl; and

vii)  $-\text{X}^1\text{-Y}^2\text{-Y}^3\text{-Ar}^3$, where $\text{X}^1$ is $-\text{O}-$; $\text{Y}^2$ is alkylene; $\text{Y}^3$ is $-\text{CR}^5\text{R}^d$ (where $\text{R}^5$ and $\text{R}^d$

 together with the carbon to which they are attached form cycloalkylene); and $\text{Ar}^3$ is

arthyll; and

wherein $\text{R}^{22}$ and $\text{R}^{23}$ are independently hydrogen, alkyl, substituted alkyl, or acyl; or

[0240] a pharmaceutically acceptable salt thereof.

[0241] 3. Another preferred group of compounds of Formula I is that wherein the stereochemistry

at $\ast\text{C}$, as indicated in the following structure, is S.

\[
\begin{array}{c}
\text{Q}^1\text{R}^1 \\
\text{R}^2 \\
\text{R}^3 \\
\text{R}^{3a}
\end{array}
\]

[0242] 4. Another preferred group is that wherein $\text{Ar}^1$ is activating heteroarylene or activating

phenylene; preferably, activating heteroarylene; more preferably, oxadiazol-diyil; even more

preferably, 1,2,4-oxadiazol-3,5-diyl or 1,3,4-oxadiazol-2,5-diyl; particularly preferably,

1,2,4-oxadiazol-3,5-diyl.

[0243] 5. Another preferred group of compounds of Formula I is that wherein $\text{W}$ is $-\text{A}^1\text{-D}-\text{A}^2$-

where $\text{D}$ is $-\text{O}-, -\text{NR}^4-, -\text{C}(\text{O})-, -\text{OC}(\text{O})-, -\text{C}(\text{O})\text{NR}^4-, -\text{NR}^4\text{C}(\text{O})-, -\text{S}(\text{O})_n-$ (where $n$ is 0, $\text{R}^1$ and $\text{R}^2$ together with the carbon to which they are attached form cycloalkylene), or a bond and

where $\text{R}^4$ and $\text{R}^5$ are independently hydrogen, alkyl, alkylcarbonyl, or haloalkylcarbonyl; where $\text{A}^1$

and $\text{A}^2$ are independently a bond, alkylene, alkenylene, alkynylene, haloalkylene, haloalkarylene,

or haloalkynylene; and where at least one of $\text{A}^1$, $\text{D}$, or $\text{A}^2$ is not a bond;

[0244] preferably, $\text{W}$ is $-\text{A}^1\text{-D}-\text{A}^2$-

\\[i) \quad \text{A}^1 \text{ is alkylene and D and A}^2 \text{ are each bond, preferably, A}^1 \text{ is } \text{-CH}_2-\text{, -CH(CH}_3\text{)_2-} \text{, or} \]

-\text{C(}\text{CH}_3\text{)}_2-;  \\
\\[\text{ii) } \text{A}^1 \text{ and A}^2 \text{ are each bond and D is CR}^1\text{'R}^2\text{'' (where R}^1 \text{ and R}^2\text{ together with the carbon to which they are attached form cycloalkylene); or} \]

\\[\text{iii) } \text{A}^1 \text{ and A}^2 \text{ are each bond and D is } \text{-C(O)-}; \]

[0245] more preferably, $\text{W}$ is $-\text{A}^1\text{-D}-\text{A}^2$-

where $\text{A}^1$ is alkylene and $\text{D}$ and $\text{A}^2$ are each bond or

where $\text{A}^1$ and $\text{A}^2$ are each bond and $\text{D}$ is CR$^1$R$^{2''}$ (where R$^1$ and R$^{2''}$ together with the carbon to
which they are attached form cycloalkylene); even more preferably, W is -CH$_2$-, -CH(CH$_3$)$_2$-, or cycloprop-1,2-diyl; particularly preferably W is -CH$_2$- or cycloprop-1,2-diyl; even more particularly preferably, W is -CH$_2$-.

[0246] 6. Another preferred group of compounds of Formula I is that wherein R$^1$ is hydrogen, alkyl, or substituted alkyl; preferably, hydrogen.

[0247] 7. Another preferred group of compounds of Formula I is that wherein R$^2$ is heteroaralkyl, alkylaminooalkyloxyalkyl, dialkylaminooalkyloxyalkyl, heterocycloalkylalkyl, R$^b$R$^b$NC(=NH)NH-S(O)$_2$alkyl, R$^b$R$^b$NC(=NH)NH-C(O)alkyl, R$^b$R$^b$NC(=NH)NH-Oalkyl, R$^a$R$^b$NC(=NH)NHalkyl, R$^a$R$^b$NC(=NH)alkyl, alkoxycarbonylalkyl, alkylaminocarbonylalkyl, dialkylaminocarbonylalkyl, alkylcarbonylalkyl, alkoxyalkyl, aminocarboyloxyalkyl, alkyl-NR$^a$-carbonyloxyalkyl, hydroxalkyl, alkoxy carbonyl amino, alkyl-NR$^a$-sulfonylalkyl, heteroaryl, heteroaralkyl, heteroaralkenyl, heteroa ralkylaminocarbonylalkyl, heteroa ralkylcarbonylalkyl, heteroa ralkylcarbonylalkyl, aryl, aralkyl, aralkenyl, aro lkoxyalkyl, aryloxyalkyl, heteroaryloxyalkyl, heteroa ralkyl-NR$^a$-carbonyloxyalkyl, heteroaralkyl-NR$^a$-sulfonylalkyl, heterocycloalkylalkyl, heterocycloalkylalkyloxyalkyl, heteroa ralkylamyloxyalkyl, heterocycloalkylalkyl-NR$^a$-alkyl, heterocycloalkylalkyl-NR$^a$-carbonylalkyl, heterocycloalkylalkyl-NR$^a$-sulfonylalkyl, heterocycloalkylalkyl-NR$^a$-carbonylalkyl, heterocycloalkylalkyl-NR$^a$-carbonylalkyl, hetero aralkyl-NR$^a$-sulfon ylalkyl, R$^6$R$^7$Nalkyl (where alkyl is optionally substituted with halo), or R$^6$R$^7$Nalkenyl (where alkenyl is optionally substituted with halo).

[0248] wherein R$^6$ and R$^7$ are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, aryl, aroyl, aminoalkylcarbonyl, alkylaminooalkylcarbonyl, dialkylaminooalkylcarbonyl, alkylcarbonylalkyl, alkylaminocarbonylalkyl, dialkylaminocarbonylalkyl, aminocar bonylalkyl, alkoxycarbonylalkyl, alkylsulfon ylalkyl, heteroaralkyl-NR$^a$-carbonylalkyl, heteroaryl, heteroarylcarbonyl, heteroaralkyl, heteroaralkylcarbonyl, heteroa ralkylaminesulfon ylalkyl, heterocycloalkylalkyl, heterocycloalkylalkyl-NR$^a$-carbonylalkyl, and heterocycloalkylalkyl-NR$^a$-carbonylalkyl, heterocycloalkylalkyl-NR$^a$-sulfonylalkyl,
or aralkyl;

[0251] more preferably, R² is 1H-pyrrolo[3,2-c]pyridin-2-ylmethyl, R⁶R⁷Nalkyl (where R⁶ and R⁷ are each hydrogen or where R⁶ is hydrogen and R⁷ is alkoxy carbonyl), R⁶R⁷Nalkenyl (where R⁶ and R⁷ are hydrogen or where R⁶ is hydrogen and R⁷ is alkoxy carbonyl), R²R²NC(=NH)NH-C(O)alkyl (where R⁸ and R⁹ are each hydrogen), or 4-(aminomethyl)-phenylmethyl;

[0252] even more preferably, R² is H₂N(CH₂)₄, t-butoxycarbonylaminobutyl, H₂NCH₂CH=CHCH₂, H₂NC(=NH)NH-C(O)ethyl, or 4-(aminomethyl)-phenylmethyl;

[0253] particularly preferably, R² is H₂N(CH₂)₄.

[0254] 8. Another preferred group of compounds of Formula I is that wherein R³ is hydroxy or -OSiR²₄₄R²₄₅R²₄₆ (where R²₄₄, R²₄₅, and R²₄₆ are independently alkyl or aryl) and R³₈ is hydrogen, hydroxy, or -OSiR²₄₄R²₄₅R²₄₆ (where R²₄₄, R²₄₅, and R²₄₆ are independently alkyl or aryl); or R³ and R³₈ together with the carbon to which they are attached form carbonyl; preferably, R³ and R³₈ together with the carbon to which they are attached form carbonyl.

[0255] 9. Another preferred group of compounds of Formula I is that wherein Q is

i) -OR⁸ wherein R⁸ is hydrogen, alkyl, substituted alkyl, acyl, aralkyl, aralkenyl, heteroaralkyl, ary1, heteroaryl, or -C(O)NR⁹R¹⁰ (wherein R⁹ and R¹⁰ are independently hydrogen, alkyl, aryl, heteroaryl, aralkyl, aralkenyl, heterocycloalkyl, heterocycloalkylalkyl, or heteroaralkyl);

ii) -S(O)₂R¹¹ where r is 0, 1, or 2 and R¹¹ is alkyl, substituted alkyl, aryl, heteroaryl, heteroaralkyl, aralkyl, or aralkenyl; or -S(O)₂R¹¹ where r is 2 and R¹¹ is -N R¹²R¹³ (wherein R¹² and R¹³ are alkyl, substituted alkyl, aryl, heteroaryl, heteroaralkyl, aralkyl, or aralkenyl);

iii) -NR¹⁴R¹⁵ wherein each R¹⁴ and R¹⁵ are independently hydrogen, alkyl, substituted alkyl, alky1carbonyl, cyanoalkylcarbonyl, haloalkylcarbonyl, haloalkoxy carbonyl, alkenyloxycarbonyl, alkoxy carbonyl, alkoxyalkylcarbonyl, alkoxyalkyloxycarbonyl, alkoxy carbonylamino carbonyl, cycloalkylcarbonyl, cycloalkylalkylcarbonyl, aryl carbonyl, aralkylcarbonyl, heteroarylcarbonyl, heterocycloalkylcarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, cycloalkyloxycarbonyl, heterocycloalkyloxycarbonyl, aralkyloxycarbonyl, aralkenyloxycarbonyl, heterocycloalkylalkyloxycarbonyl, heteroaralknyloxycarbonyl, aryl, aralkyl, aralkenyl,
heteroaryl, heteroaralkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, (R^{18}R^{17}N=) (R^{16})C- (wherein R^{16}, R^{17}, and R^{18} are independently hydrogen, alkyl, or substituted alkyl), R^{19}R^{20}NC(O)-, R^{21}S(O)_{2}-, or R^{19}R^{20}NS(O)_{2}-, wherein R^{19}, R^{20}, and R^{21} are independently hydrogen, alkyl, substituted alkyl, alkenyl, aryl, heteroaryl, heterocycloalkyl, cycloalkyl, aralkyl, aralkenyl, heterocycloalkylalkyl, heteroaralkyl, cycloalkylalkyl, or heteroaralkenyl, or R^{14} and R^{15} together with the nitrogen to which they are attached form heterocycloalkyl or heteroaryl;

iv) heterocycloalkylalkylcarbonylamino;
v) fused-heterocycloalkylalkylcarbonylamino;
vi) heteroaralkylcarbonylamino; or
vii) hydrogen.

[0256] 10. Within Preferred Embodiment 9 is a more preferred group where Q is –NR^{14}R^{15}, where R^{14} is hydrogen, alkyl, or heterocycloalkylcarbonyl and R^{15} is aralkyloxy carbonyl, alkoxycarbonyl, alkenyloxycarbonyl, alkylcarbonyl, heterocycloalkylcarbonyl, cycloalkylcarbonyl, heteroarylcarbonyl, substituted alkyl (preferably haloalkyl), haloalkylcarbonyl, arylcarbonyl, R^{21}S(O)_{2}- (where R^{21} is alkyl or aryl), alkoxyalkyloxy carbonyl, -C(O)NR^{19}R^{20} (where R^{19} is alkyl and R^{20} is hydrogen, alkyl, or aryl), alkoxyalkylcarbonyl, alkoxycarbonylaminocarbonyl, R^{19}R^{20}NS(O)_{2}- (where R^{19} is alkyl and R^{20} is hydrogen, alkyl, or aryl),

[0257] preferably, Q is phenylmethyloxycarbonylamino, methoxycarbonylamino, ethoxycarbonylamino, isoproxyoxycarbonylamino, 2,2-dimethylpropyloxycarbonylamino, N-(prop-1-en-3-yloxy carbonyl)-amino, methyloxycarbonylamino, n-pentyloxycarbonylamino, tert-butyloxycarbonylamino, isoproxyoxycarbonylamino, morpholinocarbonylamino, N,N-bis-(morpholin-4-ylcarbonyl)amino, pyrrolidin-1-ylcarbonylamino, tetrahydrofuran-3-ylcarbonylamino, piperidin-1-ylcarbonylamino, [N-(methylcarbonyl)-pyrrolidin-2-yl]carbonylamino, cyclopentylcarbonylamino, cyclopropylcarbonylamino, 1-cyanocycloprop-1-ylcarbonylamino, furan-2-ylcarbonylamino, 2,5-dimethylfuran-3-ylcarbonylamino, benzo[1,3]dioxol-5-ylcarbonylamino, 2,2,2-trifluoroethylamino, trifluoromethylcarbonylamino, 2-fluorophenylcarbonylamino, 3-fluorophenylcarbonylamino, 4-fluorophenylcarbonylamino, 3,4-difluorophenylcarbonylamino, 2,4-difluorophenylcarbonylamino, 3,5-difluorophenylcarbonylamino, 4-chlorophenylcarbonylamino, methyloxysulfonlamino,
4-fluorophenylsulfonylamino, methoxyethylxycarbonylamino, dimethylaminocarbonylamino, diethylaminocarbonylamino, methoxymethylcarbonylamino, ethoxycarbonylamino, or N,N-dimethylaminosulfonylamino,

more preferably, Q is phenylmethoxyxycarbonylamino, ethoxycarbonylamino, tert-butylcarbonylamino, morpholinocarbonylamino, piperidin-1-ylcarbonylamino, furan-2-ylcarbonylamino, benzo[1,3]dioxol-5-ylcarbonylamino, 2-fluorophenylcarbonylamino, 3-fluorophenylcarbonylamino, 4-fluorophenylcarbonylamino, 3,4-difluoro-phenylcarbonylamino, 2,4-difluorophenylcarbonylamino, 3,5-difluorophenylcarbonylamino, 4-chlorophenylcarbonylamino, or methoxyethylxycarbonylamino;

even more preferably, Q is ethoxycarbonylamino, morpholinocarbonylamino, 3-fluorophenylcarbonylamino, 4-fluorophenylcarbonylamino, or 3,4-difluorophenylcarbonylamino.

Within Preferred Embodiment 9 is a more preferred group where Q is hydrogen.

Within Preferred Embodiment 9 is a more preferred group where Q is \(-\text{NR}^1\text{R}^2\) where \text{R}^1 and \text{R}^2 together with the nitrogen to which they are attached form heterocycloalkyl or heteroaryl, preferably, 2,5-dioxopyrrolidinyl, 2,5-dioxo-3,3-dimethylpyrrolidinyl, or phthalimidyl.

Ar is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl where Ar is further substituted with E where E is selected from the group consisting of

\[-\text{Y}^1\text{-X}^1\text{-Y}^2\text{-Z}^1\text{-Y}^3\text{-Ar}^3, \text{wherein X}^1 \text{ and Z}^1 \text{ are independently } \text{-O}, \text{-NR}^2, \text{-C(O)}, \text{-C(O)O}, \text{-OC(O)}\text{-, -C(O)NR}^2\text{-, -NR}^2\text{C(O)}, \text{-S(O)h}(- \text{where n is 0, 1, or 2)}, \text{-NR}^2\text{S(O)}\text{-, -S(O)2NR}^2\text{-, -NR}^2\text{C(O)O}, \text{-OC(O)NR}^2\text{-, or -NR}^2\text{C(O)NR}^2\text{-; and Y}^1\text{-Y}^2\text{-Y}^3\text{ and Ar}^3\text{ are as defined below};

\[-\text{X}^1\text{-Z}^2\text{-Y}^3\text{-Ar}^3, \text{wherein X}^1 \text{ is } \text{-O}, \text{-NR}^2, \text{-C(O)O}, \text{-OC(O)O}, \text{-C(O)NR}^2\text{-, -NR}^2\text{C(O)O}, \text{-S(O)h}(- \text{where n is 0, 1, or 2)}, \text{-NR}^2\text{S(O)}\text{-, -S(O)2NR}^2\text{-, -NR}^2\text{C(O)O}, \text{-OC(O)NR}^2\text{-, or -NR}^2\text{C(O)NR}^2\text{-; Z}^2 \text{ is cycloalkylene or heterocycloalkylene; and Y}^1\text{ and Ar}^3\text{ are as defined below};

\[-\text{X}^1\text{-Y}^2\text{-Ar}^3, \text{wherein X}^1 \text{ is } \text{-O}, \text{-NR}^2, \text{-C(O)}, \text{-C(O)O}, \text{-OC(O)}, \text{-C(O)NR}^2\text{-, -NR}^2\text{C(O)}, \text{-S(O)h}(- \text{where n is 0, 1, or 2)}, \text{-NR}^2\text{S(O)}\text{-, -S(O)2NR}^2\text{-, -NR}^2\text{C(O)O}, \text{-OC(O)NR}^2\text{-, or -NR}^2\text{C(O)NR}^2\text{-; and Y}^2\text{ and Ar}^3\text{ are as defined below};

\[-\text{X}^2\text{-Ar}^3\text{, wherein X}^2 \text{ is } \text{-O}, \text{-C(O)NR}^2\text{-, or -NR}^2\text{C(O)NR}^2\text{-; and Ar}^3\text{ is substituted aryl, heteroaryl, cycloalkyl, or heterocycloalkyl;}

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v) \(-X^3\cdot Ar^3\), wherein \(X^3\) is \(-\text{NR}^{22}\), \(-\text{C(0)}\), \(-\text{C(0)O}^\cdot\), \(-\text{OC(0)}\), \(-\text{S(0)}_n^\cdot\) (where \(n\) is 0, 1, or 2), \(-\text{NR}^{22}\cdot \text{S(0)}_2^\cdot\), \(-\text{S(0)}_2\text{NR}^{22}\), \(-\text{NR}^{22}\cdot \text{C(0)}\text{O}^\cdot\), \(-\text{OC(0)}\text{NR}^{22}\), or \(-\text{NR}^{22}\cdot \text{C(0)}\text{NR}^{23}\); and \(Ar^3\) is as defined below;

vi) \(-X_1\cdot Y^2\cdot Z_1\cdot Ar^3\), wherein \(X^1\) and \(Z^1\) are independently \(-\text{O}^\cdot\), \(-\text{NR}^{22}\), \(-\text{C(0)}\), \(-\text{C(0)O}^\cdot\), \(-\text{OC(0)}\), \(-\text{C(0)NR}^{22}\), \(-\text{C(0)S}^{2}\), \(-\text{NR}^{22}\cdot \text{S(0)}_2^\cdot\), \(-\text{S(0)}_2\text{NR}^{22}\), \(-\text{NR}^{22}\cdot \text{C(0)}\text{O}^\cdot\), \(-\text{OC(0)}\text{NR}^{22}\), or \(-\text{NR}^{22}\cdot \text{C(0)}\text{NR}^{23}\); and \(Y^2\) and \(Ar^3\) are as defined below;

vii) \(-Y^1\cdot Ar^3\) where \(Y^1\) and \(Ar^3\) are as defined below;

viii) \(-Y^1\cdot X^1\cdot Y^2\cdot Ar^3\), wherein \(X^1\) is \(-\text{O}^\cdot\), \(-\text{NR}^{22}\), \(-\text{C(0)}\), \(-\text{C(0)O}^\cdot\), \(-\text{OC(0)}\), \(-\text{C(0)NR}^{22}\), \(-\text{NR}^{22}\cdot \text{C(0)}\text{O}^\cdot\), \(-\text{S(0)}_n^\cdot\) (where \(n\) is 0, 1, or 2), \(-\text{NR}^{22}\cdot \text{S(0)}_2^\cdot\), \(-\text{S(0)}_2\text{NR}^{22}\), \(-\text{NR}^{22}\cdot \text{C(0)}\text{O}^\cdot\), \(-\text{OC(0)}\text{NR}^{22}\), or \(-\text{NR}^{22}\cdot \text{C(0)}\text{NR}^{23}\); and \(Y^1\), \(Y^2\), and \(Ar^3\) are as defined below;

ix) \(-Y^1\cdot X^1\cdot Ar^3\), wherein \(X^1\) is \(-\text{O}^\cdot\), \(-\text{NR}^{22}\), \(-\text{C(0)}\), \(-\text{C(0)O}^\cdot\), \(-\text{OC(0)}\), \(-\text{C(0)NR}^{22}\), \(-\text{NR}^{22}\cdot \text{C(0)}\text{O}^\cdot\), \(-\text{S(0)}_n^\cdot\) (where \(n\) is 0, 1, or 2), \(-\text{NR}^{22}\cdot \text{S(0)}_2^\cdot\), \(-\text{S(0)}_2\text{NR}^{22}\), \(-\text{NR}^{22}\cdot \text{C(0)}\text{O}^\cdot\), \(-\text{OC(0)}\text{NR}^{22}\), or \(-\text{NR}^{22}\cdot \text{C(0)}\text{NR}^{23}\); and \(Y^1\) and \(Ar^3\) are as defined below;

x) \(-X^1\cdot Y^2\cdot Z^1\cdot Ar^3\), wherein \(X^1\) is \(-\text{O}^\cdot\), \(-\text{NR}^{22}\), \(-\text{C(0)}\), \(-\text{C(0)O}^\cdot\), \(-\text{OC(0)}\), \(-\text{C(0)NR}^{22}\), \(-\text{NR}^{22}\cdot \text{C(0)}\text{O}^\cdot\), \(-\text{S(0)}_n^\cdot\) (where \(n\) is 0, 1, or 2), \(-\text{NR}^{22}\cdot \text{S(0)}_2^\cdot\), \(-\text{S(0)}_2\text{NR}^{22}\), \(-\text{NR}^{22}\cdot \text{C(0)}\text{O}^\cdot\), \(-\text{OC(0)}\text{NR}^{22}\), or \(-\text{NR}^{22}\cdot \text{C(0)}\text{NR}^{23}\); and \(Y^2\), \(Y^3\), and \(Ar^3\) are as defined below; and

\[0263\] wherein \(R^{22}\) and \(R^{23}\) are independently hydrogen, alkyl, substituted alkyl, or acyl; wherein \(Y^1\), \(Y^2\), and \(Y^3\) are independently alkylene, alkenylene, haloalkylene, haloalkenylen, halooalkylen, carboxyalkylene, or \(-\text{CR}^c\text{R}^d\) (where \(\text{R}^c\) and \(\text{R}^d\) together with the carbon to which they are attached form cycloalkylene); and wherein \(Ar^3\) is aryl, heteroaryl, cycloalkyl, or heterocyloalkyl.

\[0264\] 14. Within Preferred Embodiment 13, a more preferred group is that wherein \(Ar^3\) is 6-membered aryl and \(E\) is \(-X^1\cdot Z^2\cdot Y^3\cdot Ar^3\), \(-X^1\cdot Y^2\cdot Ar^3\), \(-X^1\cdot Y^2\cdot Z^1\cdot Ar^3\), or \(-X^1\cdot Y^2\cdot Y^3\cdot Ar^3\), preferably, \(-X^1\cdot Y^2\cdot Ar^3\), more preferably \(-O\cdot Y^2\cdot Ar^3\) or \(-\text{C(O)}\text{NH}\cdot Y^2\cdot Ar^3\), even more preferably,
-OCH₂CH₂Ar³ or -C(O)NHCH₂CH₂Ar³.

[0265] 15. Within Preferred Embodiment 13, a more preferred group is that wherein Ar² is heterocycloalkyl, preferably piperidinyl or piperaizinyl, more preferably piperaizinyl, and E is -Y¹- Ar³, -X¹-Y²-Ar³, or -Y¹-X¹-Ar³, more preferably -C(O)-Y²-Ar³, -C(O)O-Y²-Ar³ or -C(O)NH-Y²-Ar³, even more preferably, -C(O)NHCH₂CH₂Ar³.

[0266] 16. Within Preferred Embodiment 13, a more preferred group is that wherein Ar² is heteroaryl, preferably benzofuranyl, and E is -Y¹-Ar³, preferably -CH₂CH₂Ar³.

[0267] 17. Another preferred group of compounds of Formula I is that wherein Ar² is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl where Ar² is further substituted with E where E is selected from the group consisting of

i) -Y¹-X¹-Y²-Z¹-Y³-Ar³, wherein X¹ and Z¹ are independently -O-, -NR²²-, -C(O)-, -C(O)O-, -OC(O)-, -C(O)NR²²-, -NR²²-C(O)-, -S(O)n- (where n is 0, 1, or 2), -NR²²S(O)₂⁻, -S(O)₂NR²²-, -NR²²C(O)O-, -OC(O)NR²²-, or -NR²²C(O)NR²³⁻; and Y¹, Y², Y³, and Ar³ are as defined below;

ii) -X¹-Z²-Y³-Ar³, wherein X¹ is -O-, -NR²²-, -C(O)-, -C(O)O-, -OC(O)-, -C(O)NR²²-, -NR²²C(O)-, -S(O)n- (where n is 0, 1, or 2), -NR²²S(O)₂⁻, -S(O)₂NR²²-, -NR²²C(O)O-, -OC(O)NR²²-, or -NR²²C(O)NR²³⁻; Z² is cycloalkylene or heterocycloalkylene; and Y¹ and Ar³ are as defined below;

iii) -X¹-Y²-Ar³, wherein X¹ is -O-, -NR²²-, -C(O)-, -C(O)O-, -OC(O)-, -C(O)NR²²-, -NR²²C(O)-, -S(O)n- (where n is 0, 1, or 2), -NR²²S(O)₂⁻, -S(O)₂NR²²-, -NR²²C(O)O-, -OC(O)NR²²-, or -NR²²C(O)NR²³⁻; and Y² and Ar³ are as defined below;

iv) -X¹-Z²-Y³-Ar³, wherein X¹ is -NR²²-, -C(O)-, -C(O)O-, -OC(O)-, -S(O)n- (where n is 0, 1, or 2), -NR²²S(O)₂⁻, -S(O)₂NR²²-, -NR²²C(O)O-, -OC(O)NR²²-, or -NR²²C(O)NR²³⁻; and Ar³ is as defined below;

v) -X¹-Y²-Z¹-Ar³, wherein X¹ and Z¹ are independently -O-, -NR²²-, -C(O)-, -C(O)O-, -OC(O)-, -C(O)NR²²-, -NR²²C(O)-, -S(O)n- (where n is 0, 1, or 2), -NR²²S(O)₂⁻, -S(O)₂NR²²-, -NR²²C(O)O-, -OC(O)NR²²-, or -NR²²C(O)NR²³⁻; and Y² and Ar³ are as defined below;

vi) -Y¹-Ar³ where Y¹ and Ar³ are as defined below;
-NR²²C(O)O-, -OC(O)NR²²-, or -NR²²C(O)NR²³⁻; and Y¹, Y², and Ar³ are as
defined below;

viii) -Y¹⁻X¹⁻Ar³, wherein X¹ is -O-, -NR²²-, -C(O)-, -C(O)O-, -OC(O)-, -C(O)NR²²-, -NR²²C(O)⁻, -S(O)ₙ⁻ (where n is 0, 1, or 2), -NR²²S(O)₂⁻, -S(O)₂NR²²-, -NR²²C(O)O⁻, -OC(O)NR²²-, or -NR²²C(O)NR²³⁻; and Y¹ and Ar³ are as defined
below;

ix) -X¹⁻Y²⁻Y³⁻Ar³, wherein X¹ is -O-, -NR²²-, -C(O)-, -C(O)O-, -OC(O)-, -C(O)NR²²-, -NR²²C(O)⁻, -S(O)ₙ⁻ (where n is 0, 1, or 2), -NR²²S(O)₂⁻, -S(O)₂NR²²-, -NR²²C(O)O⁻, -OC(O)NR²²-, or -NR²²C(O)NR²³⁻; and Y², Y³, and Ar³ are as
defined below; and

x) -Y¹⁻X¹⁻Y²⁻Z¹⁻Ar³, wherein X¹ and Z¹ are independently -O-, -NR²²-, -C(O)-, -C(O)O-, -OC(O)-, -C(O)NR²²-, -NR²²C(O)⁻, -S(O)ₙ⁻ (where n is 0, 1, or 2), -NR²²S(O)₂⁻, -S(O)₂NR²²-, -NR²²C(O)O⁻, -OC(O)NR²²-, or -NR²²C(O)NR²³⁻; and Y¹, Y², and Ar³ are as defined below; and

wherein R²² and R²³ are independently hydrogen, alkyl, substituted alkyl, or acyl;
wherein Y¹, Y², and Y³ are independently alkylene, alkenylene, alkynylene, haloalkylene, haloalkenylene, haloalkynylene, carboxyalkylene, or -CR⁵⁻R⁶⁻ (where R⁵ and R⁶ together with the carbon to which they are attached form cycloalkylene); and

wherein Ar³ is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl.

[0268] 18. Within the above preferred group, a more preferred group is that wherein Ar² is
6-membered aryl and E is -X¹⁻Z²⁻Y³⁻Ar₃, -X¹⁻Y²⁻Ar³, -X²⁻Ar³, -X¹⁻Y²⁻Z¹⁻Ar₃, or -X¹⁻Y²⁻Z¹⁻Ar₃, preferably, -X¹⁻Y²⁻Ar³, more preferably -O⁻Y²⁻Ar³ or -C(O)NH⁻Y²⁻Ar³, even more preferably, -OCH₂CH₂Ar³ or -C(O)NHCH₂CH₂Ar³.

[0269] 19. Within Preferred Embodiment 17, a more preferred group is that wherein Ar² is
heterocycloalkyl, preferably piperidinyl or piperezinyl, more preferably piperazineyl, and E is -Y¹⁻Ar³, -X¹⁻Y²⁻Ar³, or -Y¹⁻X¹⁻Ar³, more preferably -C(O)⁻Y²⁻Ar³, -C(O)O⁻Y²⁻Ar³ or -C(O)NH⁻Y²⁻Ar³, even more preferably, -C(O)NHCH₂CH₂Ar³.

[0270] 20. Within Preferred Embodiment 17, a more preferred group is that wherein Ar² is
heteroaryl, preferably benzofuranyl, and E is -Y¹⁻Ar³, preferably -CH₂CH₂Ar³.

[0271] 21. One preferred group of compounds of Formula I is that wherein:

[0272] Ar¹ is oxadiazol-diyl, preferably, 1,2,4-oxadiazol-3,5-diyl or 1,3,4-oxadiazol-2,5-diyl,
more preferably, 1,2,4-oxadiazol-3,5-diyl;
[0273] \( R^3 \) and \( R^{3b} \) together with the carbon to which they are attached form carbonyl and is located at the 3- or 5-position of the 1,2,4-oxadiazol-3,5-diyl ring or in the 2-position of the 1,3,4-oxadiazol-2,5-diyl ring, preferably the carbonyl is located in the 3-position of the 1,2,4-oxadiazol-3,5-diyl ring;

[0274] \( R^1 \) is hydrogen;

[0275] \( R^2 \) is aralkyl or \( R^6R^7 \)-Nalkyl; preferably, \( R^2 \) is aralkyl or \( R^6R^7 \)-Nalkyl where \( R^6 \) and \( R^7 \) are each hydrogen; more preferably, \( R^2 \) is 4-(aminomethyl)-phenylmethyl, 4-(tert-butoxycarbonylaminomethyl)-phenylmethyl, or \( \text{H}_2\text{N}((\text{CH}_2)_4 \); even more preferably, \( R^2 \) is \( \text{H}_2\text{N}((\text{CH}_2)_4 \);

[0276] \( Q \) is \(-\text{NR}^{14}\text{R}^{15} \), where \( R^{14} \) is hydrogen and \( R^{15} \) is aralkyloxy carbonyl, where \( R^{14} \) is hydrogen and \( R^{15} \) is alkoxycarbonyl, or where \( R^{14} \) is hydrogen and \( R^{15} \) is arylcarbonyl; preferably, \( Q \) is phenylmethylxycarbonylamino, ethoxycarbonylamino, 4-fluorophenylcarbonylamino, or 3,4-difluorophenylcarbonylamino, more preferably, \( Q \) is phenylmethylxycarbonylamino or 4-fluorophenylcarbonylamino, even more preferably, \( Q \) is 4-fluorophenylcarbonylamino; and

[0277] \( \text{Ar}^2 \) is heterocycloalkyl.

[0278] 22. Within Preferred Embodiment 21, a more preferred group is that wherein \( \text{Ar}^2 \) is piperazinyl and \( W \) is \(-\text{A}^1\text{-D-A}^2\)- where \( \text{A}^1 \) is alkylene, preferably \(-\text{CH}_2\), and \( D \) and \( A^2 \) are each bond; and \( E \) is in a 1,4-relationship with \( W \).

[0279] Within the above more preferred group, an even more preferred group is that wherein:

[0280] \( E \) is \(-Y^1\text{-Ar}^3 \) where \( Y^1 \) is alkylene, preferably, \(-\text{CH}_2\text{CH}_2\text{CH}_2\text{-} \) or \(-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{-} \), more preferably, \(-\text{CH}_2\text{CH}_2\text{CH}_2\text{-} \); and \( \text{Ar}^3 \) is aryl, preferably, 6-membered aryl, more preferably, phenyl;

[0281] \( E \) is \(-X^1\text{-Y}^2\text{-Ar}^3 \) where \( X^1 \) is \(-\text{C(O)}\text{-O-} \), \(-\text{C(O)}\text{-NH-} \), or \(-\text{C(O)}\text{-} \), preferably, \(-\text{C(O)}\text{NH-} \); \( Y^2 \) is alkylene, preferably, \(-\text{CH}_2\text{-} \), \(-\text{CH}_2\text{CH}_2\text{-} \), or \(-\text{CH}_2\text{CH}_2\text{CH}_2\text{-} \), more preferably, \(-\text{CH}_2\text{CH}_2\text{-} \); and \( \text{Ar}^3 \) is aryl, preferably, 6-membered aryl, more preferably, phenyl; or

[0282] \( E \) is \(-Y^1\text{-X}^1\text{-Ar}^3 \) where \( Y^1 \) is alkylene, preferably, \(-\text{CH}_2\text{-} \); \( X^1 \) is \(-\text{C(O)}\text{-} \); and \( \text{Ar}^3 \) is heterocycloalkyl, preferably, morpholin-4-yl.

[0283] 23. Within Preferred Embodiment 21, a more preferred group is that wherein \( \text{Ar}^2 \) is piperazinyl and \( W \) is \(-\text{A}^1\text{-D-A}^2\)- where \( D \) is carbonyl and \( A^1 \) and \( A^2 \) are each bond; and \( E \) is in a 1,4-relationship with \( W \).

[0284] 24. Within Preferred Embodiment 21, a more preferred group is that wherein \( \text{Ar}^2 \) is piperidinyl; \( W \) is \(-\text{A}^1\text{-D-A}^2\)- where \( A^1 \) is alkylene, preferably \(-\text{CH}_2\), and \( D \) and \( A^2 \) are each bond; \( E \) is \(-X^1\text{-Y}^2\text{-Ar}^3 \) where \( X^1 \) is \( \text{C(O)}\text{NH-} \); \( Y^2 \) is alkylene, preferably, \(-\text{CH}_2\text{CH}_2\text{-} \); and \( \text{Ar}^3 \) is aryl,
preferably, 6-membered aryl, more preferably, phenyl; and where W is attached at the 4-position
and E is at the 1-position of the piperidinyl group.

[0285] Another preferred group of compounds of Formula I is that wherein:

[0286] Ar¹ is oxadiazol-diyl, preferably, 1,2,4-oxadiazol-3,5-diyl or 1,3,4-oxadiazol-2,5-diyl,
more preferably, 1,2,4-oxadiazol-3,5-diyl;

[0287] R³ and R³a together with the carbon to which they are attached form carbonyl and is
located at the 3- or 5-position of the 1,2,4-oxadiazol-3,5-diyl ring or in the 2-position of the
1,3,4-oxadiazol-2,5-diyl ring, preferably the carbonyl is located in the 3-position of the
1,2,4-oxadiazol-3,5-diyl ring;

[0288] R¹ is hydrogen;

[0289] R² is heteroaralkyl, R⁶R⁸NOC(-NH)NH-C(O)alkyl, R⁶R⁸Nalkenyl, or R⁶R⁸Nalkyl;
preferably, R⁶R⁸Nalkyl where R⁶ and R⁸ are each hydrogen, or where R⁶ is hydrogen and R⁸ is
alkoxycarbonyl; more preferably, R² is H₂N(CH₂)₄ or t-butoxycarbonylamino; even more
preferably, R² is H₂N(CH₂)₄;

[0290] W is –A¹-D-A²- where
i) A¹ is alkylene and D and A² are each bond, preferably, A¹ is -CH₂-, -CH(CH₃)-, or
-C(CH₃)₂-; or
ii) A¹ and A² are each bond and D is CR’R” (where R’ and R” together with the
carbon to which they are attached form cycloalkylene), preferably D is cycloprop-
1,2-diyl; and

[0291] Ar² is aryl.

[0292] Within Preferred Embodiment 25, a more preferred group is that wherein:

[0293] Ar² is 6-membered aryl optionally substituted with one or two substituents selected from
the group acyl, cyano, and alkyl; preferably, Ar² is phenyl, acetylphenyl, cyanophenyl, or tert-
butylphenyl; more preferably, Ar² is phenyl, 3-acetylphenyl, 3-cyanophenyl, or 3-tert-
butylphenyl, where W is attached at the 1-position of the 6-membered aryl and E is at the 4-position; even more
preferably, Ar² is phenyl, where W is attached at the 1-position and E is at the 4-position; and

[0294] E is -X¹-Y²-Ar³, where X¹ is –O-, –C(O)NH-, or -OC(O)NH-, more preferably, -O- or
-C(O)NH--; and Y² is alkylene, alkenylene, or carboxyalkylene, preferably, -CH₂-, -CH₂CH₂-, -CH₂CH₂CH₂-, prop-1-en-1,3-diyl, -CH(S-COOH)CH₂-, or -CH(R-COOH)CH₂-, more preferably, -CH₂CH₂-.

[0295] Within the above more preferred group, an even more preferred group is that wherein Ar³
is aryl; preferably, Ar³ is napthyl, phenyl, or phenyl substituted with one or two substituents selected from the group consisting of halo, haloalkyl, alkoxy, alkyl, haloalkoxy, and nitro;

[0296] more preferably, Ar³ is napth-1-yl, napth-2-yl, phenyl, chlorophenyl, dichlorophenyl, fluorophenyl, difluorophenyl, bromophenyl, dibromophenyl, trifluoromethylphenyl, bis-trifluoromethylphenyl, methoxyphenyl, dimethoxyphenyl, methylphenyl, dimethylphenyl, trifluoromethoxyphenyl, bis-trifluoromethoxyphenyl, nitrophenyl, or dinitrophenyl;

[0297] even more preferably, Ar³ is napth-1-yl, napth-2-yl, phenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2,4-dichlorophenyl, 3,4-dichlorophenyl, 3,5-dichlorophenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2,4-difluorophenyl, 3,4-difluorophenyl, 3,5-difluorophenyl, 4-bromophenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 3,4-dimethoxyphenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 2,5-dimethylphenyl, 3,4-dimethylphenyl, 2-trifluoromethylphenyl, 3-trifluoromethylphenyl, 4-trifluoromethylphenyl, 3-nitrophenyl, 2-trifluoromethoxyphenyl, 3-trifluoromethoxyphenyl, or 4-trifluoromethoxyphenyl;

[0298] particularly preferably, Ar³ is phenyl, 3-chlorophenyl or 3,4-dichlorophenyl.

[0299] Within the above more preferred group, an even more preferred group is that wherein Ar³ is heteroaryl, preferably, thiencyl, more preferably, thien-2-yl or thien-3-yl, even more preferably, thien-2-yl.

[0300] Within the above more preferred group, an even more preferred group is that wherein Ar³ is cycloalkyl, preferably cyclohexyl.

[0301] 27. Within Preferred Embodiment 25, a more preferred group is that wherein Ar² is 6-membered aryl, preferably, phenyl;

[0302] W is -A¹-D-A²- where A¹ is alkylene, D and A² are each bond, and W is attached at the 1-position of Ar²; preferably, A¹ is -CH₂-, D and A² are each bond, and W is attached at the 1-position of Ar²; and

[0303] E (located in the 4-position of Ar² when Ar² is 6-membered aryl) is -X¹-Y²-Z¹-Ar³, wherein X¹ is -C(O)NH- or -O-; Y² is alkylene, preferably, methylene or -CH₂CH₂-; and Z¹ is -C(O)- or -O-.

[0304] Within the above more preferred group, an even more preferred group is that wherein Ar³ is heteroaryl, preferably, thiencyl or thienyl substituted with chloro, more preferably, thien-2-yl, thien-3-yl or 2,3-dichlorothien-5-yl, even more preferably, thien-3-yl.

[0305] Within the above more preferred group, an even more preferred group is that wherein Ar³ is aryl, preferably phenyl or phenyl substituted with one or two substituents selected from the
group consisting of haloalkoxy, halo, cyano, and alkylsulfonyl, more preferably, Ar$_3$ is phenyl or
phenyl substituted with one or two substituents selected from the group consisting of
difluoromethoxy, chloro, fluoro, cyano, and methylsulfonyl, even more preferably, Ar$_3$ is phenyl,
4-difluoromethoxyphenyl, 3,4-dichlorophenyl, 4-fluorophenyl, 4-cyanophenyl, or
4-methylsulfonylphenyl.

[0306] 28. Within Preferred Embodiment 25, a more preferred group is that wherein Ar$_2$ is
6-membered aryl, preferably, phenyl;

[0307] W is –A$_1$-D-A$_2$- where A$_1$ is alkylene, D and A$_2$ are each bond, and W is attached at the
1-position of Ar$_2$, preferably, A$_1$ is -CH$_2$-, D and A$_2$ are each bond, and W is attached at the
1-position of Ar$_2$; and

[0308] E (located in the 4-position of Ar$_2$ when Ar$_2$ is 6-membered aryl) is -X$_2$-Ar$_3$ where X$_2$ is
-O$_2$-, -C(O)NR$_{22}$-, or -NR$_{22}$C(O)-, (where each R$_{22}$ and R$_{22}$ are independently hydrogen, alkyl,
substituted alkyl, or acyl), preferably, X$_2$ is -C(O)NH- or -O-; and Ar$_3$ is substituted aryl,
heteroaryl, cycloalkyl, or heterocycloalkyl.

[0309] 29. Within Preferred Embodiment 25, a more preferred group is that wherein:

[0310] W is –A$_1$-D-A$_2$- where A$_1$ is alkylene, D and A$_2$ are each bond, and W is attached at the
1-position of Ar$_2$, preferably, A$_1$ is -CH$_2$-, D and A$_2$ are each bond, and W is attached at the
1-position of Ar$_2$;

[0311] Ar$_2$ is 6-membered aryl, preferably, phenyl; and

[0312] E is –X$_3$-Ar$_3$ where X$_3$ is -NR$_{22}$-, -C(O)-, -C(O)O-, -OC(O)-, -S(O)$_n$- (where n is 0, 1, or 2),
-NR$_{22}$S(O)$_2$-, -S(O)$_2$NR$_{22}$-, -NR$_{22}$C(O)O-, -OC(O)NR$_{22}$-, or -NR$_{22}$C(O)NR$_{23}$ (wherein R$_{22}$ and R$_{23}$
are independently hydrogen, alkyl, substituted alkyl, or acyl), preferably, X$_3$ is -O(C)ONH-; and
Ar$_3$ is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl, preferably, 6-membered aryl, more
preferably, phenyl.

[0313] Within the above more preferred group, an even more preferred group is that wherein E is
located in the 4-position of Ar$_2$ when Ar$_2$ is 6-membered aryl.

[0314] Within the above more preferred group, an even more preferred group is that wherein E is
located in the 3-position of Ar$_2$ when Ar$_2$ is 6-membered aryl.

[0315] 30. Another preferred group of compounds of Formula I is that wherein Ar$_2$ is a
6-membered aryl, 6-membered heteroaryl, 6-membered cycloalkyl, or 6-membered
heterocycloalkyl group where W is located in a 1,4-relationship with E.

[0316] 31. Another preferred group of compounds of Formula I is that wherein:
[0317] Ar is oxadiazol-diyl, preferably, 1,2,4-oxadiazol-3,5-diyl or 1,3,4-oxadiazol-2,5-diyl, more preferably, 1,2,4-oxadiazol-3,5-diyl;

[0318] R³ and R³⁺ together with the carbon to which they are attached form carbonyl and is located at the 3- or 5-position of the 1,2,4-oxadiazol-3,5-diyl ring or in the 2-position of the 1,3,4-oxadiazol-2,5-diyl ring, preferably the carbonyl is located in the 3-position of the 1,2,4-oxadiazol-3,5-diyl ring;

[0319] R¹ is hydrogen;

[0320] R² is R⁶R⁷Nalkyl, preferably, where R⁶ and R⁷ are each hydrogen, or where R⁶ is hydrogen and R⁷ is alkoxy carbonyl; more preferably, R² is H₂N(CH₂)₄ or t-butoxycarbonylamino; even more preferably, R² is H₂N(CH₂)₄;

[0321] W is –A¹₁-D-A²₂⁻ where
a) A¹ is alkylene, preferably, A¹ is methylene, methylmethylene, or dimethylmethylene, and D and A² are each bond;
b) A¹ and A² are each bond and D is CRʻR” (where Rʻ and R” together with the carbon to which they are attached form cycloalkylene), preferably D is cycloprop-1,2-diyl; or
c) A¹ and A² are each bond and D is -C(O)-; and

[0322] 32. Within Preferred embodiment 31, a more preferred group is that wherein Q is hydrogen or -NR₁⁴R₁⁵, where R¹⁴ is hydrogen, alkyl, or heterocycloalkyl carbonyl and R₁⁵ is aralkyloxy carbonyl, alkoxy carbonyl, alkenyloxy carbonyl, alkyl carbonyl, heterocycloalkyl carbonyl, cycloalkyl carbonyl, heteroaryl carbonyl, substituted alkyl (preferably haloalkyl), haloalkyl carbonyl, arylicarbonyl, R₂¹S(O)₂⁻ (where R₂¹ is alkyl or aryl), alkoxyalkyloxy carbonyl, -C(O)NR₁⁹R₂⁰ (where R₁⁹ is alkyl and R₂⁰ is hydrogen, alkyl, or aryl), alkoxyalkyl carbonyl, alkoxy carbonylamidocarbonyl, R¹⁹R₂⁰NS(O)₂⁻ (where R¹⁹ is alkyl and R₂⁰ is hydrogen, alkyl, or aryl),

[0323] preferably, Q is hydrogen, phenylmethylxycarbonylamino, methoxy carbonylamino, ethoxy carbonylamino, isopropoxycarbonylamino, 2,2-dimethylpropoxy carbonylamino, N-(prop-1-en-3-yloxy carbonyl)-amino, methyl carbonylamino, n-pentyl carbonylamino, tert-butyl carbonylamino, isopropyl carbonylamino, morpholinocarbonylamino, N,N-bis-(morpholin-4-yl carbonyl) amino, pyrrolidin-1-y carbonylamino, tetrahydrofuran-3-yl carbonylamino, piperidin-1-y carbonylamino, [N-(methyl carbonyl)-pyrrolidin-2-yl] carbonylamino, cyclopentyl carbonylamino, cyclopropyl carbonylamino, 1-cyanocyclopentyl-
ylcarbonylaminoo, furan-2-ylcarbonylaminoo, 2,5-dimethylfuran-3-ylcarbonylaminoo, benzo[1,3]dioxol-5-ylcarbonylaminoo, 2,2,2-trifluoroethylaminoo, trifluoromethylcarbonylaminoo, 2-fluorophenylcarbonylaminoo, 3-fluorophenylcarbonylaminoo, 4-fluorophenylcarbonylaminoo, 3,4-difluorophenylcarbonylaminoo, 2,4-difluorophenylcarbonylaminoo, 3,5-difluorophenylcarbonylaminoo, 4-chlorophenylcarbonylaminoo, methylsulfonilaminoo, 4-fluorophenylsulfonilaminoo, methoxethylxoycarbonylaminoo, dimethylaminocarbonylaminoo, diethylaminocarbonylaminoo, methoxymethylcarbonylaminoo, ethoxycarbonylaminocarbonylaminoo, or $N,N$-dimethylaminosulfonilaminoo,

[0324] more preferably, Q is phenylmethoxycarbonylaminoo, ethoxycarbonylaminoo, tert-butylcarbonylaminoo, morpholinocarbonylaminoo, piperidin-1-ylcarbonylaminoo, furan-2-ylcarbonylaminoo, benzo[1,3]dioxol-5-ylcarbonylaminoo, 2-fluorophenylcarbonylaminoo, 3-fluorophenylcarbonylaminoo, 4-fluorophenylcarbonylaminoo, 3,4-difluoro-phenylcarbonylaminoo, 2,4-difluorophenylcarbonylaminoo, 3,5-difluorophenylcarbonylaminoo, 4-chlorophenylcarbonylaminoo, or methoxyethylxoycarbonylaminoo;

[0325] even more preferably, Q is ethoxycarbonylaminoo, morpholinocarbonylaminoo, 3-fluorophenylcarbonylaminoo, 4-fluorophenylcarbonylaminoo, or 3,4-difluorophenylcarbonylaminoo.

[0326] 33. Within Preferred embodiment 31, a more preferred group is that wherein:

[0327] W is $-A^1 \cdot D \cdot A^2 -$ where $A^1$ is alkylene, D and $A^2$ are each bond, and W is attached at the 1-position of Ar$^2$; preferably, $A^1$ is -CH$_2$-, -CH(CH$_3$)$_2$-, or -C(CH$_3$)$_2$-, D and $A^2$ are each bond, and W is attached at the 1-position of Ar$^2$; and

[0328] Q is $-NR^1 \cdot R^15$ wherein R$^{14}$ and R$^{15}$ together with the nitrogen to which they are attached form heterocycloalkyl or heteroaryl, preferably, Q is 2,5-dioxopyrrolidinyl, 2,5-dioxo-3,3-dimethylpyrrolidinyl, or phthalimidyl.

[0329] 34. Yet another preferred group is that wherein this invention is directed to a method of treating an immunomediated inflammatory disease responsive to the inhibition of trypptase in an animal suffering said disease, comprising administering to said animal a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula I.

[0330] Preferably the immunomediated inflammatory disease is one associated with the respiratory tract, such as asthma, the hyperresponsiveness phase associated with chronic asthma, allergic rhinitis, and Chronic Obstructive Pulmonary Disease (COPD) or is one associated with mast cells, such as conjunctivitis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other
arthritic conditions, inflammatory bowel disease (IBD), peptic ulcers and various skin conditions, and particularly rheumatoid arthritis.

[0331] More preferably, the disease is asthma, allergic rhinitis, COPD, rheumatoid arthritis, or IBD. Even more preferably the disease is asthma or allergic rhinitis. Particularly preferably the disease is asthma.

[0332] Reference to the preferred embodiments set forth above is meant to include all combinations of particular and preferred groups unless stated otherwise. A person of ordinary skill in the art would recognize that certain groups listed above in the preferred embodiments can exist as geometric or stereoisomers. The present invention includes individual stereoisomers and geometric isomers and mixtures thereof.

[0333] Representative compounds of Formula I:

\[
\text{Ar}^1 \xrightarrow{\text{Q}} \text{R}^2_{1} \xrightarrow{\text{R}^3} \text{W} \xrightarrow{\text{Ar}^2} \text{R}^{3a}
\]

where \(\text{Ar}^1\) is 1,2,4-oxadiazol-3,5-diyl and \(\text{W}\) is located at the 5-position, \(\text{R}^1\) is hydrogen, \(\text{R}^2\) is \(\text{H}_2\text{N}(\text{CH}_2)_4\), \(\text{R}^3\) and \(\text{R}^{3a}\) together with the carbon to which they are attached form carbonyl, \(\text{Q}\) is \(-\text{NR}^{14}\text{R}^{15}\), and \(\text{Ar}^2\) is phenyl further substituted at the 4-position with \(\text{E}\) where \(\text{E}\) is \(-\text{X}^1\cdot\text{Y}^2\cdot\text{Ar}^3\) as defined below:

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<th>Cmpd. No.</th>
<th>(\text{R}^{14})</th>
<th>(\text{R}^{15})</th>
<th>(\text{W})</th>
<th>(\text{X}^1)</th>
<th>(\text{Y}^2)</th>
<th>(\text{Ar}^3)</th>
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<td>C(O)NH</td>
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<td>Y&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Ar&lt;sup&gt;3&lt;/sup&gt;</td>
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and are named:

**[0334]** [5-((phenylmethylxycarbonyl)amino]-6-{5-[4-(3-chlorophenethylaminocarbonyl)-phenylmethyl]-[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine;

**[0335]** [5-((phenylmethylxycarbonyl)amino]-6-{5-[4-(2-(thien-2-yl)ethylaminocarbonyl)-phenylmethyl]-[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine;

**[0336]** [5-((phenylmethylxycarbonyl)amino]-6-{5-[4-(3-(phenyl)prop-2-enyl-aminocarbonyl)-phenylmethyl]-[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine;
phenylmethyl]-[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine;

[0337] [5-[(phenethylmethyloxyacarbonyl)amino]-6-[1H]-[4-[(5S)-carboxy-2-phenylethyl-
aminocarbonyl]-phenylmethyl]-[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine;

[0338] [5-[(cyclopentylcarbonyl)amino]-6-[5-4-{(phenyl)prop-2-enyl-aminocarbonyl]-
phenylmethyl]-[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine;

[0339] [5-[(n-pentylcarbonyl)amino]-6-[5-4{(3,4-dichlorophenethoxy)-phenylmethyl]-
[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine;

[0340] [5-[(2,4-difluorophenylcarbonyl)amino]-6-[5-4{(3,4-dichlorophenethoxy)-
phenylmethyl]-[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine;

[0341] [5-[(tert-butylcarbonyl)amino]-6-[5-4{(3,4-dichlorophenethoxy)-phenylmethyl]-
[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine;

[0342] [5-[(4-chlorophenylcarbonyl)amino]-6-[5-4{(3,4-dichlorophenethoxy)-phenylmethyl]-
[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine;

[0343] [5-[(3,4-difluorophenylcarbonyl)amino]-6-[5-4{(3,4-dichlorophenethoxy)-
phenylmethyl]-[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine;

[0344] [5-[(methylsulfonyl)amino]-6-[5-4{(3,4-dichlorophenethoxy)-phenylmethyl]-
[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine;

[0345] [5-[(prop-1-en-3-yl)oxycarbonyl]amino]-6-[5-4{(phenethoxy)-phenylmethyl]-
[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine;

[0346] [5-[(phenethylmethyloxyacarbonyl)amino]-6-[5-4{(3,4-dichlorophenethoxy)methyl-
aminocarbonyl)-phenylmethyl]-[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine;

[0347] [5-[(ethoxyacarbonyl)amino]-6-[5-4{(3,4-dichlorophenethoxy)-phenylmethyl]-
[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine;

[0348] [5-[(morpholinocarbonyl)amino]-6-[5-4{(3,4-dichlorophenethoxy)-phenylmethyl]-
[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine;

[0349] [5-[(bis-(morpholinocarbonyl)amino]-6-[5-4{(3,4-dichlorophenethoxy)-phenylmethyl]-
[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine;

[0350] [5-[(phenethylmethyloxyacarbonyl)amino]-6-[5-4{(3,4-difluorophenethoxy)-phenylmethyl]-
[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine;

[0351] [5-[(phenethylmethyloxyacarbonyl)amino]-6-[5-4{(phenethoxy)-phenylmethyl]-
[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine;

[0352] [5-[(phenethylmethyloxyacarbonyl)amino]-6-[5-4{(thien-3-yl)ethoxy)-phenylmethyl]-
[1,2,4]oxadiazol-3-yl)-6-oxo-hexyl]-amine;

[0353] [5-[(phenylmethyloxyacarbonyl)amino]-6-{5-[4-(phenethyloxy)-1-phenyl-1,1-
dimethylmethyl]-[1,2,4]oxadiazol-3-yl}-6-oxo-hexyl]-amine;

[0354] [5-[(phenylmethyloxyacarbonyl)amino]-6-{5-[4-(phenethyloxy)-1-phenyl-1-methylmethyl]-
[1,2,4]oxadiazol-3-yl}-6-oxo-hexyl]-amine;

[0355] [5-[(phenylmethyloxyacarbonyl)amino]-6-{5-[4-(phenethyloxy)-phenylcycloprop-1-yl]-
[1,2,4]oxadiazol-3-yl}-6-oxo-hexyl]-amine;

[0356] [5-[ethoxycarbonyl]amino]-6-{5-[4-(3-chlorophenethyloxyaminocarbonyl)-phenylmethyl]-
[1,2,4]oxadiazol-3-yl}-6-oxo-hexyl]-amine;

[0357] [5-{[furan-2-ylcarbonyl]amino]-6-{5-[4-(3,4-dichlorophenethyloxy)-phenylmethyl]-
[1,2,4]oxadiazol-3-yl}-6-oxo-hexyl]-amine;

[0358] [5-[(4-fluorophenylcarbonyl)amino]-6-{5-[4-(3,4-dichlorophenethyloxy)-phenylmethyl]-
[1,2,4]oxadiazol-3-yl}-6-oxo-hexyl]-amine;

[0359] [5-{[trifluoromethylenecarbonyl]amino]-6-{5-[4-(3,4-dichlorophenethyloxy)-phenylmethyl]-
[1,2,4]oxadiazol-3-yl}-6-oxo-hexyl]-amine;

[0360] [5-[(phenylmethyloxyacarbonyl)amino]-6-{5-[4-(3-phenylpropylaminocarbonyl)]-
phenylmethyl]-[1,2,4]oxadiazol-3-yl}-6-oxo-hexyl]-amine;

[0361] [5-[(phenylmethyloxyacarbonyl)amino]-6-{5-[4-(phenethylaminocarbonyl)]-phenylmethyl]-
[1,2,4]oxadiazol-3-yl}-6-oxo-hexyl]-amine;

[0362] [5-[(isopropoxycarbonyl)amino]-6-{5-[4-(3,4-dichlorophenethyloxy)-phenylmethyl]-
[1,2,4]oxadiazol-3-yl}-6-oxo-hexyl]-amine;

[0363] [5-[(phenylmethyloxyacarbonyl)amino]-6-{5-[4-(3,5-difluorophenethyloxyaminocarbonyl)]-
phenylmethyl]-[1,2,4]oxadiazol-3-yl}-6-oxo-hexyl]-amine;

[0364] [5-{[methoxymethylenecarbonyl]amino]-6-{5-[4-(3,4-dichlorophenethyloxy)-phenylmethyl]-
[1,2,4]oxadiazol-3-yl}-6-oxo-hexyl]-amine;

[0365] [5-{[cyclopropylcarbonyl]amino]-6-{5-[4-(3,4-dichlorophenethyloxy)-phenylmethyl]-
[1,2,4]oxadiazol-3-yl}-6-oxo-hexyl]-amine;

[0366] [5-{[methoxyethyloxyacarbonyl]amino]-6-{5-[4-(3,4-dichlorophenethyloxy)-
phenylmethyl]-[1,2,4]oxadiazol-3-yl}-6-oxo-hexyl]-amine;

[0367] [5-{[3-fluorophenylcarbonyl]amino]-6-{5-[4-(3,4-dichlorophenethyloxy)-phenylmethyl]-
[1,2,4]oxadiazol-3-yl}-6-oxo-hexyl]-amine;

[0368] [5-{[2-fluorophenylcarbonyl]amino]-6-{5-[4-(3,4-dichlorophenethyloxy)-phenylmethyl]-
[1,2,4]oxadiazol-3-yl}-6-oxo-hexyl]-amine;
[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine;

[0369] [5-[(isopropylcarbonyl)amino]-6-\{5-\{4-(3,4-dichlorophenethyloxy)-phenylmethyl\}-
[1,2,4]oxadiazol-3-yl\}-6-oxo-hexyl]-amine;

[0370] [5-\{(phenethylcarboxylicarbonyl)amino\}-6-\{5-\{4-(4-bromophenethyloxy)-phenylmethyl\}-
[1,2,4]oxadiazol-3-yl\}-6-oxo-hexyl]-amine;

[0371] [5-\{(phenethylcarboxylicarbonyl)amino\}-6-\{5-\{4-(3-fluorophenethyloxy)-phenylmethyl\}-
[1,2,4]oxadiazol-3-yl\}-6-oxo-hexyl]-amine;

[0372] [5-\{(phenethylcarboxylicarbonyl)amino\}-6-\{5-\{4-(3,4-dichlorophenethyloxy)-phenylmethyl\}-
ethylaminocarbonyl\}-phenylmethyl\}-[1,2,4]oxadiazol-3-yl\}-6-oxo-hexyl]-amine;

[0373] [5-\{(ethoxycarbonyl)amino\}-6-\{5-\{4-(phenethyloxy)-phenylmethyl\}-[1,2,4]oxadiazol-3-
yl\}-6-oxo-hexyl]-amine;

[0374] [5-\{(piperidin-1-yl)carbonyl\}amino\}-6-\{5-\{4-(3,4-dichlorophenethyloxy)-phenylmethyl\}-
[1,2,4]oxadiazol-3-yl\}-6-oxo-hexyl]-amine;

[0375] [5-\{(dimethylaminocarbonyl)amino\}-6-\{5-\{4-(3,4-dichlorophenethyloxy)-phenylmethyl\}-
[1,2,4]oxadiazol-3-yl\}-6-oxo-hexyl]-amine;

[0376] [5-\{(phenethylcarboxylicarbonyl)amino\}-6-\{5-\{4-(3,4-dichlorophenethyloxy)-
phenylmethyl\}-[1,2,4]oxadiazol-3-yl\}-6-oxo-hexyl]-amine;

[0377] [5-\{(2,2-dimethylpropylcarbonyl)amino\}-6-\{5-\{4-(3,4-dichlorophenethyloxy)-
phenylmethyl\}-[1,2,4]oxadiazol-3-yl\}-6-oxo-hexyl]-amine;

[0378] [5-\{(phenethylcarboxylicarbonyl)amino\}-6-\{5-\{4-\{(napth-2-ylmethyl)aminocarbonyl\}-
phenylmethyl\}-[1,2,4]oxadiazol-3-yl\}-6-oxo-hexyl]-amine;

[0379] [5-\{(phenethylcarboxylicarbonyl)amino\}-6-\{5-\{4-\{(napth-1-ylmethyl)aminocarbonyl\}-
phenylmethyl\}-[1,2,4]oxadiazol-3-yl\}-6-oxo-hexyl]-amine;

[0380] [5-(methylsulfonylamino)-6-\{5-\{4-(3,4-dichlorophenethyloxy)-phenylmethyl\}-
[1,2,4]oxadiazol-3-yl\}-6-oxo-hexyl]-amine;

[0381] [5-\{(phenethylcarboxylicarbonyl)amino\}-6-\{5-\{4-(3-nitrophenethyloxy)-phenylmethyl\}-
[1,2,4]oxadiazol-3-yl\}-6-oxo-hexyl]-amine;

[0382] [5-\{(phenethylcarboxylicarbonyl)amino\}-6-\{5-\{4-(3,4-dichlorophenethyloxy)aminocarbonyl\}-
phenylmethyl\}-[1,2,4]oxadiazol-3-yl\}-6-oxo-hexyl]-amine;

[0383] [5-\{(methoxyacarbonyl)amino\}-6-\{5-\{4-(3,4-dichlorophenethyloxy)-phenylmethyl\}-
[1,2,4]oxadiazol-3-yl\}-6-oxo-hexyl]-amine;

[0384] [5-\{(phenethylcarboxylicarbonyl)amino\}-6-\{5-\{4-(4-methoxyphenethyloxy)-phenylmethyl\}-
[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine;

[0385] [5-[(tetrahydrofuran-3-ylcarbonyl)amino]-6-{5-[4-(3,4-dichlorophenethyl)oxy]-phenylmethyl}-[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine;

[0386] [5-[(phenylmethoxy carbonyl)amino]-6-{5-[4-(3,4-dimethoxyphenethyl)oxy]-phenylmethyl}-[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine;

[0387] [5-[(phenylmethoxy carbonyl)amino]-6-{5-[4-[(napth-2-ylmethyl)oxy]-phenylmethyl}-[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine;

[0388] [5-[(pyrrolidin-1-ylcarbonyl)amino]-6-{5-[4-(3,4-dichlorophenethyl)oxy]-phenylmethyl}-[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine;

[0389] [5-[(phenylmethoxy carbonyl)amino]-6-{5-[4-(thien-2-ylthioxy)-phenylmethyl}-[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine;

[0390] [5-[(phenylmethoxycarbonyl)amino]-6-{5-[4-[(phenylmethyl)-aminocarboxyl]-phenylmethyl}-[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine;

[0391] [5-[(phenylmethoxy carbonyl)amino]-6-{5-[4-[(phenylmethyl)-aminocarboxyl]-phenylmethyl}-[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine;

[0392] [5-[(phenylmethoxycarbonyl)amino]-6-{5-[4-[(3,4-dimethylphenethylmethyl)-aminocarboxyl]-phenylmethyl}-[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine;

[0393] [5-[(2,5-dimethylfurany-3-yl carbonyl)amino]-6-{5-[4-(3,4-dichlorophenethyl)oxy]-phenylmethyl}-[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine;

[0394] [5-[(phenylmethoxycarbonyl)amino]-6-{5-[4-(3-trifluoromethoxyphenethyl)oxy]-phenylmethyl}-[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine;

[0395] [5-[(phenylmethoxycarbonyl)amino]-6-{5-[4-[phenethylaminocarboxyl]-phenylmethyl}-[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine;

[0396] [5-[(phenylmethoxycarbonyl)amino]-6-{5-[4-[4-phenylbutyl]-aminocarboxyl]-phenylmethyl}-[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine;

[0397] [5-[(phenylmethoxycarbonyl)amino]-6-{5-[4-[3-phenylpropyl]-oxy]-phenylcyclopropyl}-[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine;

[0398] [5-[(phenylmethoxycarbonyl)amino]-6-{5-[4-[3-phenylpropyl]-oxy]-phenylmethyl}-[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine;

[0399] [5-[(phenylmethoxycarbonyl)amino]-6-{5-[4-[1(\text{R})-carboxy-2-phenylethylaminocarboxyl]-phenylmethyl}-[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine;

[0400] [5-[(phenylmethoxycarbonyl)amino]-6-{5-[4-[(phenylmethyl)-oxy]-phenylmethyl]-
[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine;

[0401] [5-[(ethoxycarbonylaminocarbonyl)amino]-6-{5-[4-(3,4-dichlorophenethoxy)-
phenylmethyl]-[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine;

[0402] [5-[(phenylethoxycarbonyl)amino]-6-{5-[4-{2-[4-(trifluoromethyl)phenyl]-
ethylaminocarbonyl}]-phenylmethyl]-[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine;

[0403] [5-[(1-cyanocycloprop-1-ylcarbonyl)amino]-6-{5-[4-(3,4-dichlorophenethoxy)-
phenylmethyl]-[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine;

[0404] [5-[(phenylethoxycarbonyl)amino]-6-{5-[4-(4-chlorophenethoxy)phenylmethyl]-
[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine;

[0405] [5-[(phenylethoxycarbonyl)amino]-6-{5-[4-(cyclohexylethoxy)phenylmethyl]-
[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine;

[0406] [5-[(3,5-difluorophenylcarbonyl)amino]-6-{5-[4-(3-chlorophenethoxymethyl)-
phenylmethyl]-[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine;

[0407] [5-[(3,4-difluorophenylcarbonyl)amino]-6-{5-[4-(3-chlorophenethoxymethyl)-
phenylmethyl]-[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine;

[0408] [5-[(3-fluorophenylcarbonyl)amino]-6-{5-[4-(3-chlorophenethoxymethyl)-
phenylmethyl]-[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine;

[0409] [5-[(4-fluorophenylcarbonyl)amino]-6-{5-[4-(3-chlorophenethoxymethyl)-
phenylmethyl]-[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine;

[0410] [5-[(4-chlorophenylcarbonyl)amino]-6-{5-[4-(3-chlorophenethoxymethyl)-
phenylmethyl]-[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine;

[0411] [5-[(3,4-difluorophenylcarbonyl)amino]-6-{5-[4-(2-(thien-2-yl)ethylaminocarbonyl)-
phenylmethyl]-[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine;

[0412] [5-[(4-fluorophenylsulfonyl)amino]-6-{5-[4-(3,4-dichlorophenethoxy)phenylmethyl]-
[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine;

[0413] [5-[(3,4-difluorophenylcarbonyl)amino]-6-{5-[4-(phenethylaminocarbonyl)-
phenylecyclopropyl]-[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine;

[0414] [5-[(4-fluorophenylcarbonyl)amino]-6-{5-[4-(2-(thien-2-yl)ethylaminocarbonyl)-
phenylmethyl]-[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine;

[0415] [5-[(tert-butylcarbonyl)amino]-6-{5-[4-(3-chlorophenethoxymethyl)-phenylmethyl]-
[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine;

[0416] [5-[(3,4-methylenedioxyphenylcarbonyl)amino]-6-{5-[4-(3-chlorophenethoxymethyl)-
phenylmethyl]-[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine;
aminocarbonyl)-phenylmethyl]-[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine; and

[0417] [5-[(tert-butylcarbonyl)amino]-6-{5-[4-(2-thien-2-yl)ethylaminocarbonyl]-phenylmethyl]-[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine.

5 [0418] Representative compounds of Formulae I

![Chemical Structure](image)

where Ar\(^1\) is 1,2,4-oxadiazol-3,5-diyyl and W is located at the 3-position, R\(^1\) is hydrogen, R\(^2\) is H\(_2\)N(CH\(_2\))\(_4\), R\(^3\) and R\(^3\)\(_a\) together with the carbon to which they are attached form carbonyl, Q is -NR\(^1\)\(_4\)R\(^1\)\(_5\), and Ar\(^2\) is phenyl further substituted at the 4-position with E where E is -X\(^1\)\.-Y\(^2\)\.-Ar\(^3\) are as defined below:

**Table 2.**

<table>
<thead>
<tr>
<th>Cmpd. No.</th>
<th>R(^1)(_4)</th>
<th>R(^1)(_5)</th>
<th>W</th>
<th>X(^1)</th>
<th>Y(^2)</th>
<th>Ar(^3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>85</td>
<td>H</td>
<td>phenyl</td>
<td>CH(_2)</td>
<td>O</td>
<td>CH(_2)CH(_2)</td>
<td>phenyl</td>
</tr>
</tbody>
</table>

and is named [5-[(phenylmethyloxy)carbonyl]amino]-6-{3-[4-(phenethyloxy)phenylmethyl]-[1,2,4]oxadiazol-5-yl]-6-oxo-hexyl]-amine.

15 [0419] Representative compounds of Formulae I:

![Chemical Structure](image)

where Ar\(^1\) is 1,2,4-oxadiazol-3,5-diyyl and W is located at the 5-position, R\(^1\) is hydrogen, R\(^2\) is H\(_2\)N(CH\(_2\))\(_4\), R\(^3\) and R\(^3\)\(_a\) together with the carbon to which they are attached form carbonyl, Q is -NR\(^1\)\(_4\)R\(^1\)\(_5\), and Ar\(^2\) is phenyl further substituted at the 4-position with E where E is -X\(^1\)\.-Y\(^2\)\.-Z\(^1\)\.-Ar\(^3\) are as defined below:

**Table 3.**

68
<table>
<thead>
<tr>
<th>Cmpd. No.</th>
<th>R^{14}</th>
<th>R^{15}</th>
<th>W</th>
<th>X^1</th>
<th>Y^2</th>
<th>Z^1</th>
<th>Ar^3</th>
</tr>
</thead>
<tbody>
<tr>
<td>86</td>
<td>H</td>
<td>phenylCH_2OC(O)-</td>
<td>CH_2</td>
<td>O</td>
<td>CH_3</td>
<td>C(O)</td>
<td>thien-3-yl</td>
</tr>
<tr>
<td>87</td>
<td>H</td>
<td>phenylCH_2OC(O)-</td>
<td>CH_2</td>
<td>O</td>
<td>CH_2</td>
<td>C(O)</td>
<td>4-difluoromethoxyphenyl</td>
</tr>
<tr>
<td>88</td>
<td>H</td>
<td>phenylCH_2OC(O)-</td>
<td>CH_2</td>
<td>O</td>
<td>CH_2</td>
<td>C(O)</td>
<td>3,4-dichlorophenyl</td>
</tr>
<tr>
<td>89</td>
<td>H</td>
<td>phenylCH_2OC(O)-</td>
<td>CH_2</td>
<td>O</td>
<td>CH_2CH_2</td>
<td>O</td>
<td>phenyl</td>
</tr>
<tr>
<td>90</td>
<td>H</td>
<td>phenylCH_2OC(O)-</td>
<td>CH_2</td>
<td>C(O)NH</td>
<td>CH_2CH_2</td>
<td>O</td>
<td>4-fluorophenyl</td>
</tr>
<tr>
<td>91</td>
<td>H</td>
<td>phenylCH_2OC(O)-</td>
<td>CH_2</td>
<td>O</td>
<td>CH_2</td>
<td>C(O)</td>
<td>4-cyanophenyl</td>
</tr>
<tr>
<td>92</td>
<td>H</td>
<td>phenylCH_2OC(O)-</td>
<td>CH_2</td>
<td>O</td>
<td>CH_2</td>
<td>C(O)</td>
<td>2,3-dichlorothien-5-yl</td>
</tr>
<tr>
<td>93</td>
<td>H</td>
<td>phenylCH_2OC(O)-</td>
<td>CH_2</td>
<td>O</td>
<td>CH_2</td>
<td>C(O)</td>
<td>4-methylsulfonylphenyl</td>
</tr>
</tbody>
</table>

and are named:

[0420] 5-[(phenylmethoxy carbonyl) amino]-6-(5-[4-(thien-3-yl carbonylmethoxy)-phenylmethyl]-[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine;

[0421] 5-[(phenylmethoxy carbonyl) amino]-6-(5-[4-(4-difluoromethoxyphenyl carbonylmethoxy)-phenylmethyl]-[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine;

[0422] 5-[(phenylmethoxy carbonyl) amino]-6-(5-[4-(3,4-dichlorophenyl carbonylmethoxy)-phenylmethyl]-[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine;

[0423] 5-[(phenylmethoxy carbonyl) amino]-6-(5-[4-(phenolxyethoxy)-phenylmethyl]-[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine;

[0424] 5-[(phenylmethoxy carbonyl) amino]-6-(5-[4-[2-(4-fluorophenoxy)-ethylaminocarbonyl]-phenylmethyl]-[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine;

[0425] 5-[(phenylmethoxy carbonyl) amino]-6-(5-[4-(4-cyanophenyl carbonylmethoxy)-phenylmethyl]-[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine;
[0426] 5-[(phenylmethyloxy carbonyl)amino]-6-{5-[4-(2,3-dichlorothien-5-yl-carbonylmethoxy)-phenylmethyl]-1,2,4]oxadiazol-3-yl}-6-oxo-hexyl]-amine; and

[0427] 5-[(phenylmethyloxy carbonyl)amino]-6-{5-[4-(4-methylsulfonylphenyl-carbonylmethoxy)-phenylmethyl]-1,2,4]oxadiazol-3-yl}-6-oxo-hexyl]-amine.

[0428] Representative compounds of Formulae I:

\[
\begin{array}{ccc}
\text{where } \text{Ar}^1 \text{ is } 1,2,4\text{-oxadiazol-3,5-diyl and } W \text{ is located at the 5-position, } \text{R}^1 \text{ is hydrogen, } \text{R}^2 \text{ is } \text{H}_2\text{N(CH}_2\text{)}_4, \text{R}^3 \text{ and } \text{R}^{3a} \text{ together with the carbon to which they are attached form carbonyl, Q is } -\text{NR}^{14}\text{R}^{15}, \text{and Ar}^2 \text{ is phenyl further substituted with E where E is } -\text{X}^3\text{-Ar}^3 \text{ are as defined below.}
\end{array}
\]

Table 4.

<table>
<thead>
<tr>
<th>Cmpd. No.</th>
<th>R^{14}</th>
<th>R^{15}</th>
<th>W</th>
<th>X^3</th>
<th>Ar^3</th>
<th>Location of -X^3-Ar^3 on Ar^2</th>
</tr>
</thead>
<tbody>
<tr>
<td>94</td>
<td>H</td>
<td>phenylCH_2OC(O)-</td>
<td>CH_2</td>
<td>OC(O)NH</td>
<td>phenyl</td>
<td>4-position</td>
</tr>
<tr>
<td>95</td>
<td>H</td>
<td>phenylCH_2OC(O)-</td>
<td>CH_2</td>
<td>OC(O)NH</td>
<td>phenyl</td>
<td>3-position</td>
</tr>
</tbody>
</table>

and are named:

[0429] 5-[(phenylmethyloxy carbonyl)amino]-6-{5-[4-(phenylaminocarbonyloxy)-phenylmethyl]-1,2,4]oxadiazol-3-yl}-6-oxo-hexyl]-amine; and

[0430] 5-[(phenylmethyloxy carbonyl)amino]-6-{5-[3-(phenylaminocarbonyloxy)-phenylmethyl]-1,2,4]oxadiazol-3-yl}-6-oxo-hexyl]-amine.

[0431] Representative compounds of Formulae I:

\[
\begin{array}{ccc}
\text{where } \text{Ar}^1 \text{ is } 1,2,4\text{-oxadiazol-3,5-diyl and } W \text{ is located at the 5-position, } \text{R}^1 \text{ is hydrogen, } \text{R}^2 \text{ is } \text{H}_2\text{N(CH}_2\text{)}_4, \text{R}^3 \text{ and } \text{R}^{3a} \text{ together with the carbon to which they are attached form carbonyl, Q is }
\end{array}
\]
-NR^{14}R^{15}\) (where \(R^{14}\) is hydrogen and \(R^{15}\) is phenylmethyloxycarbonyl), and \(\text{Ar}^2\) is piperazin-1-yl further substituted at the 4-position with \(E\) where \(E\) is \(-Y^1-\text{Ar}^3\) as defined below:

**Table 5.**

<table>
<thead>
<tr>
<th>Compd. No.</th>
<th>(R^{14})</th>
<th>(R^{15})</th>
<th>(W)</th>
<th>(\text{Ar}^2)</th>
<th>(Y^1)</th>
<th>(\text{Ar}^3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>96</td>
<td>H</td>
<td>phenylCH₂OC(O)</td>
<td>C(O)</td>
<td></td>
<td>CH₂CH₂CH₂</td>
<td>phenyl</td>
</tr>
<tr>
<td>97</td>
<td>H</td>
<td>phenylCH₂OC(O)</td>
<td>CH₂</td>
<td></td>
<td>CH₂CH₂CH₂CH₂</td>
<td>phenyl</td>
</tr>
<tr>
<td>98</td>
<td>H</td>
<td>phenylCH₂OC(O)</td>
<td>CH₂</td>
<td></td>
<td>CH₂CH₂CH₂</td>
<td>phenyl</td>
</tr>
<tr>
<td>99</td>
<td>H</td>
<td>ethoxycarbonyl</td>
<td>CH₂</td>
<td></td>
<td>CH₂</td>
<td>phenyl</td>
</tr>
</tbody>
</table>

and are named:

5. **[0432]** 5-[(phenylmethyloxycarbonyl)amino]-6-\{5-[4-(3-phenylpropyl)-piperazin-1-ylcarbonyl]-[1,2,4]oxadiazol-3-yl\}-6-oxo-hexyl]-amine;

6. **[0433]** 5-[(phenylmethyloxycarbonyl)amino]-6-\{5-[4-(4-phenylbutyl)-piperazin-1-ylmethyl]-[1,2,4]oxadiazol-3-yl\}-6-oxo-hexyl]-amine;

7. **[0434]** 5-[(phenylmethyloxycarbonyl)amino]-6-\{5-[4-(3-phenylpropyl)-piperazin-1-ylmethyl]-[1,2,4]oxadiazol-3-yl\}-6-oxo-hexyl]-amine; and

8. **[0435]** 5-[(ethoxycarbonyl)amino]-6-\{5-[2-(phenylmethyl)-benzofuran-5-ylmethyl]-[1,2,4]oxadiazol-3-yl\}-6-oxo-hexyl]-amine.

9. **[0436]** Representative compounds of Formulae I:
where $\text{Ar}^1$ is 1,2,4-oxadiazol-3,5-diyl and $W$ is located at the 5-position, $R^1$ is hydrogen, $R^2$ is $\text{H}_2\text{N}$(CH$_2$)$_4$, $R^3$ and $R^{3a}$ together with the carbon to which they are attached form carbonyl, $Q$ is -$\text{NR}^{14}$-$\text{R}^{15}$, $\text{Ar}^2$ is further substituted at the 4-position with $E$ where $E$ is -$X^1$-$Y^2$-$\text{Ar}^3$, and where $\text{Ar}^3$ is 6-membered aryl are as defined below:

**Table 6.**

<table>
<thead>
<tr>
<th>Cmpd. No.</th>
<th>$Q$</th>
<th>$W$</th>
<th>$\text{Ar}^2$</th>
<th>$X^1$</th>
<th>$Y^2$</th>
<th>$\text{Ar}^3$</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>phenylCH$_2$OC(O)NH</td>
<td>CH$_2$</td>
<td>$\text{C}(O)$</td>
<td>CH$_3$CH$_2$CH$_2$</td>
<td>phenyl</td>
<td></td>
</tr>
<tr>
<td>101</td>
<td>phenylCH$_2$OC(O)NH</td>
<td>CH$_2$</td>
<td>$\text{O}$</td>
<td>CH$_3$CH$_2$</td>
<td>phenyl</td>
<td></td>
</tr>
<tr>
<td>102</td>
<td>phenylCH$_2$OC(O)NH</td>
<td>CH$_2$</td>
<td>$\text{C}(O)$</td>
<td>CH$_3$CH$_2$</td>
<td>phenyl</td>
<td></td>
</tr>
<tr>
<td>104</td>
<td>phenylCH$_2$OC(O)NH</td>
<td>CH$_2$</td>
<td>$\text{O}$</td>
<td>CH$_3$CH$_2$</td>
<td>phenyl</td>
<td></td>
</tr>
<tr>
<td>105</td>
<td>phenylCH$_2$OC(O)NH</td>
<td>CH$_2$</td>
<td>$\text{C}(O)$O</td>
<td>CH$_2$</td>
<td>phenyl</td>
<td></td>
</tr>
<tr>
<td>Cmpd. No.</td>
<td>Q</td>
<td>W</td>
<td>Ar²</td>
<td>X¹</td>
<td>Y²</td>
<td>Ar³</td>
</tr>
<tr>
<td>-----------</td>
<td>--------------------</td>
<td>-------</td>
<td>--------</td>
<td>-----</td>
<td>-----</td>
<td>-------------</td>
</tr>
<tr>
<td>106</td>
<td>phenylCH₂OC(O)NH</td>
<td>CH₂</td>
<td>[Diagram]</td>
<td>OC(O)NH</td>
<td>CH₂CH₂</td>
<td>phenyl</td>
</tr>
<tr>
<td>107</td>
<td>phenylCH₂OC(O)NH</td>
<td>CH₂</td>
<td>[Diagram]</td>
<td>OC(O)NH</td>
<td>CH₂</td>
<td>phenyl</td>
</tr>
<tr>
<td>108</td>
<td>1,3-dioxo-isoinol-2-yl</td>
<td>CH₂</td>
<td>[Diagram]</td>
<td>O</td>
<td>CH₂CH₂</td>
<td>3,4-dichloro-phenyl</td>
</tr>
<tr>
<td>109</td>
<td>H</td>
<td>CH₂</td>
<td>[Diagram]</td>
<td>O</td>
<td>CH₂CH₂</td>
<td>phenyl</td>
</tr>
<tr>
<td>110</td>
<td>3,4-difluoro-phenyl(C(O)NH</td>
<td>CH₂</td>
<td>[Diagram]</td>
<td>C(O)NH</td>
<td>CH₂CH₂</td>
<td>phenyl</td>
</tr>
<tr>
<td>111</td>
<td>succinimidyl</td>
<td>CH₂</td>
<td>phenyl</td>
<td>O</td>
<td>CH₂CH₂</td>
<td>3,4-dichloro-phenyl</td>
</tr>
<tr>
<td>112</td>
<td>phthalimidyl</td>
<td>CH₂</td>
<td>phenyl</td>
<td>O</td>
<td>CH₂CH₂</td>
<td>3,4-dichloro-phenyl</td>
</tr>
<tr>
<td>113</td>
<td>4-fluorophenyl(C(O)NH</td>
<td>CH₂</td>
<td>[Diagram]</td>
<td>C(O)NH</td>
<td>CH₂CH₂</td>
<td>phenyl</td>
</tr>
</tbody>
</table>

and are named:

**[0437]** 5-[(phenylmethyloxycarbonyl)amino]-6-{5-[(3-phenylpropyl)carbonyl]-piperazin-1-ylmethyl}·[1,2,4]oxadiazol-3-yl)-6-oxo-hexyl]-amine;

**[0438]** 5-[(phenylmethyloxycarbonyl)amino]-6-{5-(4-(phenylethoxy)-(3-acetylphenyl)methyl}·[1,2,4]oxadiazol-3-yl)-6-oxo-hexyl]-amine;
[0439] [5-[(phenylmethoxyxycarbonyl)amino]-6-{5-[(4-phenylethoxy)-(3-cyanophenyl)-methyl]-[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine;

[0440] [5-[(phenylmethoxyxycarbonyl)amino]-6-{5-[(4-phenethylcarbonyl)-piperazin-1-ylmethyl]-[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine;

[0441] [5-[(phenylmethoxyxycarbonyl)amino]-6-{5-[(4-phenylethoxy)-(3-tert-butylphenyl)-methyl]-[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine;

[0442] [5-[(phenylmethoxyxycarbonyl)amino]-6-{5-[(4-phenylmethoxyxycarbonyl)-piperazin-1-ylmethyl]-[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine;

[0443] [5-[(phenylmethoxyxycarbonyl)amino]-6-{5-[(3-phenethylaminocarboxyloxy)-phenylmethyl]-[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine;

[0444] [5-[(phenylmethoxyxycarbonyl)amino]-6-{5-[[3-(phenylmethyl)aminocarboxyloxy]-phenylmethyl]-[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine;

[0445] [5-[1,3-dioxo-isindol-2-yl]-6-{5-[(4-(3,4-dichlorophenylethoxy)-phenylmethyl]-[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine;

[0446] [6-{5-[(4-phenylethoxy)-phenylmethyl]-[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine;

[0447] [5-{(3,4-difluorophenylcarbonyl)amino}-6-{5-[(1-phenethylaminocarbonyl)-piperidin-4-ylmethyl]-[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine;

[0448] [5-[succinimidyl]-6-{5-[(4-(3,4-dichlorophenylethoxy)-phenylmethyl]-[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine; and

[0450] [5-{(4-fluorophenylcarbonyl)amino}-6-{5-[(4-phenethylaminocarboxyloxy)-piperazin-1-ylmethyl]-[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine.

[0451] Representative compounds of Formulae I:

\[ \text{where } \text{Ar}^1 \text{ is } 1,2,4-\text{oxadiazol-3,5-diyl and } \text{W is located at the 5-position, R}^1 \text{ is hydrogen, R}^2 \text{ is } \text{H}_2\text{N(CH}_2\text{)}_4, \text{ R}^3 \text{ and R}^{3a} \text{ together with the carbon to which they are attached form carbonyl, Q is } -\text{NR}^{14}\text{R}^{15}, \text{ W is } -\text{CH}_2-, \text{ Ar}^2 \text{ is further substituted at the 4-position with E where E is } -\text{X}^1-\text{Z}^2-\text{Y}^3-\text{Ar}^3, \text{ and Ar}^3 \text{ is 6-membered aryl are as defined below:} \]

Table 7.
and is named [5-[(phenylmethyloxycarbonyl)amino]-6-{5-[(4-(2-fluorophenylmethyl)-piperazin-1-yl)carbonyl]-phenylmethyl}]-[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine.

[0452] Representative compounds of Formulae I:

![Chemical Structure](image)

where Ar¹ is 1,2,4-oxadiazol-3,5-diyl and W is located at the 5-position, R³ and R³a together with the carbon to which they are attached form carbonyl, Q is –NR¹⁴R¹⁵, and Ar² is further substituted at the 4-position with E where E is -X¹-Y²-Ar³, and Ar³ is 6-membered aryl are as defined below:

**Table 8.**

<table>
<thead>
<tr>
<th>Cmpd. No.</th>
<th>R¹⁴</th>
<th>R¹⁵</th>
<th>R¹</th>
<th>R²</th>
<th>W</th>
<th>Ar²</th>
<th>X¹</th>
<th>Y²</th>
<th>Ar³</th>
</tr>
</thead>
<tbody>
<tr>
<td>115</td>
<td>H</td>
<td>phenylCH₂OC(O)-</td>
<td>H</td>
<td>H₂NCH₂CH=CHCH₂</td>
<td>CH₂</td>
<td>phenyl</td>
<td>O</td>
<td>CH₂CH₂</td>
<td>phenyl</td>
</tr>
<tr>
<td>116</td>
<td>H</td>
<td>phenylCH₂OC(O)-</td>
<td>H</td>
<td>tert-butoxycarbonylamin obutyl</td>
<td>CH₂</td>
<td>3-acetyl-phenyl</td>
<td>O</td>
<td>CH₂CH₂</td>
<td>phenyl</td>
</tr>
<tr>
<td>117</td>
<td>H</td>
<td>phenylCH₂OC(O)-</td>
<td>H</td>
<td></td>
<td>CH₂</td>
<td>phenyl</td>
<td>O</td>
<td>CH₂CH₂</td>
<td>phenyl</td>
</tr>
<tr>
<td>Cmpd. No.</td>
<td>R^{14}</td>
<td>R^{15}</td>
<td>R^{1}</td>
<td>R^{2}</td>
<td>W</td>
<td>Ar^{2}</td>
<td>X^{1}</td>
<td>Y^{2}</td>
<td>Ar^{3}</td>
</tr>
<tr>
<td>-----------</td>
<td>--------</td>
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<td>-------------------</td>
<td>---------------</td>
<td>-----</td>
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<td>---------</td>
<td>---------</td>
</tr>
<tr>
<td>118</td>
<td>H</td>
<td>H</td>
<td>tert-</td>
<td>CH$_2$</td>
<td>phenyl</td>
<td>O</td>
<td>CH$_3$CH$_2$</td>
<td>phenyl</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
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<td>butoxycarbonylamino</td>
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<td></td>
</tr>
<tr>
<td>119</td>
<td>H</td>
<td>H</td>
<td>aminomethylphenyl</td>
<td>CH$_2$</td>
<td></td>
<td>C(O)NH</td>
<td>CH$_3$CH$_2$</td>
<td>phenyl</td>
<td></td>
</tr>
<tr>
<td></td>
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<td>120</td>
<td>H</td>
<td>H</td>
<td>aminomethylphenyl</td>
<td>CH$_2$</td>
<td></td>
<td>C(O)</td>
<td>CH$_3$CH$_2$</td>
<td>phenyl</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>methyl</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>121</td>
<td>H</td>
<td>H</td>
<td>aminomethylphenyl</td>
<td>CH$_2$</td>
<td></td>
<td>C(O)NH</td>
<td>CH$_3$CH$_2$</td>
<td>phenyl</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>methyl</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>122</td>
<td>H</td>
<td>H</td>
<td>guanidinocarboxylic</td>
<td>CH$_2$</td>
<td>phenyl</td>
<td>O</td>
<td>CH$_3$CH$_2$</td>
<td>3,4-dichlorophenyl</td>
<td></td>
</tr>
</tbody>
</table>
|           |        |        | hyd                |               |      |        |         |         |         | and are named:  

[0453] [5-[(phenylmethyloxy carbonyl)amino]-6- (5-[4-(phenethyloxy)-phenylmethyl]-1,2,4]oxadiazol-3-yl]-6-oxo-hex-2-enyl]-amine;  

[0454] [5-[(phenylmethyloxy carbonyl)amino]-6- (5-[4-(phenethyloxy)-3-acetyl-phenylmethyl]-1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-tert-butoxy carbonylamine;  

[0455] 2-[(phenylmethyloxy carbonyl)amino]-3- (5-[4-(phenethyloxy)-phenylmethyl]-1,2,4]oxadiazol-3-yl]-3-oxo-1- (1H-pyrrolo[3,2-c]pyridin-2-yl) propane;  

[0456] [5-[(phenylmethyloxy carbonyl)amino]-6- (5-[4-(phenethyloxy)-phenylmethyl]-1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-tert-butoxy carbonylamine;  

[0457] 2-[(ethoxy carbonyl)amino]-3- (5-[4-(phenethylaminocarbonyl)-piperazinylmethyl]-1,2,4]oxadiazol-3-yl]-3-oxo-1- [4-(aminomethyl)phenyl]-propane;  

[0458] 2-[(ethoxy carbonyl)amino]-3- (5-[4-(phenylpropyl carbonyl)-piperazinylmethyl]-1,2,4]oxadiazol-3-yl]-3-oxo-1- [4-(aminomethyl)phenyl]-propane;
[1,2,4]oxadiazol-3-yl]-3-oxo-1-[4-(aminomethyl)phenyl]-propane;  

[0459] 2-[(ethoxycarbonyl)amino]-3-[5-[4-(phenethylaminocarbonyl)-piperazinylmethyl]-[1,2,4]oxadiazol-3-yl]-3-oxo-1-[4-(aminomethyl)phenyl]-propane; and  

[0460] 3-[[phenylmethylxycarbonyl]amino]-4-[5-[4-(3,4-dichlorophenethoxy)-phenylmethyl]-[1,2,4]oxadiazol-3-yl]-4-oxo]-1-(guanidinocarbonyl)-butane.

[0461] Representative compounds of Formulae I:

where Ar\(^1\) is 1,2,4-oxadiazol-3,5-diyl and W is located at the 5-position, R\(^1\) is hydrogen, R\(^2\) is -(CH\(_2\))\(_n\)NH\(_2\), R\(^3\) and R\(^{3a}\) together with the carbon to which they are attached form carbonyl, Q is -NR\(^{14}\)R\(^{15}\), and Ar\(^2\) is further substituted at the 4-position with E where E is -X\(^1\)-Y\(^2\)-Y\(^3\)-Ar\(^3\) and Ar\(^3\) is 6-membered aryl are as defined below:

Table 9.

<table>
<thead>
<tr>
<th>Cmpd. No.</th>
<th>R(^{14})</th>
<th>R(^{15})</th>
<th>W</th>
<th>X(^1)</th>
<th>Y(^2)</th>
<th>Y(^3)</th>
<th>Ar(^3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>123</td>
<td>H</td>
<td>phenylCH(_2)OC(O)-</td>
<td>CH(_2)</td>
<td>O</td>
<td>CH(_2)</td>
<td></td>
<td>4-chlorophenyl</td>
</tr>
</tbody>
</table>

[0462] and is named [5-[[phenylmethylxycarbonyl]amino]-6-[5-{4-[1-(4-chlorophenyl)-cycloprop-1-ylmethylxoy]-phenylmethyl}-[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine.

[0463] Representative compounds of Formulae I:

where Ar\(^1\) is 1,2,4-oxadiazol-3,5-diyl and W is located at the 5-position, R\(^1\) is hydrogen, R\(^2\) is -(CH\(_2\))\(_n\)NH\(_2\), R\(^3\) and R\(^{3a}\) together with the carbon to which they are attached form carbonyl, Q is -NR\(^{14}\)R\(^{15}\), and Ar\(^2\) is further substituted at the 4-position with E where E is -X\(^1\)-Y\(^2\)-Y\(^3\)-Ar\(^3\) and Ar\(^3\) is 6-membered aryl are as defined below:
is heterocycloalkyl are as defined below:

Table 10.

<table>
<thead>
<tr>
<th>Cmpd. No.</th>
<th>R^{14}</th>
<th>R^{15}</th>
<th>W</th>
<th>Ar^2</th>
<th>Y^1</th>
<th>X^1</th>
<th>Ar^3</th>
</tr>
</thead>
<tbody>
<tr>
<td>124</td>
<td>H</td>
<td>4-fluorophenylcarbonyl</td>
<td>CH_2</td>
<td>N</td>
<td>CH_2</td>
<td>C(O)</td>
<td>morpholin-4-yl</td>
</tr>
</tbody>
</table>

[0464] and is named [5-[(4-fluorophenylcarbonyl)amino]-6-{5-[(morpholin-4-ylcarbonylmethyl)-piperazinylmethyl]-[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine.

**GENERAL SYNTHESIS**

[0465] Compounds of this invention can be made by the synthetic procedures described below.

[0466] The starting materials and reagents used in preparing these compounds are either available from commercial suppliers such as Aldrich Chemical Co. (Milwaukee, Wis.), or Bachem (Torrance, Calif.), or are prepared by methods known to those skilled in the art following procedures set forth in references such as Fieser and Fieser’s Reagents for Organic Synthesis, Volumes 1-17 (John Wiley and Sons, 1991); Rodd’s Chemistry of Carbon Compounds, Volumes 1-5 and Supplementals (Elsevier Science Publishers, 1989); Organic Reactions, Volumes 1-40 (John Wiley and Sons, 1991), March’s Advanced Organic Chemistry, (John Wiley and Sons, 4th Edition) and Larock’s Comprehensive Organic Transformations (VCH Publishers Inc., 1989). In particular, 2-chloro-oxazole-4-carboxylic acid ethyl ester can be prepared according to methods described in K.J. Hodgetts, M.T. Kershaw, *Org. Lett.*, **2002**, 4, 2905-7. These schemes are merely illustrative of some methods by which the compounds of this invention can be synthesized, and various modifications to these schemes can be made and will be suggested to one skilled in the art having referred to this disclosure.

[0467] The starting materials and the intermediates of the reaction may be isolated and purified if desired using conventional techniques, including but not limited to filtration, distillation,
crystallization, chromatography and the like. Such materials may be characterized using conventional means, including physical constants and spectral data.

[0468] Unless specified to the contrary, the reactions described herein take place at atmospheric pressure over a temperature range from about –78 °C to about 150 °C, more preferably from about 0 °C to about 125 °C and most preferably at about room (or ambient) temperature, e.g., about 20 °C. Unless otherwise stated (as in the case of an hydrogenation), all reactions are performed under an atmosphere of nitrogen.

[0469] Compounds of Formula I that may be prepared through the syntheses described herein may exist as a single isomer or a mixture of isomers.

[0470] Compounds of Formula I can be prepared by the procedures illustrated and described in Schemes A-G below.

[0471] Intermediate 5, which may be prepared as shown in Scheme A below, can be used in the preparation of compounds of Formula I where R^{1} is hydrogen, R^{2} is H_{2}N(CH_{2})_{4}, R^{3} and R^{3a} together with the carbon to which they are attached form carbonyl, Ar^{1} is 1,2,4-oxadiazol-3,5-diyl and W is in the 5-position, Q is –NR^{14}R^{15} where R^{14} is hydrogen and R^{15} is phenylmethyloxycarbonyl, Ar^{2} is aryl, heteroaryl, or heterocycloalkyl further substituted with E where E is -X^{1}-Y^{2}-Ar^{3} and X^{1} is -O-, -OC(O)NH-, or -C(O)NH-, and all other groups are as defined in the Summary of the Invention.

Scheme A

![Diagram of chemical reactions involving intermediates 1, 2, 3, 4, and 5.]

[0472] The protected lysine is commercially available. Compounds of formula 2 can be prepared by first converting 1 to a reactive acid derivative followed by treatment with
$N,O$-dimethylhydroxylamine. Specifically, 1 can be first converted to an acid halide derivative such as acid chloride, and the like with a chlorinating agent such as thionyl chloride, oxalyl chloride, and the like. Suitable solvents are halogenated organic solvents such as methylene chloride, and the like. The resulting acid halide is then reacted with $N,O$-dimethylhydroxylamine. The amination reaction is carried out in the presence of a suitable base such as triethylamine, pyridine, and the like and in a suitable organic solvent such as THF, dioxane, $N,N$-dimethylformamide and the like.

[0473] Alternatively, an intermediate of formula 2 can be prepared by reacting 1 with $N,O$-dimethylhydroxylamine in the presence of a coupling agent such as benzotriazol-1-yloxytrispyrrolidino-phosphonium hexafluorophosphate (PyBOP®), bromo-trispyrrolidino-phosphonium hexafluorophosphate (PyBrop®), $O$-benzotriazol-1-yl-$N,N,N',N'$-tetramethyl-uronium hexafluorophosphate (HBTU), $O$-(7-azabenzoazol-1-yl)-$N,N,N',N'$-tetramethyluronium hexafluorophosphate (HATU), or 1,3-dicyclohexylcarbodiimide (DCC) or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) optionally in the presence of 1-hydroxybenzotriazole (HOBT). As appropriate, a base such as $N,N$-diisopropylethylamine, triethylamine, or $N$-methylmorpholine can be used. Suitable solvents are dichloromethane, dichloroethane, dimethylformamide, tetrahydrofuran, or acetonitrile.

[0474] An intermediate of formula 3 can be prepared by reduction of 2 with hydride reagents such as lithium aluminum hydride (LAH), di-isobutyl aluminum hydride (DIBAL-H), or lithium tri-tert-butoxyluminum hydride, and the like. Suitable solvents are tetrahydrofuran or diethyl ether and the like.

[0475] An intermediate of formula 4 can be prepared by reacting aldehyde 3 with acetone cyanohydrin in the presence of a base such as triethylamine or $N,N$-diisopropylethylamine, and the like. Suitable solvents are dichloromethane, chloroform, tetrahydrofuran, acetonitrile, dioxane, or $N,N$-dimethylformamide, and the like. Alternatively, an intermediate of formula 4 can be prepared by reacting 3 with a cyanide source such as sodium cyanide, potassium cyanide, or trimethylsilylcyanide, and the like. Suitable solvents are $N,N$-dimethylformamide, dimethylsulfoxide, or tetrahydrofuran, and the like.

[0476] An intermediate of formula 5 can be prepared by reacting 4 with aqueous hydroxylamine in solvents such as ethanol or methanol, and the like. Alternatively, the hydrochloride salt of hydroxylamine can be used in the presence of a base such as sodium methoxide, sodium ethoxide,
sodium bicarbonate, postassium bicarbonate, sodium hydroxide, potassium hydroxide, or triethylamine, and the like.

[0477] Intermediate 5 can then be used to prepare compounds of Formula I as illustrated and described in Scheme B below where R₁ is hydrogen, R² is H₂N(CH₂)₄, R³ and R³₈ together with the carbon to which they are attached form carbonyl, Ar¹ is 1,2,4-oxadiazol-3,5-diyl and W is located at the 5-position, W is A¹ where A¹ is alkylene or where W is D and D is –CR’R” (where R’ and R” together with the carbon to which they are attached form cycloalkylene), Q is –NR¹⁴R¹⁵ where R¹⁴ is hydrogen and R¹⁵ is phenylmethyloxycarbonyl, Ar² is aryl or heteroaryl further substituted with E where E is -X¹-Y²-Ar³ where X¹ is -O- or -OC(O)NH-, and all other groups are as defined in the Summary of the Invention.

Scheme B

[0478] An intermediate of formula 7(a) can be prepared by first converting acid 6 to an acid halide derivative such as an acid chloride with a chlorinating reagent such as thionyl chloride or oxalyl chloride, and the like. Other methods of activating carboxylic acids are well known to those skilled in the art. Suitable solvents are dichloromethane, and the like. The resulting acid halide is then reacted with compound 5 in the presence of a base such as triethylamine or pyridine, and the like,
in a suitable solvent such as tetrahydrofuran, dioxane, or N,N-dimethylformamide and the like. The reaction can then be heated in a solvent such as pyridine, N,N-dimethylformamide, or tetrahydrofuran, and the like; or alternatively, the cyclization can also be carried out under microwave conditions.

Alternatively, an intermediate of formula 7(a) can be prepared by reacting 5 and 6 in the presence of

[0480] a coupling agent such as benzotriazol-1-yloxytrispyrrolidino-phosphonium hexafluorophosphate (PyBOP®), bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (PyBrop®), O-benzotriazol-1-yl-N,N,N',N′-tetramethyl-uronium hexafluorophosphate (HBTU), O-(7-azabenzotriazol-1-yl)-N,N,N′,N′-tetramethyluronium hexafluorophosphate (HATU), or 1,3-dicyclohexylcarbodiimide (DCC) or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) optionally in the presence of 1-hydroxybenzotriazole (HOBT). As appropriate, a base such as N,N-diisopropylethylamine, triethylamine, or N-methylmorpholine can be used. Suitable solvents are dichloromethane, N,N-dimethylformamide or tetrahydrofuran, and the like. The intermediate can then be heated in solvents such as pyridine, N,N-dimethylformamide or tetrahydrofuran, and the like; or alternatively, this cyclization can also be carried out under microwave conditions.

[0481] A compound of formula 10 where X¹ is -O- can be prepared by reacting the intermediate 7(a) with an alcohol of formula Ar³-Y²-OH (8). The reaction is carried out with an activating agent such as diisopropyl azodicarboxylate or diethyl azodicarboxylate, and the like, in the presence of a solid-supported or trisubstituted phosphine, such as triphenylphosphine, and the like. Examples of solvents of the reaction include dichloromethane, dioxane, or N,N-dimethylformamide, and the like.

[0482] A compound of formula 10 where X¹ is -OC(O)NH- can be prepared by reacting an isocyanate of formula Ar³-Y²-NCO (9) with 7(a) in the presence of a non-nucleophilic organic base such as N,N-diisopropylethylamine, triethylamine, or pyridine, and the like. Examples of solvents of the reaction include dichloromethane, THF, dioxane, or N,N-dimethylformamide, and the like. Isocyanates of the formula Ar³-Y²-NCO (9) are commercially available or may be prepared according to procedures well known in the art.

[0483] Compounds of formula 11 can be prepared by reacting compounds of formula 10 with commercially available Dess-Martin periodinane reagent in a suitable solvent such as dichloromethane. Alternatively, compounds of formula 11 can be prepared by means of the
Swern oxidation method that involves reacting compounds of formula 10 with an “activated” DMSO reagent in a suitable solvent such as methylene chloride and then quenching the reaction with a non-nucleophilic base such as triethylamine. The “activated” DMSO is first formed by reaction of DMSO with an acylating agent such as oxalyl chloride or trifluoroacetic anhydride in a suitable solvent such as methylene chloride. Alternatively, compounds of formula 11 can be synthesized by oxidizing compounds of formula 10 using a variety of other oxidizing methods known to those skilled in the art, such as oxidation with MnO2, pyridinium chlorochromate, and other methods such as those described in House’s Modern Synthetic Reactions (W.A. Benjamin, Inc, 1972, 2nd edition).

[0484] The tert-butoxycarbonyl protecting group (Boc) on 11 may then be removed under acidic reaction conditions to yield a compound of formula 12. A comprehensive list of suitable conditions for removing protective groups can be found in T.W. Greene, Protective Groups in Organic Synthesis, John Wiley & Sons, Inc. 1991, the disclosure of which is incorporated herein by reference in its entirety.

[0485] Detailed descriptions of preparation where R1 is hydrogen, R2 is H2N(CH2)4, R3 and R3a together with the carbon to which they are attached form carbonyl, Ar1 is 1,2,4-oxadiazol-3,5-diyl and W is located at the 5-position, W is A1 where A1 is alkylene or where W is D and D is –CR’R” (where R’ and R” together with the carbon to which they are attached form cycloalkylene), Q is –NR14R15 where R14 is hydrogen and R15 is phenylmethylxycarbonyl, Ar2 is 6-membered aryl further substituted with E where E is -X1-Y2-Ar3 where X1 is -O- or -OC(O)NH-, are described below in the working examples.

[0486] Intermediate 5 can also be used to prepare compounds of Formula I where R1 is hydrogen, R2 is H2N(CH2)4, R3 and R3a together with the carbon to which they are attached form carbonyl, Ar1 is 1,2,4-oxadiazol-3,5-diyl and W is located at the 5-position, W is A1 where A1 is alkylene or where W is D and D is –CR’R” (where R’ and R” together with the carbon to which they are attached form cycloalkylene), Q is -NR14R15 where R14 is hydrogen and R15 is phenylmethylxycarbonyl, Ar2 is aryl or heteroaryl further substituted with E where E is -X1-Y2-Z1-Ar3 where X1 is -O- or -OC(O)NH-, Y2 is alkylene, and Z1 is -C(O)- and all other groups are as defined in the Summary of the Invention using conditions similar to those in Scheme B. Instead of reacting an intermediate of formula 7(a) with 8 or 9, 7(a) can be reacted with an intermediate of formula LG-Y2-Z1-Ar3, where LG is halide, preferably bromide, or a tosylate, and the like, in the presence of an inorganic base such as lithium carbonate or potassium carbonate, and the like or a
non-nucleophilic base such as N,N-diisopropylethylamine, triethylamine, or pyridine, and the like. Examples of solvents of the reaction include acetonitrile, acetone, dichloromethane, THF, dioxane, or DMF, and the like. LG-Y²-Z¹-Ar³ are commercially available.

[0487] A compound of Formula I where R¹ is hydrogen, R² is H₂N(CH₂)₄, R³ and R⁴ together with the carbon to which they are attached form carbonyl, Ar¹ is 1,2,4-oxadiazol-3,5-diyI and W is located at the 5-position, W is A¹ where A¹ is alkylene, Q is -NR¹⁴R¹⁵ where R¹⁴ is hydrogen and R¹⁵ is phenylmethyloxycarbonyl, Ar² is aryl or heteroaryl further substituted with -X¹⁻Y²⁻Ar³ where X¹ is -C(O)NH- can be prepared as described in Scheme C below.

**Scheme C**
Intermediate 5 can be reacted with an acid of the formula HO(O)-C-A^1-Ar^2-C(O)-OMe (13) to prepare 14 using conditions described above in Scheme B. Acids of formula 13 are commercially available or may be prepared by methods well known in the art. An intermediate of formula 15 may be prepared by cyclization reaction of the intermediate 14 using conditions as described above in Scheme B.

Hydrolysis of the ester 15 provides an intermediate of formula 16(a). The hydrolysis can be carried out in the presence of an aqueous base such as aqueous sodium hydroxide, lithium hydroxide, and the like in a suitable organic solvent such as methanol, ethanol, THF, and the like.

Compounds of formula 16(a) may then be converted to a compound of formula 46 by first converting 16(a) to a reactive acid derivative followed by treatment an amine of formula NHR'-Y^2-Ar^3 (17). Specifically, 16(a) can be first converted to an acid halide derivative such as acid chloride, and the like with a chlorinating agent such as thionyl chloride, oxalyl chloride, and the like. Suitable solvents are halogenated organic solvents such as methylene chloride, and the like. The resulting acid halide is then reacted with an amine of formula NHR'-Y^2-Ar^3 (17). The amination reaction is carried out in the presence of a suitable base such as triethylamine, pyridine, and the like and in a suitable organic solvent such as THF, dioxane, N,N-dimethylformamide and the like.

Alternatively, a compound of formula 46 can be prepared by reacting 16(a) with the amine in the presence of a coupling agent such as benzotriazol-1-yloxytrispyrrolidino-phosphonium hexafluorophosphate (PyBOP®), bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (PyBrop®), O-benzotriazol-1-yl-N,N,N',N'-tetramethyl-uronium hexafluorophosphate (HBTU), O-(7-azabenzo triazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU), or 1-hydroxybenzotriazole (HOBT) in the presence of 1,3-dicyclohexylcarbodiimide (DCC) or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC), or a base such as N,N-diisopropylethylamine, triethylamine, or N-methylmorpholine. Suitable solvents are dichloromethane, dioxane, dichloroethane, dimethylformamide, tetrahydrofuran, or acetonitrile.

The hydroxy group in 46 can then be oxidized using conditions described for Scheme B.

The tert-butoxycarbonyl protecting group (Boc) on 18 can be removed using conditions described above to yield a compound of formula 19.

Detailed descriptions of preparation where R^1 is hydrogen, R^2 is H_2N(CH_2)_4, R^3 and R^{3a} together with the carbon to which they are attached form carbonyl, Ar^1 is 1,2,4-oxadiazol-3,5-diyl and W is located at the 5-position, W is A^1 where A^1 is alkylene, Q is -NR^{14}R^{15} where R^{14} is
hydrogen and $R^{15}$ is aralkyloxy carbonyl, $Ar^2$ is 6-membered aryl or heteroaryl further substituted with E where E is -X$^1$-Y$^2$-Ar$^3$ and X$^1$ is -C(O)NH$^-$ are described below in the working examples.

[0495] A compound of Formula I where $R^1$ is hydrogen, $R^2$ is H$_2$N(CH$_2$)$_4$-N$^-$, $R^3$ and $R^{3a}$ together with the carbon to which they are attached form carbonyl, $Ar^1$ is 1,2,4-oxadiazol-3,5-diyl and $W$ is located at the 5-position, $W$ is A$^1$ where A$^1$ is alkylene, $Ar^2$ is 6-membered aryl substituted with E where E is -X$^1$-Y$^2$-Ar$^3$ and X$^1$ is -O$^-$, -NR$^{14}$R$^{15}$ where R$^{14}$ is hydrogen and R$^{15}$ is alkylcarbonyl, cyanoalkylcarbonyl, haloalkylcarbonyl, haloalkoxy carbonyl, alkenyloxy carbonyl, alkoxy carbonyl, alkoxyalkylcarbonyl, alkoxyalkyloxy carbonyl, alkoxy carbonylamino carbonyl, cycloalkyl carbonyl, cycloalkylalkylcarbonyl, aryl carbonyl, aralkylcarbonyl, heteroaryl carbonyl, heterocycloalkylcarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, cycloalkyloxycarbonyl, heterocycloalkyloxycarbonyl, aralkyloxy carbonyl, aralkenyloxy carbonyl, heterocycloalkylalkyloxy carbonyl, heteroarylalkyloxy carbonyl, heteroarylalkenyloxy carbonyl, or $R^{19}$R$^{20}$NC(O$^-$), and all other groups are as defined in the Summary of the Invention, can be prepared as illustrated and described in Scheme D below.
[0496] The phenylmethylxycarbonyl group (Cbz) in 2 may be removed under hydrogenation conditions and replaced by an Alloc protecting group. The Alloc group can be added in the
presence of a base such as $N,N$-diisopropylethylamine, triethylamine, or $N$-methylmorpholine, and
the like. Suitable solvents are dichloromethane, dioxane, dichloroethane, dimethylformamide,
tetrahydrofuran, or acetonitrile, and the like. A comprehensive list of suitable protective groups
and the means by which to add and remove them can be found in T.W. Greene, *Protective Groups
in Organic Synthesis*, John Wiley & Sons, Inc. 1991, the disclosure of which is incorporated
herein by reference in its entirety.

[0497] Intermediates 21 and 22 may be prepared from 20 using conditions as described above.

[0498] The newly formed hydroxyl group of 22 can then be protected with tert-butylimidethylsilyl
chloride (TBDMScI) or tert-butylimidethylsilyl trifluoromethanesulfonate in the presence of a
base such as imidazole or triethylamine, and the like, with $N,N$-dimethylaminopyridine (DMAP)
to yield 23. Suitable solvents are dichloromethane, $N,N$-dimethylformamide, or tetrahydrofuran
and the like.

[0499] Intermediate 24 can be prepared using conditions as described above.

[0500] Reagent 25 can be prepared by reacting the corresponding acid with $N$-hydroxysuccinimide
in the presence of dicyclohexylcarbodiimide (DCC) in a solvent such as tetrahydrofuran and the
like.

[0501] Intermediate 26 can be prepared by reacting 24 and 25 in the presence of a base such as
$N,N$-diisopropylethylamine, triethylamine, or $N$-methylmorpholine, and the like. Suitable
solvents are dichloromethane, dioxane, dichloroethane, dimethylformamide, tetrahydrofuran, or
acetonitrile, and the like.

[0502] The Alloc protecting group in 26 can be removed in the presence of catalytic amount of
palladium catalyst such as tetrakis(triphenylphosphine)palladium(0) or palladium acetate, and the
like, in the presence of phenylsilane, an amine (like diethylamine), or a hydride source (like
tributyltin hydride), or using other methods as described in T.W. Greene, *Protective Groups in
Organic Synthesis*, John Wiley & Sons, Inc. 1991. Suitable solvents are dichloromethane,
acetonitrile, or tetrahydrofuran, and the like.

[0503] 28 can be prepared using amide formation conditions as described above. In Scheme D, R
is alkyl, cyanoalkyl, haloalkyl, haloalkoxy, alkenyloxy, alkoxy, alkoxyalkyl, alkoxyalkyloxy,
alkoxycarbonylamino, cycloalkyl, cyanoalkylalkyl, aryl, aralkyl, heteroaryl, heterocycloalkyl,
aryloxy, heteroaryloxy, cycloalkyloxy, heterocycloalkyloxy, aralkyloxy, aralkenyloxy,
heterocycloalkylalkyloxy, heteroaralkyloxy, or heteroaralkenyloxy.

[0504] The TBDMS protecting group on 28 can be removed, for example, with a solution of
TBAF in THF. The resulting alcohol is oxidized using Swern conditions, Dess-Martin periodinane, or TPAP conditions, and the like, in a suitable solvent. The tert-butoxycarbonyl protecting group (Boc) is removed under acidic reaction condition to yield 29.

[0505] A compound of Formula I where R¹ is hydrogen, R² is H₂N(CH₂)₄, R³ and R⁴ together with the carbon to which they are attached form carbonyl, Ar¹ is 1,2,4-oxadiazol-3,5-diyl and W is located at the 5-position, W is A¹ where A¹ is alkylene, Ar² is 6-membered aryl substituted with E where E is -X¹-Y²-Ar³ and X¹ is -O-, Q is -NR¹⁴R¹⁵ where R¹⁴ is hydrogen and R¹⁵ is R²¹S(O)₂⁻ or R¹⁹R²⁰NS(O)₂⁻, and all other groups are as defined in the Summary of the Invention, can be prepared as illustrated and described in Scheme D above by substituting the acyl halide with an intermediate of formula R¹⁹R²⁰NC(O)-LG, R²¹S(O)₂-LG, or R¹⁹R²⁰NS(O)₂-LG utilizing the reaction conditions described herein. LG is a leaving group under sulfonylating conditions, such as a halo. The reaction can be carried out in the presence of a non-nucleophilic organic base such as triethylamine or pyridine, and the like. Examples of solvents of the reaction include dichloromethane, THF, dioxane, or DMF, and the like. Compounds of formula R²¹S(O)₂-LG, and R¹⁹R²⁰NS(O)₂-LG are commercially available or may be prepared by methods well known in the art.

[0506] A compound of Formula I where R¹ is hydrogen, R² is H₂N(CH₂)₄, R³ and R⁴ together with the carbon to which they are attached form carbonyl, Ar¹ is 1,2,4-oxadiazol-3,5-diyl and W is located at the 5-position, W is A¹ where A¹ is alkylene, Ar² is 6-membered aryl substituted with E where E is -X¹-Y²-Ar³ and X¹ is -O-, Q is -NR¹⁴R¹⁵ where R¹⁴ is hydrogen and R¹⁵ is R¹⁹R²⁰NC(O)-, and all other groups are as defined in the Summary of the Invention, can be prepared as illustrated and described in Scheme D above by substituting LG-C(O)NR¹⁵R²⁰ or R¹⁹N=C=O for R¹⁴C(O)Cl or R¹⁴C(O)OH in the scheme. The urea products can be prepared by

1) reacting 27(a) with a carbamoyl halide of formula LG-C(O)NR¹⁹R²⁰ in the presence of a non-nucleophilic organic base using suitable solvents such as dichloromethane, 1,2-dichloroethane, or THF, and the like; or

2) reacting 27(a) with the isocyanate R¹⁹N=C=O in suitable solvents such as benzene, THF, or dimethylformamide, and the like.

[0507] A compound of Formula I where R¹ is hydrogen, R² is H₂N(CH₂)₄, R³ and R⁴ together with the carbon to which they are attached form carbonyl, Ar¹ is 1,2,4-oxadiazol-3,5-diyl and W is located at the 5-position, W is A¹ where A¹ is methylene, Ar² is piperazin-1,4-diyl substituted with E where E is -X¹-Y²-Ar³ and X¹ is -C(O)-, Q is -NR¹⁴R¹⁵ where R¹⁴ is hydrogen and R¹⁵ is
phenylmethyloxycarbonyl, and all other groups are as defined in the Summary of the Invention, can be prepared as illustrated and described in Scheme E below.

Scheme E

\[ \text{5} \xrightarrow{\text{Cl}_2\text{C}=\text{O}} \text{30(a)} \xrightarrow{\text{Dess-Martin ox.}} \text{34} \]

5 \[ \text{5} \] may be prepared using conditions as described above.

[0509] An intermediate of formula 30(a) can be prepared by coupling 5 with chloroacetyl chloride. The reaction can be carried out in suitable solvents such as dichloromethane, chloroform, tetrahydrofuran, dioxane, acetonitrile, or benzene, and the like and optionally in the presence of a base such as triethylamine or pyridine, and the like. The cyclization reaction of the resulting intermediate can be executed in solvents such as DMF, pyridine, or toluene, and the like. Amination of 30(a) with an appropriately prepared piperazine derivative of formula 31(a) gave 32. The reaction can be carried out in the presence of inorganic base such as Na\(_2\)CO\(_3\) or K\(_2\)CO\(_3\), and the like or non-nucleophilic base such as triethylamine or pyridine, and the like, in suitable solvents such as tetrahydrofuran, dioxane, or acetonitrile, and the like. A compound of formula 32 can be subjected to oxidation to give 33. The oxidation condition can be accomplished under Swern conditions, using Dess-Martin periodinane, or under TPAP conditions, and the like, in a suitable solvent. The tert-butoxycarbonyl protecting group (Boc) on 33 is removed under acidic reaction condition to give the desired product 34.
A compound of Formula I where $R^1$ is hydrogen, $R^2$ is $H_2N(CH_2)_n$, $R^3$ and $R^{3a}$ together with the carbon to which they are attached form carbonyl, $Ar^1$ is 1,2,4-oxadiazol-3,5-diyl and $W$ is located at the 5-position, $W$ is $A^1$ where $A^1$ is methylene, $Ar^2$ is piperazin-1,4-diyl substituted with $E$ where $E$ is $-Y^1-Ar^3$ and $Y^1$ is alkylene, $Q$ is $-NR^{14}R^{15}$ where $R^{14}$ is hydrogen and $R^{15}$ is phenylmethoxy carbonyl, and all other groups are as defined in the Summary of the Invention, can be prepared as illustrated and described in Scheme F below.

**Scheme F**

An intermediate of formula 36(a) can be prepared by monoalkylation of 35 with excess amount of piperazine in suitable solvent such as acetonitrile, dioxane, or THF and the like. 36(a) is then treated with an intermediate of formula $Ar^1$-$Y^2$-$Cl$ (37) in the presence of potassium iodide, a base such as potassium carbonate or lithium carbonate, and the like, and in a solvent such as acetonitrile, and the like. The reaction is then be refluxed to yield 38. The hydroxy group can then be oxidized using oxaly chloride in the presence of DMSO and triethylamine and carried out in a solvent like dichloromethane to yield 39. The Boc-protecting group can be removed under acidic conditions as described above to yield the final product 40.
[0512] A compound of Formula I where R¹ is hydrogen, R² is H₂N(CH₂)₄, R³ and R⁴ together with the carbon to which they are attached form carbonyl, Ar¹ is 1,2,4-oxadiazol-3,5-diyl and W is located at the 5-position, W is A¹ where A¹ is methylene, Ar² is piperidin-4-yl substituted at the 1-position with E where E is X¹-Y²-Ar³ and X¹ is -C(O)- or -C(O)NH- and Y¹ is alkylene, Q is -NR¹⁴R¹⁵ where R¹⁴ is hydrogen and R¹⁵ is alkylcarbonyl, cyanoalkylcarbonyl, haloalkylcarbonyl, haloalkoxy carbonyl, alkenyloxy carbonyl, alkoxy carbonyl, alkoxyalkyl carbonyl, alkoxyalkyloxy carbonyl, alkoxy carbonylamino carbonyl, cycloalkyl carbonyl, cycloalkylalkyl carbonyl, aryl carbonyl, aralkyl carbonyl, heteroaryl carbonyl, heterocycloalkyl carbonyl, aryloxycarbonyl, heteroaryloxy carbonyl, cycloalkyloxy carbonyl, heterocycloalkyloxy carbonyl, aralkyloxy carbonyl, aralkenyl carbonyl, heterocycloalkylalkyloxy carbonyl, heteroaralkyloxy carbonyl, or heteroaralkenyl carbonyl, and all other groups are as defined in the Summary of the Invention, can be prepared as illustrated and described in Scheme G below.

![Scheme G](image)

[0513] In Scheme G, R is alkyl, cyanoalkyl, haloalkyl, haloalkoxy, alkenyloxy, alkoxy, alkoxyalkyl, alkoxyalkyloxy, alkoxy carbonylamino, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, heterocycloalkyl, aryloxy, heteroaryloxy, cycloalkyloxy, heterocycloalkyloxy,
aralkyloxy, aralkenylxoy, heterocycloalkylalkyloxy, heteroaralkyloxy, or heteroaralkenyloxy.

[0514] The Alloc protecting group in 23 (Scheme D) can be removed as described above in Scheme D. The free amine can then be reacted with an intermediate of formula \( R^{19}_1 R^{20}_1 NC(O)Cl \), \( RC(O)Cl \) or \( RC(O)OH \) using conditions as described in Scheme C to form the amide which may then be treated with hydroxylamine using conditions described above in Scheme A to yield 41.

[0515] Alternatively, an intermediate of formula 41 can be prepared from 19 (Scheme D) using conditions described in Scheme D but where the alloc-Cl is replaced with an intermediate of formula \( R^{19}_1 R^{20}_1 NC(O)Cl \), \( RC(O)Cl \) or \( RC(O)OH \) and conditions for this amide forming step are as described in Scheme C.

[0516] An intermediate of formula 42 can be prepared from commercially available 4-carboxymethylpiperidine by making the methyl ester which can then be reacted with an intermediate of formula \( Ar^2_1Y^2_1-C(O)-LG \) or \( Ar^2_1Y^2_1-NCO \) to form the amide or urea. The intermediate can then be hydrolyzed to give the acid (42).

[0517] 43 may be prepared from 42 using coupling methods and cyclization reaction previously described in Scheme B. The TBDMS protecting group on 43 can be removed with a solution of TBAF in THF. The resulting alcohol can be oxidized to 44 using Swern conditions, Dess-Martin periodinane, or TPAP conditions, and the like, in a suitable solvent. The tert-butoxycarbonyl protecting group (Boc) on 45 is removed under acidic reaction condition.

[0518] A compound of Formula I where \( R^1 \) is hydrogen, \( R^2 \) is \( H_2N(CH_2)_4 \), \( R^3 \) and \( R^{3a} \) together with the carbon to which they are attached form carbonyl, \( Ar^1 \) is 1,2,4-oxadiazol-3,5-diyl and \( W \) is located at the 5-position, \( W \) is \( A^1 \) when \( A^1 \) is methylene, \( Ar^2 \) is aryl or heteroaryl substituted with \( E \) where \( E \) is \(-X^2_1 Ar^{3a}_1 \), \( Q \) is \(-NR^{14}_1 R^{15}_1 \) where \( R^{14} \) is hydrogen and \( R^{15} \) is phenylmethylxycarbonyl, and all other groups are as defined in the Summary of the Invention, can be prepared as described herein in addition to using methods well known in the art.

[0519] A Compound of Formula I where \( Ar^1 \) is activating heteroarylene, other than [1,2,4]oxadiazol-3,5-diyl where \( W \) is located at the 5-position, can be prepared by methods known to one skilled in the art following procedures set forth in references such as Comprehensive Heterocyclic Chemistry II. A Review of the Literature from 1982-1995: the Structure, Reactions, Synthesis, and uses of Heterocyclic Compounds; Katritzky, A., et. al.; Pergamon, 1996; Vol. 3 and 4. Specifically, where \( Ar^1 \) is oxazol-diyl where the carbonyl is located at the 2-position and \( W \) is located at the 4- or 5-position, see Donnodi, A. et al., J. Org. Chem. 1987, 52, 3413-20. Where \( Ar^1 \) is pyrazol-diyl where the carbonyl is at the 3-position and \( W \) is at the 4- or 5-position, see
Nagarajan, A. et al., *Tetrahedron Lett.* **1996**, *37*, 6835-8. Where Ar$^1$ is [1,3,4]oxadiazol-diyl where the carbonyl is at the 2-position and W is at the 5-position, see Ohimoto, K. et al., *J. Med. Chem.* **2001**, *44*, 1268-85. Where Ar$^1$ is [1,3,4]thiadiazol-diyl and the carbonyl is located at the 2-position and W is located at the 5-position, see Berkelhammer, G. et al., US 3,666,860, May 30,1972. Where Ar$^1$ is [1,2,4]oxadiazol-diyl and the carbonyl is located at the 5-position and W is located at the 3-position, see Rice K. et al., *Bioorg. Med. Chem. Lett.* **2001**, *11*, 753-6. Where Ar$^1$ is [1,2,4]thiadiazol-diyl and the carbonyl is located at the 5-position and W is located at the 3-position, see LaMattina C. J. et al., *J. Org. Chem.* **1984**, *49*, 4800-5. Where Ar$^1$ is [1,2,4]thiadiazol-diyl and the carbonyl is located at the 3-position and W is located at the 5-position, see Tatsuta K. et al., *Tetrahedron Lett.* **1993**, *34*, 6423-6. Where Ar$^1$ is tetrazol-diyl and the carbonyl is located at the 5-position and W is located at the 1-position, see May B. et al. *Tetrahedron Lett.* **2001**, *42*, 5641. Where Ar$^1$ is thiazol-diyl and the carbonyl is located at the 2-position and W is located at the 4- or 5-position, see Davies D. et al., *Chem. Soc. Perkin Trans. 1991*, *11*, 2691-8. Where Ar$^1$ is imidazol-diyl and the carbonyl is located at the 2-position and W is located at the 4- or 5-position, see Hayakawa S. et al. *Heterocycles*, **1988**, *27*, 457-74. Where Ar$^1$ is [1,2,4]triazin-diyl and the carbonyl is located at the 3- or 5-position and W is located at the 5- or 3-position, see Mendoza J. et al., *Synthesis 1992*, *4*, 398-402. Where Ar$^1$ is pyrimidin-diyl and the carbonyl is located at the 2-position and W is located at the 4-, 5-, or 6-position, see Chumoyer M. et al., *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1477. Where Ar$^1$ is pyridin-diyl where the carbonyl is located at the 2-position and W is located at the 3-, 4-, 5-, or 6-position, see Takei Y., *Agric. Biol. Chem.* **1974**, *38*, 2329. Where Ar$^1$ is pyridazin-diyl and the carbonyl is located at the 3-position and W is located at the 4-, 5-, or 6-position, see Prathapan S. et al., *J. Amer. Chem. Soc.* **1992**, *114*, 1838-43. Where Ar$^1$ is [1,3,5]triazin-diyl and the carbonyl is located at the 2-position and W is located at the 4- or 6-position, see Ried W. et al., *Liebigs Ann. Chem.* **1988**, *141*, 48. Where Ar$^1$ is [1,2,4]triazin-diyl and the carbonyl is located at the 3-position and W is located at 5- or 6-position, see Girardot M. et al. *J. Org. Chem.* **1998**, *63*, 10063.

[0520] A compound of Formula I where Q is --OR$^8$ can be prepared by methods known to one skilled in the art following procedures set forth in references such as McNelis, B. et al., *Tetrahedron Lett.* **1994**, *50*, 6767-82.

[0521] A compound of Formula I where Q is --S(O)$_2$R$^{11}$ can be prepared by methods known to those skilled in the art following procedures set forth in references such as but not limited to Pascal, *Ann. Chim. (Paris)* **1968**, *3*, 247-72.
Detailed description of a method to prepare a compound of Formula I where Q is \(-\text{NR}^{14}\text{R}^{15}\) where \(\text{R}^{14}\) is hydrogen and \(\text{R}^{15}\) is phenylmethylxoycarbonyl, \(\text{R}^{1}\) is hydrogen, \(\text{R}^{2}\) is \(\text{H}_2\text{N(CH}_2)_4\), \(\text{R}^{3}\) and \(\text{R}^{3a}\) together with the carbon to which they are attached form carbonyl, \(\text{Ar}^{1}\) is 1,2,4-oxadiazol-3,5-diyl and \(\text{W}\) is located at the 5-position, \(\text{W}^{1}\) where \(\text{A}^{1}\) is \(-\text{CH}_2\)-, and \(\text{Ar}^{2}\) is 6-membered aryl substituted with \(\text{E}\) where \(\text{E}\) is \(-\text{X}^{1}\text{-Y}^{2}\text{-Ar}^{3}\) or \(-\text{X}^{1}\text{-Y}^{2}\text{-Z}^{1}\text{-Ar}^{3}\) and \(\text{X}^{1}\) is \(-\text{O-}\) or \(-\text{OC(O)NH-}\), is given in the working examples below.

Detailed description of a method to prepare a compound of Formula I where Q is \(-\text{NR}^{14}\text{R}^{15}\) where \(\text{R}^{14}\) is hydrogen and \(\text{R}^{15}\) is alkylcarbonyl or arylcarbonyl, \(\text{R}^{1}\) is hydrogen, \(\text{R}^{2}\) is \(\text{H}_2\text{N(CH}_2)_4\), \(\text{R}^{3}\) and \(\text{R}^{3a}\) together with the carbon to which they are attached form carbonyl, \(\text{Ar}^{1}\) is 1,2,4-oxadiazol-3,5-diyl and \(\text{W}\) is located at the 5-position, \(\text{W}^{1}\) where \(\text{A}^{1}\) is \(-\text{CH}_2\)-, and \(\text{Ar}^{2}\) is 6-membered aryl substituted with \(\text{E}\) where \(\text{E}\) is \(-\text{X}^{1}\text{-Y}^{2}\text{-Ar}^{3}\) or \(-\text{X}^{1}\text{-Y}^{2}\text{-Z}^{1}\text{-Ar}^{3}\) and \(\text{X}^{1}\) is \(-\text{O-}\), are given in the working examples below.

Detailed description of a method to prepare a compound of Formula I where Q is \(-\text{NR}^{14}\text{R}^{15}\) where \(\text{R}^{14}\) is hydrogen and \(\text{R}^{15}\) is \(-\text{S(O)}_2\text{R}^{21}\) (where \(\text{R}^{21}\) is alkyl), \(\text{R}^{1}\) is hydrogen, \(\text{R}^{2}\) is \(\text{H}_2\text{N(CH}_2)_4\), \(\text{R}^{3}\) and \(\text{R}^{3a}\) together with the carbon to which they are attached form carbonyl, \(\text{Ar}^{1}\) is 1,2,4-oxadiazol-3,5-diyl and \(\text{W}\) is located at the 5-position, \(\text{W}^{1}\) where \(\text{A}^{1}\) is \(-\text{CH}_2\)-, and \(\text{Ar}^{2}\) is 6-membered aryl substituted with \(\text{E}\) where \(\text{E}\) is \(-\text{X}^{1}\text{-Y}^{2}\text{-Ar}^{3}\) and \(\text{X}^{1}\) is \(-\text{O-}\), is given in the working examples below.

Detailed description of a method to prepare a compound of Formula I where Q is \(-\text{NR}^{14}\text{R}^{15}\) where \(\text{R}^{14}\) is hydrogen and \(\text{R}^{15}\) is phenylmethylxoycarbonyl, \(\text{R}^{1}\) is hydrogen, \(\text{R}^{2}\) is \(\text{H}_2\text{N(CH}_2)_4\), \(\text{R}^{3}\) and \(\text{R}^{3a}\) together with the carbon to which they are attached form carbonyl, \(\text{Ar}^{1}\) is 1,2,4-oxadiazol-3,5-diyl and \(\text{W}\) is located at the 5-position, \(\text{W}^{1}\) where \(\text{A}^{1}\) is \(-\text{CH}_2\)-, and \(\text{Ar}^{2}\) is 6-membered aryl substituted with \(\text{E}\) where \(\text{E}\) is \(-\text{X}^{1}\text{-Y}^{2}\text{-Ar}^{3}\) and \(\text{X}^{1}\) is \(-\text{OC(O)NH-}\), is given in the working examples below.

Detailed description of a method to prepare a compound of Formula I where Q is \(-\text{NR}^{14}\text{R}^{15}\) where \(\text{R}^{14}\) is hydrogen and \(\text{R}^{15}\) is phenylmethylxoycarbonyl, \(\text{R}^{1}\) is hydrogen, \(\text{R}^{2}\) is \(\text{H}_2\text{N(CH}_2)_4\), \(\text{R}^{3}\) and \(\text{R}^{3a}\) together with the carbon to which they are attached form carbonyl, \(\text{Ar}^{1}\) is 1,2,4-oxadiazol-3,5-diyl and \(\text{W}\) is located at the 5-position, \(\text{W}^{1}\) where \(\text{A}^{1}\) is \(-\text{CH}_2\)-, and \(\text{Ar}^{2}\) is piperazinyl substituted with \(\text{E}\) where \(\text{E}\) is \(-\text{X}^{1}\text{-Y}^{2}\text{-Ar}^{3}\) and \(\text{X}^{1}\) is \(-\text{C(O)-}\), is given in the working examples below.
and R^{3a} together with the carbon to which they are attached form carbonyl, Ar^{1} is 1,2,4-oxadiazol-3,5-diyl and W is located at the 5-position, W is A^{1} where A^{1} is -CH_{2}-, and Ar^{2} is piperazinyl substituted with E where E is -Y^{1}-Ar^{3}, is given in the working examples below.

[0528] Detailed description of a method to prepare a compound of Formula I where Q is -NR^{14}R^{15}
where R^{14} is hydrogen and R^{15} is phenylmethylxoycarbonyl, R^{1} is hydrogen, R^{2} is H_{2}N(CH_{2})_{4}, R^{3} and R^{3a} together with the carbon to which they are attached form carbonyl, Ar^{1} is 1,2,4-oxadiazol-3,5-diyl and W is located at the 5-position, W is D where D is cycloprop-diyl, CH(CH_{3}), or C(CH_{3})_{2}, and Ar^{2} is 6-membered aryl substituted with E where E is -X^{1}-Y^{2}-Ar^{3} and X^{1} is -O-, is given in the working examples below.

Utility

[0529] The compounds of this invention are tryptase inhibitors. As such the compounds of Formula I are useful for treating diseases, particularly immunemediated inflammatory diseases in which tryptase activity contributes to the pathology and/or symptomatology of the disease. For example, immunemediated inflammatory diseases in which tryptase activity contributes to its pathology and/or symptomatology include asthma, allergic rhinitis, rheumatoid spondylitis, osteoarthritis, gouty arthritis, rheumatoid arthritis, arthritic conditions in general, urticaria, angioedema, eczematous dermatitis, anaphylaxis, hyper proliferative skin disease, peptic ulcers, inflammatory bowel disease, ocular and vernal conjunctivitis, inflammatory skin conditions, chronic obstructive pulmonary disease, and the like.

[0530] Suitable in vitro assays for measuring tryptase activity and the inhibition thereof by compounds are known (e.g., see Sturzebecher et al., Biol. Chem. Hoppe-Seyler, 1992, 373, 1025-1030). Typically, the assay will measure tryptase induced hydrolysis of peptide base substrate. For further details of an in vitro assay for measuring tryptase activity see Biological Examples, Example 1 infra.

[0531] Assays for measurement of efficacy in treatment of skin diseases, ulcers, and Syncytial Virus Infection are described in Biological Examples, Example 3, 5, and 6, infra.


ADMINISTRATION AND PHARMACEUTICAL COMPOSITIONS

[0533] In general, the compounds of this invention will be administered in a therapeutically effective amount by any of the accepted modes of administration for agents that serve similar utilities. The actual amount of the compound of this invention, i.e., the active ingredient, will depend upon numerous factors such as the severity of the disease to be treated, the age and relative health of the subject, the potency of the compound used, the route and form of administration, and other factors.

[0534] Therapeutically effective amounts of compounds of Formula I may range from approximately 0.1-50 mg per kilogram body weight of the recipient per day; preferably about 0.5-20 mg/kg/day. Thus, for administration to a 70 kg person, the dosage range would most preferably be about 35 mg to 1.4 g per day. If a known β-2 adrenoreceptor agonist(s), corticosteroid(s), leukotriene antagonist(s), and/or phosphodiesterase 4 inhibitor(s) is also administered, each is administered in an amount which is effective to achieve its intended purpose.

The amounts of such known β-2 adrenoreceptor agonist(s), corticosteroid(s), leukotriene antagonist(s), and/or phosphodiesterase 4 inhibitor(s) effective for asthma are well known to those of skill in the art.

[0535] Therapeutic agents that may be useful for administration in combination with compounds of Formula I in treating asthma include β-2 adrenoreceptor agonists (e.g., salmeterol, albuterol, terbutaline, formoterol, fenoterol, prenaline and the like), methylxanthines (e.g., caffeine, theophylline, aminophylline, theobromine and the like), cromoglycates (e.g., cromolyn, nedocromil, and the like), corticosteroids (e.g., budesonide, fluticasone, beclomethasome, triamcinolone, flurisolidé, dexamethasone and the like), leukotriene D4 antagonists (e.g., montelukast and the like), and phosphodiesterase 4 inhibitors (e.g., roflumilast and the like). In general, one of ordinary skill in the art, acting in reliance upon personal knowledge and the disclosure of this application, will be able to ascertain a therapeutically effective amount of a compound of Formula I for treating a given inflammatory disease.
In general, compounds of this invention will be administered as pharmaceutical compositions by any one of the following routes: oral, systemic (e.g., transdermal, intranasal or by suppository), or parenteral (e.g., intramuscular, intravenous or subcutaneous) administration. The preferred manner of administration is oral or parenteral using a convenient daily dosage regimen, which can be adjusted according to the degree of affliction. Oral compositions can take the form of tablets, pills, capsules, semisolids, powders, sustained release formulations, solutions, suspensions, elixirs, aerosols, or any other appropriate compositions.

The choice of formulation depends on various factors such as the mode of drug administration (e.g., for oral administration, formulations in the form of tablets, pills or capsules are preferred) and the bioavailability of the drug substance. Recently, pharmaceutical formulations have been developed especially for drugs that show poor bioavailability based upon the principle that bioavailability can be increased by increasing the surface area i.e., decreasing particle size. For example, U.S. Pat. No. 4,107,288 describes a pharmaceutical formulation having particles in the size range from 10 to 1,000 nm in which the active material is supported on a crosslinked matrix of macromolecules. U.S. Pat. No. 5,145,684 describes the production of a pharmaceutical formulation in which the drug substance is pulverized to nanoparticles (average particle size of 400 nm) in the presence of a surface modifier and then dispersed in a liquid medium to give a pharmaceutical formulation that exhibits remarkably high bioavailability.

The compositions are comprised of in general, a compound of Formula I in combination with at least one pharmaceutically acceptable excipient. Acceptable excipients are non-toxic, aid administration, and do not adversely affect the therapeutic benefit of the compound of Formula I. Such excipient may be any solid, liquid, semi-solid or, in the case of an aerosol composition, gaseous excipient that is generally available to one of skill in the art.

Solid pharmaceutical excipients include starch, cellulose, talc, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, magnesium stearate, sodium stearate, glycerol monostearate, sodium chloride, dried skim milk and the like. Liquid and semisolid excipients may be selected from glycerol, propylene glycol, water, ethanol and various oils, including those of petroleum, animal, vegetable or synthetic origin, e.g., peanut oil, soybean oil, mineral oil, sesame oil, etc. Preferred liquid carriers, particularly for injectable solutions, include water, saline, aqueous dextrose, and glycols.

Compressed gases may be used to disperse a compound of this invention in aerosol form. Inert gases suitable for this purpose are nitrogen, carbon dioxide, etc.

[0542] The amount of the compound in a formulation can vary within the full range employed by those skilled in the art. Typically, the formulation will contain, on a weight percent (wt %) basis, from about 0.01-99.99 wt % of a compound of Formula I based on the total formulation, with the balance being one or more suitable pharmaceutical excipients. Preferably, the compound is present at a level of about 1-80 wt %. Representative pharmaceutical formulations containing a compound of Formula I are described below.

[0543] The compounds of this invention can be administered in combination with known asthma, COPD, and/or allergic rhinitis agents. Such known asthma, COPD, and/or allergic rhinitis agents include β-2 adrenoreceptor agonists, corticosteroids, leukotriene antagonists, and phosphodiesterase 4 inhibitors. Preferred β-2 adrenoreceptor agonists include salmeterol. Preferred corticosteroids include budesonide and fluticasone. Preferred leukotriene antagonists include montelukast. Preferred phosphodiesterase 4 inhibitors include roflumilast.

[0544] If formulated as a fixed dose, such combination products employ the compounds of this invention within the dosage range described above and the other pharmaceutically active agent(s) within its approved dosage range. Compounds of the instant invention may alternatively be used sequentially with known pharmaceutically acceptable agent(s) when a combination formulation is inappropriate.

**Examples**

[0545] The following preparations and examples are given to enable those skilled in the art to more clearly understand and to practice the present invention. They should not be considered as limiting the scope of the invention, but merely as being illustrative and representative thereof.

**Synthetic Examples**

Example 1

Synthesis of [5-[(phenylmethyloxycarbonylamino)]-6-[5-[4-(phenethyloxy)-phenylmethyl]-[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine HCl
Step 1

To a solution of Cbz-L-Lys(Boc)-OH (commercially available from Novabiochem) (101.4 g, 0.2666 mol) in DMF (500 mL) was added EDC-HCl (63.88 g, 0.3332 mol), HOBr (51.02 g, 0.3332 mol), N,O-dimethylhydroxylamine (32.50 g, 0.3332 mol) and diisopropylethylamine (186 mL, 1.066 mol) at room temperature. After 19 hours, the solvent was removed under reduced pressure. The crude oil was diluted with ethyl acetate (1.4 L) and washed successively with brine (800 mL), 1 N HCl (3 x 700 mL), saturated aq solution of NaHCO₃ (3 x 500 mL), and brine (500 mL). The organic layer was filtered through a pad of silica gel followed by the removal of solvent to give the desired Weinreb amide [5-(phenylmethylxycarbonyl)amino-5-(N-methoxy-N-methyl carbamoyl)-pentyl]-carbamic acid tert-butyl ester as oil (112.0 g, 99%). MS observed 424.1 (MH⁺); MS cald: 423.2.

Step 2

To a solution of [5-(phenylmethylxycarbonyl)amino-5-(N-methoxy-N-methyl carbamoyl)-pentyl]-carbamic acid tert-butyl ester (112.0 g, 0.2643 mol) in THF (1 L) at 0 °C was added lithium aluminum hydride (10.0 g, 0.264 mol) in 2 portions. After 30 min, the reaction was quenched by the dropwise addition of water (50 mL) followed by 1 N HCl (150 mL). The precipitate was filtered through Celite and the filtrate was diluted with ethyl acetate (1 L). The aqueous phase was separated and extracted with ethyl acetate (2 x 200 mL). The combined organic phase was washed with brine (2 x 250 mL) and filtered through a pad of silica gel. The filtrate was concentrated under reduced pressure to give [5-(phenylmethylxycarbonyl)amino-6-oxo-hexyl]-carbamic acid tert-butyl ester (95.39 g) as an oil, which was used for the next step without further purification. MS observed 365.2 (MH⁺); MS cald: 364.2.

Step 3

To a solution of [5-(phenylmethylxycarbonyl)amino-6-oxo-hexyl]-carbamic acid tert-butyl ester (95.39 g, 0.2617 mol) in dichloromethane (700 mL) was added acetone cyanohydrin (95.6 mL, 1.05 mol) and triethylamine (224 mL, 2.09 mol) at room temperature. After 14.5 hr, the solvent was removed under reduced pressure. The crude oil was dissolved in
ethyl acetate (1 L) and washed with water (3 x 400 mL), saturated solution of NaHCO₃ (aq) (400 mL), and brine (400 mL). The organic phase was filtered through a pad of silica gel and the solvent was removed under reduced pressure to give [5-(phenylmethoxy carbonyl)amino-6-cyano-6-hydroxy-hexyl]-carbamic acid tert-butyl ester (97.56 g) as a yellow oil. This material was used for the next step without further purification. MS observed 392.3 (MH⁺); MS cald: 391.2.

Step 4

[0549] To a solution of [5-(phenylmethoxy carbonyl)amino-6-cyano-6-hydroxy-hexyl]-carbamic acid tert-butyl ester (97.56 g, 0.2492 mol) in EtOH (300 mL) at 50 °C was added an aqueous solution of hydroxylamine (50 wt% in H₂O, 99 mL, 1.5 mol). After 75 min, the mixture was diluted with ethyl acetate (1 L), and washed with water (400 mL), 0.5 N HCl (400 mL), saturated aq solution of NaHCO₃ (400 mL), and brine (400 mL). The extract was dried over Na₂SO₄, filtered, and concentrated to give a crude oil (97 g). The crude oil was dissolved with ethanol (150 mL) at 50 °C followed by the addition of n-hexane/diethyl ether (1:2 L, 1:1 v/v) to give a precipitate. The precipitate was filtered to give a single diastereoisomer (22.9 g). The filtrate was concentrated and column chromatographed [gradient elution with n-hexane/ethyl acetate (7:3 v/v) to n-hexane/ethyl acetate (1:8 v/v) followed by 4% methanol in ethyl acetate] to give a mixture of diastereoisomers of [5-(phenylmethoxy carbonyl)amino-6-hydroxy-6-(N-hydroxycarbamimidoyl)-hexyl]-carbamic acid tert-butyl ester (36.5 g). MS observed 425.2 (MH⁺); MS cald: 424.2. The combined yield from the precipitate and the column eluant was 59.4 g (52.5% over Steps 1-4).

Step 5

[0550] To a stirred solution of [5-(phenylmethoxy carbonyl)amino-6-hydroxy-6-(N-hydroxycarbamimidoyl)-hexyl]-carbamic acid tert-butyl ester (16.00 g, 37.69 mmol), EDC·HCl (8.67 g, 45.2 mmol), HOBt (5.77 g, 45.2 mmol), and 4-methylmorpholine (12.4 mL, 113 mmol) in DMF (100 mL) was added 4-hydroxyphenyl acetic acid (5.73 g, 37.7 mmol). After 2 hours, the solvent was removed under reduced pressure. The crude oil was dissolved in ethyl acetate (1 L) and washed successively with water (300 mL), 0.5 N HCl (300 mL), saturated solution of NaHCO₃ (aq) (300 mL), and brine (500 mL). The extracts were passed through a pad of silica gel and the filtrate was concentrated to give a foam (12 g), which was used for the cyclization without further purification. The crude ester (12 g) was then heated in pyridine (45 mL) at 120 °C for 2 hours followed by the concentration of solvent under reduced pressure.
crude product was dissolved in ethyl acetate (1 L) and washed successively with water (700 mL),
0.5 N HCl (500 mL), water (300 mL), and brine (500 mL). The extracts were dried over Na₂SO₄,
filtered and concentrated. The crude oil was column chromatographed [n-hexane:ethyl acetate
(1:1 v/v) to (2:3 v/v)] to give the desired product {5-(phenethylmethylcarbonyl)amino-6-hydroxy-6-[5-(4-hydroxy-phenylmethyl)-[1,2,4]oxadiazol-3-yl]-hexyl}-carbamic acid tert-butyl ester (8.0
g, 39%) as a solid. MS observed 541.4 (MH⁺); MS calcd: 540.3.

Step 6

[0551] To a solution of triphenylphosphine (437 mg, 1.66 mmol) in anhydrous THF (3 mL) was
added diisopropyl azodicarboxylate (DIAD) (0.327 mL, 1.66 mmol) at 0 °C. Following
precipitation of a white solid after approximately one minute, a solution of
{5-(phenethylmethylcarbonyl)amino-6-hydroxy-6-[5-(4-hydroxy-phenylmethyl)-
[1,2,4]oxadiazol-3-yl]-hexyl}-carbamic acid tert-butyl ester (600 mg, 1.10 mmol) and phenethyl
alcohol (0.14 mL, 1.2 mmol) in THF (3 mL) was added dropwise at 0 °C. As the addition
proceeded, the mixture became homogenous. The mixture was then allowed to warm to room
temperature over 3 hours. Concentration of the mixture resulted in a yellow residue that was
purified by column chromatography [n-hexane:ethyl acetate (1:1 v/v) to give
{5-[(phenethylmethylcarbonyl)amino]-6-[5-(4-phenethoxy)-phenylmethyl]-[1,2,4]oxadiazol-
3-yl]-6-hydroxy-hexyl}-carbamic acid tert-butyl ester (392 mg, 55%) as a colorless oil.

Step 7

[0552] To a solution of {5-[(phenethylmethylcarbonyl)amino]-6-[5-(4-phenethoxy)-
phenylmethyl]-[1,2,4]oxadiazol-3-yl]-6-hydroxy-hexyl}-carbamic acid tert-butyl ester (392 mg,
0.608 mmol) in dichloromethane was added 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-
one (Dess-Martin periodinane) (309 mg, 0.730 mmol). After stirring at room temperature for 30
min, the suspension was filtered and concentrated under reduced pressure to yield a beige oil. The
residue was purified by column chromatography [n-hexane:ethyl acetate (1:1 v/v)] to give
{5-[(phenethylmethylcarbonyl)amino]-6-[5-(4-phenethoxy)-phenylmethyl]-[1,2,4]oxadiazol-
3-yl]-6-oxo-hexyl}-carbamic acid tert-butyl ester (222 mg, 56.8%) as a colorless oil.

Step 8

[0553] To a stirred solution of {5-[(phenethylmethylcarbonyl)amino]-6-[5-(4-phenethoxy)-
phenylmethyl]-[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl}-carbamic acid tert-butyl ester (220 mg, 0.34
mmol) in dichloromethane (1 mL) was added 4 N HCl in dioxane (1 mL). The mixture was
allowed to stir at room temperature for 40 min. The solution was then concentrated and purified
by preparative RP-HPLC to yield [5-[(phenylmethyloxy carbonyl)amino]-6-{5-[4-(phenethyloxy)phenylmethyl]-[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine hydrochloride (62 mg, 31%) as a white solid.

Example 2-6

[0554] The following compounds were synthesized using methods similar to those described in Example 1.

<table>
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<th>Cmpd No.</th>
<th>Ar²</th>
<th>-X¹-Y²-Ar³</th>
<th>MS cal’d. (M)</th>
<th>MS obs’d (MH⁺)</th>
<th>¹H NMR (dD-DMSO)</th>
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<td>549.5</td>
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<td>579.3</td>
<td>NA</td>
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<tr>
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<td><img src="image6.png" alt="Image" /></td>
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<td>559.3</td>
<td>δ 1.30-1.56 (m, 5H), 1.75 (m, 1H), 2.68 (brs, 2H), 4.24 (s, 4H), 4.34 (s, 2H), 4.75 (ddd, 1H, J = 3.8, 7, 10.5 Hz), 4.93 (d, 2H, J = 12.5 Hz), 4.97 (d, 2H, J = 12.5 Hz), 6.86-6.94 (m, 5H), 7.21-7.29 (m, 9H), 7.69 (brs, 3H), 7.92 (d, 1H, J = 7 Hz)</td>
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<td><img src="image8.png" alt="Image" /></td>
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<td>585.3</td>
<td>δ 1.38-1.59 (m, 5H), 1.80 (m, 1H), 2.35 (s, 3H), 2.74 (m, 2H), 3.11 (t, 2H, J = 6.7 Hz), 4.36 (t, 2H, J = 6.7 Hz), 4.43 (s, 2H), 4.80 (ddd, 1H, J = 7 Hz)</td>
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and are named:

[0555] 5-[(phenylmethylxoxycarbonyl)amino]-6-{5-{4-[(thien-3-yl)ethoxy]-phenylmethyl}-[1,2,4]oxadiazol-3-yl}-6-oxo-hexyl]-amine hydrochloride;

[0556] 5-[(phenylmethylxoxycarbonyl)amino]-6-{5-[4-(3,4-difluorophenethoxy)-phenylmethyl]-[1,2,4]oxadiazol-3-yl}-6-oxo-hexyl]-amine hydrochloride;

[0557] 5-[(phenylmethylxoxycarbonyl)amino]-6-{5-[4-(phenylxyethoxy)-phenylmethyl]-[1,2,4]oxadiazol-3-yl}-6-oxo-hexyl]-amine hydrochloride;

[0558] 5-[(phenylmethylxoxycarbonyl)amino]-6-{5-[4-(phenethylthoxy)-(3-acetylphenyl) methyl]-[1,2,4]oxadiazol-3-yl}-6-oxo-hexyl]-amine hydrochloride; and

[0559] 5-[(phenylmethylxoxycarbonyl)amino]-6-{5-[4-(phenethylthoxy)-(3-cyanophenyl) methyl]-[1,2,4]oxadiazol-3-yl}-6-oxo-hexyl]-amine hydrochloride.

Example 7

Synthesis of 5-[(phenylmethylxoxycarbonyl)amino]-6-{5-[4-[1-(3,4-dichlorophenyl)methyl-aminocarboxyloxy]-phenylmethyl]-[1,2,4]oxadiazol-3-yl}-6-oxo-hexyl]-amine HCl
Step 1

[0560] To a stirred, cooled (0 °C) solution of 5-benzyloxy carbonylamino-6-hydroxy-6-[5-(4-hydroxy-benzyl)-[1,2,4]oxadiazol-3-yl]-hexyl]-carbamic acid tert-butyl ester (0.20 g, 0.37 mmol) in dichloromethane (3 mL) were added 3,4-dichlorobenzylisocyanate (0.057 mL, 0.39 mmol) and N,N-diisopropylethylamine (0.064 mL, 0.37 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 20 hours. Additional dichloromethane (100 mL) was added and the resulting solution was washed with 1N aqueous HCl (100 mL), saturated aqueous sodium bicarbonate (100 mL) and then brine (100 mL). The organic phase was dried with anhydrous sodium sulfate and filtered. The solvent was removed by rotary evaporation and the crude intermediate was purified by flash SiO₂ chromatography using 1:1 ethyl acetate:hexane as eluant. The yield of purified 5-benzyloxy carbonylamino-6-{5-[4-(3,4-dichloro-benzyl carbamoyloxyl)-benzyl]-[1,2,4]oxadiazol-3-yl]-6-hydroxy-hexyl]-carbamic acid tert-butyl ester was 0.158 g (0.213 mmol, 57.5%). MS (M+Na)⁺: 764.2.

Step 2

[0561] To a stirred, cooled (0 °C) solution of 5-benzyloxy carbonylamino-6-{5-[4-(3,4-dichloro-benzyl carbamoyloxyl)-benzyl]-[1,2,4]oxadiazol-3-yl]-6-hydroxy-hexyl]-carbamic acid tert-butyl ester (0.158 g, 0.213 mmol) in dichloromethane (3 mL) was added Dess-Martin periodinane (0.136 g, 0.319 mmol). The mixture was allowed to warm to room temperature and stirred for 18 hours. Additional dichloromethane (100 mL) was added and the resulting solution was washed with 1N aqueous HCl (100 mL), saturated aqueous sodium bicarbonate (100 mL) and then brine (100 mL). The organic phase was dried with anhydrous sodium sulfate and filtered. The solvent was removed by rotary evaporation and the crude intermediate was purified by flash SiO₂ chromatography using 30% ethyl acetate in dichloromethane as eluant. The yield of purified 5-benzyloxy carbonylamino-6-{5-[4-(3,4-dichloro-benzyl carbamoyloxyl)-benzyl]-[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-carbamic acid tert-butyl ester was 0.148 g (0.200 mmol, 93.9%). MS (M+Na)⁺: 762.5.
A portion of the (5-benzyloxy carbonylamino-6-{5-[4-(3,4-dichloro-benzyl carbamoyloxy)-benzyl]-[1,2,4]oxadiazol-3-yl}-6-oxo-hexyl)-carbamic acid tert-butyl ester (0.075 g, 0.10 mmol) was dissolved in 4 mL of acetonitrile and 2 mL of 4 N aqueous HCl was added. The reaction mixture was stirred for 20 hours at room temperature and then 6 mL of water was added. The solvents were removed by lyophilization to yield 0.043 g (0.064 mmol) of [5-[(phenylmethylxycarbonyl)amino]-6-{5-[4-(3,4-dichlorophenyl)methyl-aminocarbonyloxy]-phenylmethyl}-[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine as the hydrochloride salt. NMR (d6-DMSO): δ 8.40-8.36 (1H, t); 7.94-7.97 (1H, d); 7.73-7.66 (3H, b); 7.62-7.59 (1H, d); 7.56-7.54 (1H, d); 7.38-7.28 (8H, m); 7.13-7.10 (2H, d); 5.04-4.95 (2H, m); 4.84-4.77 (1H, m); 4.48-4.43 (2H, s); 4.28-4.24 (2H, d); 2.79-2.69 (2H, b); 1.84-1.36 (6H, m). MS (M+1): 640.1.

Example 8

Synthesis of [5-{(4-chlorophenyl) carbonyl} amino]-6-{5-[4-(3,4-dichlorophenethyl oxy)-phenylmethyl]-[1,2,4]oxadiazol-3-yl}-6-oxo-hexyl]-amine HCl

Step 1

To a cooled (0 °C) solution of Cbz-L-Lys(Boc)OH (101.08 g, 266 mmol) in dichloromethane (800 mL) were added N,N-dimethylhydroxylamine hydrochloride (25.92 g, 266 mmol), triethylamine (37.0 mL, 266 mmol), and dicyclohexyl carbodiimide (266 mL of a 1.0 M dichloromethane solution). The mixture was stirred for 3 hours while warming to room temperature. The solvent was removed under reduced pressure. Ethyl acetate (800 mL) was added. The solids were filtered off and then washed with 200 mL ethyl acetate. The filtrate was concentrated to dryness to give the desired product [5-benzyloxy carbonylamino-5-(N-methoxy-N-methyl-carbamoyl)-pentyl]-carbamic acid tert-butyl ester.

Step 2

The [5-benzyloxy carbonylamino-5-(N-methoxy-N-methyl-carbamoyl)-pentyl]-carbamic acid tert-butyl ester from Step 1 was dissolved in ethanol (400 mL) and charged with 10%
Palladium on Carbon (6 g), hydrogenated on a Parr shaker at 50 psi for 3 hours, filtered through Celite, and concentrated to dryness to yield [5-amino-5-(N-methoxy-N-methyl-carbamoyl)-pentyl]-carbamic acid tert-butyl ester.

[0565] Step 3

[5-amino-5-(N-methoxy-N-methyl-carbamoyl)-pentyl]-carbamic acid tert-butyl ester from Step 2 was dissolved in THF (500 mL). The mixture was cooled to 0°C, and allyl chloroformate (28.27 mL, 266 mmol) was added. Triethylamine (44.49 mL, 319 mmol) was added. The solution was stirred for 1 hour. 1M HCl (200 mL) and ethyl acetate (500 mL) were added. The organic phase was separated, washed with saturated aqueous NaHCO₃ (300 mL), brine (300 mL), dried over MgSO₄, filtered, and concentrated to give the product, [5-(allyloxy carbonylamino)-5-(N-methoxy-N-methyl-carbamoyl)-pentyl]-carbamic acid tert-butyl ester. The product was used without additional purification.

[0566] Step 4

[5-(Allyloxy carbonylamino)-5-(N-methoxy-N-methyl-carbamoyl)-pentyl]-carbamic acid tert-butyl ester from Step 3 was dissolved in THF (300 mL) and cooled to 0 °C. A solution of lithium aluminum hydride in THF (1.0 M, 266 mL) was added via an addition funnel over 10 minutes. After an additional 15 minutes of stirring, water (15 mL) was carefully added to quench excess hydride. 1 N HCl (1L) was added. The product was extracted into ethyl acetate (500 mL), washed with saturated aqueous NaHCO₃ (500 mL) and brine (300 mL). The organic layer was dried over MgSO₄, filtered, and concentrated to dryness. The product, [5-(allyloxy carbonylamino)-6-oxo-hexyl]-carbamic acid tert-butyl ester, was used immediately without purification.

[0567] Step 5

To a solution of the [5-(allyloxy carbonylamino)-6-oxo-hexyl]-carbamic acid tert-butyl ester from Step 4 in dichloromethane (500 mL) were added acetone cyanohydrin (63.2 mL, 691 mmol) and triethylamine (22.2 mL, 160 mmol). The solution was stirred at room temperature overnight. The solvent and excess reagents were removed under reduced pressure to give the cyanohydrin, [5-(allyloxy carbonylamino)-6-cyano-6-hydroxy-hexyl]-carbamic acid tert-butyl ester, which was used in the next step without further purification.

[0568] Step 6

The [5-(allyloxy carbonylamino)-6-cyano-6-hydroxy-hexyl]-carbamic acid tert-butyl ester from Step 5 was dissolved in dichloromethane (300 mL). Imidazole (54.33 g, 0.7897 mol) was
added, followed by \( N,N \)-dimethylaminopyridine (3.25 g, 26.6 mmol). tert-Butyldimethylchlorosilane (60.14 g, 0.3990 mol) was added. The solution was stirred at room temperature for 3 hours. The solvent was removed under reduced pressure. Ethyl acetate (500 mL) was added. The mixture was washed with 1M HCl (2 \( \times \) 500 mL), saturated aqueous NaHCO\(_3\) (300 mL), and brine (150 mL). The organic layer was dried over MgSO\(_4\), filtered, and evaporated to give the silyl protected product, [5-(allyloxy carbonylamino)-6-cyano-6-(tert-butyl-dimethylsilyloxy)-hexyl]-carbamic acid tert-butyl ester as a mixture of diastereomers at the silyl ether position (100.71 g, 82.5% yield over Steps 1-6).

Step 7

[0569] [5-(allyloxy carbonylamino)-6-cyano-6-(tert-butyl-dimethylsilyloxy)-hexyl]-carbamic acid tert-butyl ester from Step 6 was dissolved in ethanol (200 mL). Hydroxylamine (aq), 50% w/w (40.6 mL, 668 mmol) was added. The mixture was heated at reflux for 1 hour, cooled, and the solvents were removed under reduced pressure. The residue was dissolved in dichloromethane (500 mL), dried over MgSO\(_4\), filtered, and concentrated to give 95 g (88% yield) of the product [5-(allyloxy carbonylamino)-6-(N-hydroxy carbamimidoyl)-6-(tert-butyl-dimethylsilyloxy)-hexyl]-carbamic acid tert-butyl ester, as a mixture of diastereomers. Trituration of the gummy, colorless, semi-solid with dichloromethane/hexane yielded a pure, single diastereomer of [5-(allyloxy carbonylamino)-6-(N-hydroxy carbamimidoyl)-6-(tert-butyl-dimethylsilyloxy)-hexyl]-carbamic acid tert-butyl ester (relative stereochemistry unknown) (18.71 g, 14.4% yield). NMR (CDCl\(_3\)): \( \delta \) 5.82 (1H, m); 5.20 (1H, d); 5.10 (1H, d); 5.00 (1H, d); 4.94 (1H, m); 4.58 (1H, m); 4.45 (2H, m); 4.04 (1H, m); 3.69 (1H, m); 2.99 (2H, m); 1.55-1.26 (9H, s, plus 6H, m); 0.81 (9H, s); 0.03 (3H, s); 0.01 (3H, s). MS (M+1): 489.

Step 8

[0570] [5-(Allyloxy carbonylamino)-6-(N-hydroxy carbamimidoyl)-6-(tert-butyl-dimethyloxy)-hexyl]-carbamic acid tert-butyl ester (18.71 g, 38.31 mmol) was condensed with {4-[2-(3,4-dichlorophenyl)-ethoxy]-phenyl}-acetic acid 2,5-dioxo-pyrrolidin-1-yl ester (19.03, 38.76 mmol) in THF (75 mL) in the presence of pyridine (5 mL). After 1 hour, diethylaminopropylamine (3 mL) was added. The solution was diluted with ethyl acetate (500 mL), washed with a 3:1 mixture of 1 N HCl and brine (500 mL). The organic phase was then washed with saturated aqueous NaHCO\(_3\) (200 mL), brine (100 mL), dried over MgSO\(_4\), filtered, and concentrated to dryness. The residue was dissolved in pyridine (30 mL) and was heated at 85 °C for 4 hours to cyclize to give [5-(allyloxy carbonylamino)-6-{5-[4-
(3,4-dichlorophenethoxy)phenylmethyl]-[1,2,4]oxadiazol-3-yl]-6-(tert-butyl-dimethylsilyloxy)-hexyl]-carbamic acid tert-butyl ester. The solution was cooled, concentrated in vacuo, diluted with ethyl acetate (500 mL), and washed with a 3:1 mixture of 1 N HCl and brine (500 mL). The organic phase was then washed with saturated aqueous NaHCO₃ (200 mL), brine (100 mL), dried over MgSO₄, filtered, and concentrated to dryness. The residue was purified on a plug of silica gel, using 20-30% ethyl acetate in hexane as the mobile phase. The yield of the product, [5-(allyloxy carbonylamino)-6-{5-[4-(3,4-dichlorophenethoxy)phenylmethyl]-[1,2,4]oxadiazol-3-yl]-6-(tert-butyl-dimethylsilyloxy)-hexyl]-carbamic acid tert-butyl ester, was 23.23 g (78.0% yield over Step 8).

Step 9

[0571] [5-(Allyloxy carbonylamino)-6-{5-[4-(3,4-dichlorophenethoxy)phenylmethyl]-[1,2,4]oxadiazol-3-yl]-6-(tert-butyl-dimethylsilyloxy)-hexyl]-carbamic acid tert-butyl ester (23.23 g, 29.86 mmol) was dissolved in dichloromethane (300 mL). Dichloropalladium(II)-bis(triphenylphosphine) (0.62 g, 0.88 mmol) was added. Over the course of 1 hour, tributylstannane (26.89 mL, 2.5 equiv) was added. After the final addition, the mixture was stirred for 1 hour. Saturated aqueous NaHCO₃ (300 mL) was added. The mixture was stirred vigorously for 1 hour, separated, and the organic phase was dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (20-30% ethyl acetate/hexane to elute tin by-products, then 5-7% methanol/dichloromethane to elute the product) to yield the product [5-amino-6-{5-[4-(3,4-dichlorophenethoxy)phenylmethyl]-[1,2,4]oxadiazol-3-yl]-6-(tert-butyl-dimethylsilyloxy)-hexyl]-carbamic acid tert-butyl ester (17.2 g, 83%). MS (M+1)ᵀ: 693.

Step 10

[0572] To a solution of [5-amino-6-{5-[4-(3,4-dichlorophenethoxy)phenylmethyl]-[1,2,4]oxadiazol-3-yl]-6-(tert-butyl-dimethylsilyloxy)-hexyl]-carbamic acid tert-butyl ester (182 mg, 0.262 mmol) in THF (2 mL) at -10 °C were added triethylamine (0.073 mL, 0.53 mmol) and 4-chlorobenzoyl chloride (0.04 mL, 0.32 mmol). The cooling bath was removed. After 2 hours, tetrabutylammonium fluoride (0.63 mL of a 1.0 M THF solution, 0.63 mmol) was added. The solution was stirred for 2 hours. Ethyl acetate (10 mL) was added. The mixture was washed with 1 N HCl (5 mL) and saturated aqueous NaHCO₃ (5 mL). The organic layer was dried over MgSO₄, filtered, and evaporated to dryness. The product, [5-(4-chlorophenylcarbonylamino)-6-{5-[4-(3,4-dichlorophenethoxy)phenylmethyl]-[1,2,4]oxadiazol-3-yl]-6-(hydroxy)-hexyl]-
carbamic acid tert-butyl ester, was purified by radial chromatography (30-50% ethyl acetate/dichloromethane).

Step 11

[0573] The [5-(4-chlorophenylcarbamylamino)-6-{5-[4-(3,4-dichlorophenethylxy)-phenylmethyl]-[1,2,4]oxadiazol-3-yl}]-6-hydroxy-hexyl]-carbamic acid tert-butyl ester from Step 10 was dissolved in dichloromethane (3 mL). Dess-Martin periodinane (0.191 g, 0.45 mmol) was added. The mixture was stirred for 1 hour. A freshly prepared solution of sodium hydrogen sulfite (aq) (6 M, 1 mL)) was added, followed by saturated aqueous NaHCO₃ (5 mL). The mixture was stirred vigorously for 10 minutes, extracted with ethyl acetate (50 mL), washed with 1:1 brine/aqueous NaHCO₃ (15 mL), dried over MgSO₄, filtered, and evaporated to dryness. The residue was crystallized from dichloromethane/hexane to yield [5-(4-chlorophenylcarbamylamino)-6-{5-[4-(3,4-dichlorophenethylxy)phenylmethyl]-[1,2,4]oxadiazol-3-yl}]-6-oxo-hexyl]-carbamic acid tert-butyl ester (125 mg, 66% yield over Steps 10-11). NMR (CDCl₃): δ 1.42 (9H, s); 1.4-1.6 (4H, m); 1.9 (1H, m); 2.16 (1H, m); 3.07 (2H, t); 3.16 (2H, m); 4.18 (2H, t); 4.28 (2H, s); 4.63 (1H, m); 5.63 (1H, m); 6.88 (2H, d); 7.12 (1H, m); 7.17 (1H, d); 7.26 (2H, m); 7.40 (2H, d); 7.55 (2H, d); 7.82 (2H, d).

Step 12

[0574] [5-(4-Chlorophenylcarbamylamino)-6-{5-[4-(3,4-dichlorophenethylxy)phenylmethyl]-[1,2,4]oxadiazol-3-yl}]-6-oxo-hexyl]-carbamic acid tert-butyl ester from Step 11 was dissolved in dichloromethane (1 mL). 4 N HCl in dioxane (1.5 mL, excess) was added. The mixture was stirred for 6 hours, poured into ether, filtered, washed with ether (2 x 10 mL), hexane (10 mL), and pumped dry to give [5-[4-(chlorophenylcarbonyl)amino]-6-{5-[4-(3,4-dichlorophenethylxy)phenylmethyl]-[1,2,4]oxadiazol-3-yl}]-6-oxo-hexyl]-amine hydrochloride, a white hygroscopic solid (101 mg, 89%). NMR (d⁶-DMSO): δ 9.07 (1H, d); 7.93-7.8 (5H, m); 7.62 (1H, d); 7.56 (3H, m); 7.33 (1H, d); 7.24 (2H, d); 6.89 (2H, d); 5.08 (1H, m); 4.39 (2H, s); 4.08 (2H, t); 3.04 (2H, t); 2.78 (2H, m); 1.94 (1H, m); 1.81 (1H, m); 1.65-1.40 (4H, m). MS (M+1)⁺: 615.
Example 9-11

The following compounds were synthesized using methods similar to those described in Example 8.

![Chemical structure](image)

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and are named:

- **[0576]** 5-[[3,4-difluorophenylcarbonyl]amino]-6-{{5-[4-(3,4-dichlorophenethoxy)-phenylmethyl]-[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine hydrochloride;
- **[0577]** 5-[[2,4-difluorophenylcarbonyl]amino]-6-{{5-[4-(3,4-dichlorophenethoxy)-phenylmethyl]-[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine hydrochloride; and
- **[0578]** 5-{{[tert-butylcarbonyl]amino}-6-{{5-[4-(3,4-dichlorophenethoxy)-phenylmethyl]-[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl}-amine hydrochloride.
Example 12

Synthesis of [5-(methylsulfonylamino)-6-{5-[4-(3,4-dichlorophenethoxy)-phenylmethyl]-1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine HCl

5 Step 1
[0579] To a solution of [5-amino-6-{5-[4-(3,4-dichlorophenethoxy)phenylmethyl]-1,2,4]oxadiazol-3-yl]-6-(tert-butyl-dimethylsilyloxy)-hexyl]-carbamic acid tert-butyl ester (224 mg, 0.324 mmol) in dichloromethane (2.5 mL) at 0 °C were added triethylamine (0.18 mL, 1.3 mmol) and methanesulfonyl chloride (0.065 mL, 0.84 mmol). The mixture was stirred for 2 hours. The solvent was then removed under reduced pressure, and THF (2 mL) was added, followed by tetrabutylammonium fluoride (0.65 mL of a 1.0 M THF solution). Subsequent workup, purification, oxidation, and cleavage of the Boc group were achieved using the same procedures as described for Example 8 to yield [5-(methylsulfonylamino)-6-{5-[4-(3,4-dichlorophenethoxy)-phenylmethyl]-1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine hydrochloride (3.6% isolated yield). NMR (δ-DMSO): δ 7.93 (1H, d); 7.80-7.70 (3H, m); 7.62 (1H, s); 7.56 (1H, d); 7.33 (1H, d); 7.27 (2H, d); 6.92 (2H, d); 4.74 (1H, m); 4.39 (2H, s); 4.18 (2H, t); 3.40 (br. s); 3.03 (2H, t); 2.94 (3H, s); 2.78 (2H, m); 1.83 (1H, m); 1.60-1.42 (5H, m). MS (M+1)^+: 555.

Example 13

Synthesis of [5-{[(phenylmethoxycarbonyl)amino]-6-{5-[4-(phenylmethyl)-aminocarbonyl]-phenylmethyl]-1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine HCl

20 Step 1
[0580] 4-Carboxymethyl-benzoic acid methyl ester (0.59g, 3.0 mmol) was dissolved in a mixture
of DMF (10 mL) and dichloromethane (10 mL) in a 200 mL round bottom flask and then [5-benzylxocarboxylamino-6-hydroxy-6-(N-hydroxycarbamimidoyl)-hexyl]-carbamic acid tert-butyl ester (1.28 g, 3.01 mmol) was added to the mixture followed by the addition of hydroxybenzotriazole (0.46 g, 3.0 mmol), 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (0.69 g, 3.61 mmol) and N,N-diisopropylethylamine (1.05 mL, 6.02 mmol). The mixture was stirred under nitrogen overnight at room temperature. The reaction was monitored by both analytical HPLC and LCMS. Upon the completion of the reaction, the mixture was diluted with ethyl acetate (200 mL) and washed with saturated sodium bicarbonate, 1 N HCl solution, water and brine. The organic phase was dried over MgSO₄ and concentrated to give a yellow colored oil crude product [5-benzylxocarboxylamino-6-hydroxy-6-{N-[(4-methoxycarbonyl)phenylmethylcarboxyloxy]-carbamimidoyl}-hexyl]-carbamic acid tert-butyl ester. LCMS: (M+1)+ 601.5.

Step 2

[0581] DMF (40 mL) was added to [5-benzylxocarboxylamino-6-hydroxy-6-{N-[(4-methoxycarbonyl)phenylmethylcarboxyloxy]-carbamimidoyl}-hexyl]-carbamic acid tert-butyl ester from Step 1 and the mixture was heated to 100 °C. The reaction was stirred under nitrogen overnight at 100 °C. The progress of the reaction was followed by analytical HPLC and LCMS. When complete (approximately 16 hours), the mixture was diluted with a mixed solvent of ether (100 mL) and ethyl acetate (100 mL), and washed with water twice. The organic layer was dried over MgSO₄, concentrated and purified by flash column chromatography (50% hexanes / ethyl acetate) to provide [5-benzylxocarboxylamino-6-hydroxy-6-{5-[4-(methoxycarbonyl)phenylmethyl]-[1,2,4]-oxadiazol-3-yl}-hexyl]-carbamic acid tert-butyl ester (0.52 g, 31%) as a yellow colored oil. LCMS: (M+1)+ 583.4.

Step 3

[0582] A mixture of [5-benzylxocarboxylamino-6-hydroxy-6-{5-[(4-methoxycarbonyl)phenylmethyl]-[1,2,4]-oxadiazol-3-yl}-hexyl]-carbamic acid tert-butyl ester (0.64g, 1.1 mmol) and lithium hydroxide monohydrate (0.185g, 4.4 mmol) was stirred together in methanol (2 mL), water (2 mL) and THF (6 mL) in a 100 mL round bottom flask at room temperature. The progress of the reaction was monitored by analytical HPLC and LCMS and upon its completion (approximately 7 hours) the solvent was removed in vacuo and ethyl acetate (200 mL) was added. The organic layer was washed with HCl solution (1 N), water and brine, dried over MgSO₄ then concentrated to a pale yellow solid [5-benzylxocarboxylamino-6-hydroxy-6-{5-[4-
(carboxy)phenylmethyl]-[1,2,4]-oxadiazol-3-yl]-hexyl]-carbamic acid tert-butyl ester. (0.63 g, yield 71%). LCMS: (M+1)^+ 569.5. Melting point: 152-154°C.

Step 4

[0583] [5-Benzylxycarbonylamino-6-hydroxy-6-{5-[4-(carboxy)phenylmethyl]-[1,2,4]-oxadiazol-3-yl}-hexyl]-carbamic acid tert-butyl ester (141 mg, 0.248 mmol) was dissolved in a mixed solvent of DMF (1 mL) and dichloromethane (2 mL) followed by the addition of benzylamine (81 µL, 0.74 mmol), hydroxybenzotriazole (38 mg, 0.248 mmol), 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (71 mg, 0.297 mmol) and N,N-diisopropylethylamine (108 µL, 0.62 mmol). The mixture was stirred overnight at room temperature. The reaction was monitored by analytical HPLC and LCMS as the intermediate alcohol compound formed. Upon the completion of the coupling reaction, the mixture was diluted with a mixed solvent of ether (25 mL) and ethyl acetate (25 mL). The organic layer was washed with saturated sodium bicarbonate, 1 N HCl solution, water, and then brine, dried over MgSO4, concentrated to obtain crude [5-benzylxycarbonylamino-6-hydroxy-6-{5-[(4-phenylmethylaminocarbonyl)phenylmethyl]-[1,2,4]-oxadiazol-3-yl}-hexyl]-carbamic acid tert-butyl ester as a yellow colored oil. LCMS: (M+1)^+ 658.7.

Step 5

[0584] [5-Benzylxycarbonylamino-6-hydroxy-6-{5-[(4-phenylmethylaminocarbonyl)-phenylmethyl]-[1,2,4]-oxadiazol-3-yl}-hexyl]-carbamic acid tert-butyl ester from Step 4 was dissolved in dichloromethane (5 mL) and cooled to 0°C. Dess-Martin periodinane (1.2 equiv, 140 mg) was added. After 5-10 minutes, the ice bath was removed and the mixture was allowed to warm up to room temperature and stirred overnight. The reaction was monitored by TLC [silica gel, hexane: ethyl acetate (2:1, v/v)] and analytical HPLC. Ether (approximately 30 mL) was then added to the reaction mixture followed by addition of aqueous Na2S2O3 (5 mL) and NaHCO3 (5 mL). The resulting mixture was stirred until a clear organic layer was obtained. The organic layer was separated, washed with saturated sodium bicarbonate (twice) and brine, dried over MgSO4, filtered, concentrated and purified by flash column chromatography (50% hexanes / ethyl acetate) to provide [5-benzylxycarbonylamino-6-oxo-6-{5-[(4-phenylmethylaminocarbonyl)-phenylmethyl]-[1,2,4]-oxadiazol-3-yl}-hexyl]-carbamic acid tert-butyl ester (128 mg, 78.7%) as a colorless liquid. LCMS: (M+1)^+ 656.6.
aminocarbonyl)-phenylmethyl]-[1,2,4]-oxadiazol-3-yl]-hexyl]-carbamic acid tert-butyl ester (from Step 5) in acetonitrile (5 mL), 4 N HCl in dioxane (0.6 mL, 2.4 mmol) was added at ambient temperature. The mixture was stirred for 20-30 minutes, monitored by analytical HPLC and LCMS. Product was purified by preparative HPLC and further lyophilized to provide 5-[[(phenylmethyloxycarbonyl)amino]-6-[[4-[(phenylmethyl)-aminocarbonyl]-phenylmethyl]-[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine hydrochloride (70 mg, 61%) as a fluffy white colored solid. $^1$H NMR (400 MHz, DMSO-d$_6$): δ 9.08 (t, 1H), 7.96 (d, 1H), 7.85 (m, 5H), 7.44 (d, 2H), 7.20-7.33 (m, 10H), 4.98 (d, 2H), 4.78-4.83 (m, 1H), 4.54 (s, 2H), 4.45 (d, 2H), 2.70 (m, 2H), 1.40-1.51 (m, 6H). LCMS: (M+1)$^+$ 556.5.

Example 14-18

0586 The following compounds were synthesized using methods similar to those described in Example 13. The benzylamine used in Step 4 of Example 13 was replaced with 3-phenylallylamine for Example 14, 2-(thien-2-yl)-ethylamine for Example 15, N-(2-fluorophenylmethyl)piperazine for Example 16, phenylalanine tert-butyl ester for Example 17, and 3-chlorophenylethylamine for Example 18. In the case of Compound No. 17, the tert-butyl group was removed under acidic conditions in the last step.

<table>
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<tr>
<th>Cmpd No.</th>
<th>Ar$^2$</th>
<th>-X$^1$.Y$^2$.Ar$^3$</th>
<th>MS cal’d. (M)</th>
<th>MS obs’d (MH$^+$)</th>
<th>$^1$H NMR (d$_6$.DMSO)</th>
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<tr>
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<td></td>
<td></td>
<td>581</td>
<td>582.2</td>
<td>NA</td>
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<tr>
<td>Ex. 15</td>
<td></td>
<td></td>
<td>575.7</td>
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<td>NA</td>
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<tr>
<td>Ex. 16</td>
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<td></td>
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<td>643.6</td>
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</tr>
<tr>
<td>Cmpd No.</td>
<td>Ar²</td>
<td>-X¹-Y²-Ar³</td>
<td>MS cal'd. (M)</td>
<td>MS obs'd (M⁺)</td>
<td>³H NMR (d₆-DMSO)</td>
</tr>
<tr>
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<td>----------------</td>
<td>------------------</td>
</tr>
<tr>
<td>Ex. 17*</td>
<td><img src="image1" alt="Structure" /></td>
<td>613.7</td>
<td>614.4</td>
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<tr>
<td>Ex. 18</td>
<td><img src="image2" alt="Structure" /></td>
<td>604.1</td>
<td>604.4</td>
<td>δ 8.59 (t, 1H), 7.97 (d, 1H), 7.76 (m, 5H), 7.44 (d, 2H), 7.18-7.35 (m, 9H), 4.99 (d, 2H), 4.78-4.83 (m, 1H), 4.53 (s, 2H), 3.47-3.48 (m, 2H), 2.85 (t, 2H), 2.71-2.73 (m, 2H), 1.37-1.80 (m, 6H)</td>
<td></td>
</tr>
</tbody>
</table>

* This product was obtained as the 2HCl salt.

and are named as

[0587] 5-[(phenylmethyloxy carbonyl)amino]-6-{5-[4-[(1-phenylpropen-3-yl)-aminocarbonyl]-phenylmethyl]-[1,2,4]oxadiazol-3-yl}-6-oxo-hexyl]-amine hydrochloride;

[0588] 5-[(phenylmethyloxy carbonyl)amino]-6-{5-[4-[(thien-2-ylethyl)-aminocarbonyl]-phenylmethyl]-[1,2,4]oxadiazol-3-yl}-6-oxo-hexyl]-amine hydrochloride;

[0589] 5-[(phenylmethyloxy carbonyl)amino]-6-{5-[4-[2-fluoro-phenylmethyl]-piperazinylcarbonyl]-phenylmethyl]-[1,2,4]oxadiazol-3-yl}-6-oxo-hexyl]-amine dihydrochloride;

[0590] 5-[(phenylmethyloxy carbonyl)amino]-6-{5-[4-[(1S-carboxy-2-phenylethyl)-aminocarbonyl]-phenylmethyl]-[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine hydrochloride; and

[0591] 5-[(phenylmethyloxy carbonyl)amino]-6-{5-[4-[(3-chlorophenylethyl)-aminocarbonyl]-phenylmethyl]-[1,2,4]oxadiazol-3-yl}-6-oxo-hexyl]-amine hydrochloride.

**Example 19**

Synthesis of [5-[(phenylmethyloxy carbonyl)amino]-6-{5-[(phenethylcarbonyl)-piperazin-1-ylmethyl]-[1,2,4]oxadiazol-3-yl}]-6-oxo-hexyl]-amine 2HCl
Step 1

[0592] To a solution of 5-benzyloxy carbamoylamino-6-hydroxy-6-(N-hydroxy-carbamimidoyl)-hexyl]-carbamic acid tert-butyl ester (3.531 g, 8.29 mmol) in chloroform (60 mL) at 0 °C, chloroacetyl chloride (0.73 mL, 9.12 mmol) in CHCl₃ (5 mL) was added slowly over 10 min. After the mixture was stirred for an hour at the same temperature, the solvent was concentrated under reduced pressure. The crude mixture was diluted with ethyl acetate (300 mL) and washed with saturated NaHCO₃ solution and brine. The organic phase was separated, dried over MgSO₄, filtered and evaporated under reduced pressure to yield 4.30 g of pale yellow liquid [5-benzyloxy carbamoylamino-6-hydroxy-6-(N-chloromethylcarbonyloxy)-carbamimidoyl]-hexyl]-carbamic acid tert-butyl ester.

Step 2

[0593] To the crude [5-benzyloxy carbamoylamino-6-hydroxy-6-(N-chloromethylcarbonyloxy)-carbamimidoyl]-hexyl]-carbamic acid tert-butyl ester from Step 1 in DMF (90 mL), pyridinium p-toluenesulfonate (50 mg, 0.20 mmol) was added and heated to 90°C for 5 h. The mixture was cooled to room temperature and diluted with ethyl acetate (300 mL). The mixture was washed with water twice and then brine. The organic phase was dried over MgSO₄, filtered and evaporated under reduced pressure. The crude product was purified by column chromatography (50 % EtOAc/hexanes) to give 3.08 g (77%) of [5-benzyloxy carbamoylamino-6-hydroxy-6-(5-chloromethyl-[1,2,4]oxadiazol-3-yl)-hexyl]-carbamic acid tert-butyl ester. ¹H NMR (400 MHz,CDCl₃): δ 7.38 (m, 5H), 5.26 (m, 1H), 5.20 (s, 2H), 5.15 (m, 1H), 4.77 (s, 2H), 4.66 (m, 1H), 4.21 (m, 1H), 3.18 (m, 2H), 1.66 (m, 6H), 1.50 (s, 9H). LCMS (M+1)⁺ 482.8.

Step 3

[0594] To a solution of [5-benzyloxy carbamoylamino-6-hydroxy-6-(5-chloromethyl-[1,2,4]oxadiazol-3-yl)-hexyl]-carbamic acid tert-butyl ester (60 mg, 0.12 mmol) in acetonitrile (3 mL), N-phenethylcarbonylpiperazine (35 mg, 0.15 mmol) was added. The mixture was heated to 60 °C for 7 h and evaporated under reduced pressure. The crude mixture was purified by column chromatography (5% MeOH/CH₂Cl₂) to give 75 mg (91%) of product.
[5-benzyloxycarbonylamino-6-hydroxy-6-{5-[N-(phenethylcarbonyl)-piperazinylmethyl]-1,2,4]oxadiazol-3-yl}-hexyl]-carbamic acid tert-butyl ester. \textsuperscript{1}H NMR (400 MHz,CDCl\textsubscript{3}) \( \delta \) (m, 10 H), 5.42 (d, 1H), 5.18 (s, 2H), 4.96 (m, 1H), 4.88 (m, 1H), 4.05 (m, 1H), 3.84 (s, 2H), 3.66 (t, 2H), 3.39 (t, 2H), 3.17 (m, 2H), 2.98 (t, 2H), 2.64 (t, 2H), 2.52 (m, 2H), 2.44 (m, 2H), 1.52 (m, 6H), 1.40 (s, 9H). LCMS (M+1\textsuperscript{+}) 665.7.

**Step 4**

[0595] To a solution of [5-benzyloxycarbonylamino-6-hydroxy-6-{5-[N-(phenethylcarbonyl)-piperazinylmethyl]-1,2,4]oxadiazol-3-yl}-hexyl]-carbamic acid tert-butyl ester (67 mg, 0.10 mmol) in dichloromethane (3 mL) at 0 °C was added Dess-Martin periodinane (55 mg, 0.13 mmol). The mixture was stirred for 1 h at the same temperature, and then diluted with ether (10 mL). To the mixture, 20% Na\textsubscript{2}S\textsubscript{2}O\textsubscript{3} solution (3 mL) and saturated NaHCO\textsubscript{3} solution (3 mL) were added. The mixture was stirred until the layers were separated. The mixture was extracted with ether (30 mL) and washed with sat. NaHCO\textsubscript{3} solution and brine. The organic phase was dried over MgSO\textsubscript{4}, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (100 % EtOAc) to give [5-benzyloxycarbonylamino-6-oxo-6-{5-[N-(phenethylcarbonyl)-piperazinylmethyl]-1,2,4]oxadiazol-3-yl}-hexyl]-carbamic acid tert-butyl ester as an off-white solid (43 mg, 64%). \textsuperscript{1}H NMR (400 MHz,CDCl\textsubscript{3}) \( \delta \) (m, 10H), 5.80 (d, 1H), 5.27 (m, 1H), 5.12 (s, 2H), 4.66 (m, 1H), 3.92 (s, 2H), 3.64 (t, 2H), 3.42 (t, 2H), 3.13 (m, 2H), 2.97 (t, 2H), 2.63 (t, 2H), 2.56 (m, 2H), 2.48 (m, 2H), 2.06-1.42 (m, 6H), 1.48 (s, 9H). LCMS (M+1\textsuperscript{+}) 663.7.

**Step 5**

[0596] To a solution of [5-benzyloxycarbonylamino-6-oxo-6-{5-[N-(phenethylcarbonyl)-piperazinylmethyl]-1,2,4]oxadiazol-3-yl}-hexyl]-carbamic acid tert-butyl ester (43 mg, 0.063 mmol) in acetonitrile (3 mL) was added a solution of 4 N HCl/1,4-dioxane (0.5 mL, 2 mmol) at ambient temperature. The mixture was stirred for 40 m, and concentrated under reduced pressure. The crude product was purified by reverse-phase HPLC, and further lyophilized to give [5-[(phenylmethyloxycarbonyl)amino]-6-{5-[4-(phenethylcarbonyl)-piperazin-1-ylmethyl]-1,2,4]oxadiazol-3-yl}-6-oxo-hexyl]-amine dihydrochloride as an off-white solid (15 mg, 36% yield). LCMS (M+1\textsuperscript{+}) 563.5

**Example 20**

Synthesis of [5-[(phenylmethyloxycarbonyl)amino]-6-{5-[4-(phenethylbutyl)-piperazin-1-
**Step 1**

[0597] To a solution of [5-benzyloxycarbonylamino-6-hydroxy-6-(5-chloromethyl-1,2,4]oxadiazol-3-yl]-hexyl]-carbamic acid tert-butyl ester (661 mg, 1.37 mmol) and piperazine (708 mg, 8.23 mmol) in acetonitrile (35 mL), K$_2$CO$_3$ (227 mg, 1.84 mmol) and KI (10 mg, 60 mmol) were added. The mixture was stirred for 1 h at 50 °C. The mixture was cooled to room temperature, filtered, washed with acetonitrile, and concentrated under reduced pressure. The crude product was purified by column chromatography (10 to 20% MeOH/CH$_2$Cl$_2$) to give 812 mg (87%) of an off-white solid product [5-benzyloxycarbonylamino-6-hydroxy-6-(5-piperazinylmethyl-1,2,4]oxadiazol-3-yl)-hexyl]-carbamic acid tert-butyl ester.

**Step 2**

[0598] To a solution of [5-benzyloxycarbonylamino-6-hydroxy-6-(5-piperazinylmethyl-1,2,4]oxadiazol-3-yl)-hexyl]-carbamic acid tert-butyl ester (201 mg, 0.377 mmol) and (76 mg, 0.45 mmol) of 1-chloro-4-phenylbutane in acetonitrile (10 mL), K$_2$CO$_3$ (63 mg, 0.45 mmol) and KI (2 mg, 12 mmol) were added. The mixture was refluxed for 39 h. The mixture was cooled to room temperature, filtered, washed with acetonitrile, and concentrated under reduced pressure. The crude product was purified by column chromatography (5% MeOH/CH$_2$Cl$_2$) to give 180 mg (72%) of white solid [5-benzyloxycarbonylamino-6-hydroxy-6-(5-[4-(phenylbutyl)-piperazinylmethyl]-1,2,4]oxadiazol-3-yl)-hexyl]-carbamic acid tert-butyl ester. LCMS (M+1)$^+$ 665.6.

**Step 3**

[0599] To a solution of oxalyl chloride (0.035 mL, 0.40 mmol) in dichloromethane (0.3 mL) at -65 °C, DMSO (0.057 mL, 0.80 mmol) in dichloromethane (0.2 mL) was added over 5 min. To the mixture, [5-benzyloxycarbonylamino-6-hydroxy-6-(5-[4-(phenylbutyl)-piperazinylmethyl]-1,2,4]oxadiazol-3-yl)-hexyl]-carbamic acid tert-butyl ester (148 mg, 0.223 mmol) in dichloromethane (0.3 mL) was added over 5 min. After the mixture had been stirred for 30 min at the same temperature, triethylamine (0.25 mL, 1.79 mmol) was added. The mixture was stirred
for 1 h at -65 °C, and 1 h at room temperature. The mixture was diluted with dichloromethane (20 mL) and quenched with water. The organic phase was separated, dried over MgSO₄, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (ethyl acetate) to give 110 mg (74%) of off-white product [5-benzylxocarbonylamino-6-oxo-6-(5-[4-(phenylbutyl)-piperazinylmethyl]-[1,2,4]oxadiazol-3-yl)-hexyl]-carbamic acid tert-butyl ester. ¹H NMR (400 MHz,CDCl₃) δ 7.42-7.18 (m, 10H), 5.82 (d, 1H), 5.24 (m, 1H), 5.17 (s, 2H), 4.75 (m, 1H), 3.92 (s, 2H), 3.12 (m, 2H), 2.70-2.35 (m, 10H), 2.04 (m, 1H), 1.78-1.40 (m, 20H); LCMS (M+1)⁺ 663.6.

Step 4

[0600] To a solution of [5-benzylxocarbonylamino-6-oxo-6-(5-[4-(phenylbutyl)-piperazinylmethyl]-[1,2,4]oxadiazol-3-yl)-hexyl]-carbamic acid tert-butyl ester (105 mg, 0.159 mmol) in acetonitrile (5 mL) was added a solution of 4 N HCl/1,4-dioxane (0.5 mL, 2 mmol) at ambient temperature. The mixture was stirred for 30 min, and concentrated under reduced pressure. The crude product was purified by reverse-phase HPLC, and further lyophilized to give the product [5-[(phenylmethyloxy carbonyl)amino]-6-{5-[4-(4-phenylbutyl)-piperazin-1-ylmethyl]-[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine as off-white solid. LCMS (M+1)⁺ 563.4

Example 21

Synthesis of [5-[(phenylmethyloxy carbonyl)amino]-6-{5-[4-(3-phenylpropyl)-piperazin-1-ylmethyl]-[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine HCl

20 [0601] The following compound was synthesized using methods similar to those described in Example 20.

![Chemical structure](image)

Calculated: MS (M)⁺ 548.7; observed: MS (M+1)⁺ 549.5.

Example 22

Synthesis of [5-[(phenylmethyloxy carbonyl)amino]-6-{5-[4-(phenethyloxy)-phenylcycloprop-1-yl]-[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine HCl
Step 1

[0602] A mixture of 1-(4-methoxyphenyl)-cyclopropanecarboxylic acid (800 mg, 4.16 mmol) and pyridinium chloride (4.00 g, 34.6 mmol) was heated to 150 °C for 28 h. The mixture was extracted with ethyl acetate (200mL) and washed with 1 N HCl solution to give 595 mg (80%) of 1-(4-hydroxyphenyl)-cyclopropanecarboxylic acid. LCMS (M+1)^+ 179.1.

Step 2

[0603] To a solution of 1-(4-hydroxyphenyl)-cyclopropanecarboxylic acid (368 mg, 2.06 mmol) in DMF (5 mL) and dichloromethane (10 mL) at 0 °C, were added [5-benzylxycarbonylamino-6-hydroxy-6-(N-hydroxycarbamidoyl)-hexyl]-carbamic acid tert-butyl ester (920 mg, 2.17 mmol) (prepared as described in Example 1), EDCI (416 mg, 2.17 mmol), HOBt (315 mg, 2.06 mmol) and N,N-diisopropylethylamine (0.54 mL, 3.09 mmol). The ice bath was removed and the mixture stirred for 4 h. The mixture was diluted with ethyl acetate (120 mL) and washed with saturated NaHCO₃ solution, water and brine. The organic phase was dried over MgSO₄, filtered and concentrated under reduced pressure. The crude product was dissolved in DMF (20 mL) and heated to 100 °C for 15 h. The mixture was diluted with ethyl acetate (120 mL) and washed with water and brine. The organic phase was dried over MgSO₄, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (60% EtOAc/hexanes) to give 727 mg (62%) of off-white solid product [5-benzylxycarbonylamino-6-hydroxy-6-(5-(4-hydroxyphenyl)cycloprop-1-yl)-1,2,4-oxadiazol-3-yl)-hexyl]-carbamic acid tert-butyl ester. ¹H NMR (400 MHz,CDCl₃): δ 7.34 (m, 7H), 6.88 (d, 2H), 5.53 (d, 1H), 5. 12 (dd, 2H), 4.87 (m, 1H), 4.78 (m, 1H), 3.81 (s, 2H), 3.06 (m, 2H), 1.78 (m, 2H), 1.58 (m, 2H), 1.48 (m, 6H), 1.42 (s, 9H). LCMS (M+1)^+ 581.6.

Step 3

[0604] To a solution of [5-benzylxycarbonylamino-6-hydroxy-6-(5-(4-hydroxyphenyl)cycloprop-1-yl)-1,2,4-oxadiazol-3-yl)-hexyl]-carbamic acid tert-butyl ester (350 mg, 0.618 mmol), phenethyl alcohol (151 mg, 1.24 mmol) and triphenylphosphine (243 mg, 0.927 mmol) in anhydrous THF (5 mL) at 0 °C, diisopropylazodicarboxylate (DIAD) (0.18 mL, 0.93 mmol) was
added over 10 min under N₂ atmosphere. The mixture was stirred overnight at room temperature, and concentrated under reduced pressure. The crude mixture was purified by column chromatography (40% EtOAc/hexanes) to give 252 mg (60%) of product [5-benzyloxy carbonylamino-6-hydroxy-6-(5-(4-(phenethyloxy)-phenylcycloprop-1-yl)-[1,2,4]oxadiazol-3-yl]-hexyl] carbamic acid tert-butyl ester. LCMS (M+1)⁺ 671.7.

Step 4

[0605] To a solution of 5-benzyloxy carbonylamino-6-hydroxy-6-(5-(4-(phenethyloxy)-phenylcycloprop-1-yl-[1,2,4]oxadiazol-3-yl)-hexyl] carbamic acid tert-butyl ester (235 mg, 0.35 mmol) in dichloromethane (10 mL) at 0 °C, Dess-Martin periodinane (178 mg, 0.42 mmol) was added. The mixture was stirred for 5 h at the same temperature, and diluted with ether (50 mL). To the mixture, 20% Na₂S₂O₃ solution (10 mL) and saturated NaHCO₃ solution (10 mL). The mixture was stirred until the layers were separated. The mixture was extracted with ether (80 mL) and washed with saturated NaHCO₃ solution and brine. The organic phase was dried over MgSO₄, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (40% EtOAc/hexanes) to give 233 mg (100%) of off-white product [5-benzyloxy carbonylamino-6-oxo-6-(5-(4-(phenethyloxy)-phenylcycloprop-1-yl)-[1,2,4]oxadiazol-3-yl)-hexyl] carbamic acid tert-butyl ester.

Step 5

[0606] To a solution of 5-benzyloxy carbonylamino-6-oxo-6-(5-(4-(phenethyloxy)-phenylcycloprop-1-yl)-[1,2,4]oxadiazol-3-yl)-hexyl] carbamic acid tert-butyl ester (80 mg, 0.12 mmol) in acetonitrile (5 mL) was added a solution of 4 N HCl/1,4-dioxane (0.5 mL, 2 mmol) at ambient temperature. The mixture was stirred for an hour, and concentrated under reduced pressure. The crude product was purified by reverse-phase HPLC, and further lyophilized to give 5-((phenylmethyloxy carbonylamino)-6-(5-(4-(phenethyloxy)-phenylcycloprop-1-yl)-[1,2,4]oxadiazol-3-yl)-6-oxo-hexyl] amine hydrochloride as an off-white solid. LCMS (M+1)⁺ 569.5.

Example 23-24

[0607] The following compounds were synthesized using methods similar to those described in Example 22.
and are named as

[0608] 5-[(phenylmethylxoycarbonyl)amino]-6-{5-[4-(phenethyloxy)-1-methyl-1-phenylmethyl]-
[1,2,4]oxadiazol-3-yl}-6-oxo-hexyl]-amine hydrochloride; and

[0609] 5-[(phenylmethylxoycarbonyl)amino]-6-{5-[4-(phenethyloxy)-1,1-dimethyl-1-
phenylmethyl]-[1,2,4]oxadiazol-3-yl}-6-oxo-hexyl]-amine hydrochloride.

Example 25

Synthesis of [5-[(3,4-difluorophenyl)carbonyl]amino]-6-{5-[1-(phenethylaminocarbonyl)-
piperidin-4-ylmethyl]-[1,2,4]oxadiazol-3-yl}-6-oxo-hexyl]-amine HCl

Step 1

[0610] To MeOH (10 mL) chilled in an ice bath, acetyl chloride (3.6 mL, 20 mmol) was slowly
added. A solution of 4-piperidine acetic acid (840 mg, 4.67 mmol) in methanol (2 mL) was added
to the above solution. The mixture was stirred at 60°C for 7 h, and then evaporated under reduced
pressure to give quantitative yield of the HCl salt of piperidin-4-yl acetic acid methyl ester.

**Step 2**

[0611] To a solution of the HCl salt of piperidin-4-yl acetic acid methyl ester (620 mg, 3.20 mmol) and \(N,N\)-diisopropylethylamine (1.67 mL, 9.60 mmol) in CH\(_2\)Cl\(_2\) (10 mL) chilled in an ice bath, phenethyl isocyanate (0.53 mL, 3.84 mmol) was added. The mixture was stirred for 3 h, and evaporated under reduced pressure. The crude mixture was purified by column chromatography (10% MeOH/CH\(_2\)Cl\(_2\)) to give 1-(phenethylaminocarbonyl)-4-(methoxycarbonylmethyl)-piperidine (680 mg, 73% yield). LCMS (M+1)\(^+\) 303.9; \(^1\)H NMR (400 MHz,CDCl\(_3\)): \(\delta\) 7.30-7.15 (m, 5H), 4.84 (t, 1H), 3.86 (m, 2H), 3.64 (s, 3H), 3.43 (m, 2H), 2.79 (t, 2H), 2.70 (m, 2H), 2.21 (d, 2H), 1.90 (m, 1H), 1.66 (m, 2H), 1.10 (m, 2H).

**Step 3**

[0612] To a solution of 1-(phenethylaminocarbonyl)-4-(methoxycarbonylmethyl)-piperidine (190 mg, 0.65 mmol) in MeOH (5 mL) and THF (2 mL), a solution of NaOH (79 mg, 1.96 mmol) in water (5 mL) was added. The mixture was stirred overnight and evaporated under the reduced pressure. The aqueous phase was acidified to pH 2 with 1 N HCl, and extracted with EtOAc (50 mL x 2). The organic phase was dried over MgSO\(_4\), filtered and concentrated under reduced pressure to give 1-(phenethylaminocarbonyl)-4-(carboxymethyl)-piperidine (180 mg, 99% yield). LCMS (M+1)\(^+\) 290.8

**Step 4**

[0613] To a solution of 1-(phenethylaminocarbonyl)-4-(carboxymethyl)-piperidine (180 mg, 0.65 mmol) and \([5-(3,4-difluorophenylcarbonyl)amino-6-(tert-butyl-dimethylsilyloxy)-6-(N-hydroxycarbamimidoyl)-hexyl]-carbamic acid tert-butyl ester (392 mg, 0.72 mmol) in DMF (10 mL) chilled in an ice bath, EDC (138 mg, 0.72 mmol), HOBr (99 mg, 0.65 mmol), and \(N,N\)-diisopropylethylamine (0.17 mL, 0.98 mmol). The mixture was stirred overnight at room temperature, and diluted with ether (50 mL) and EtOAc (50 mL). The solution was washed with sat. NaHCO\(_3\), 1 N HCl, water, and brine. The organic phase was dried, filtered and concentrated under reduced pressure. The crude product was dissolved in DMF (10 mL), and stirred at 100 °C for 37 hr. The mixture was cooled down and diluted with ether (50 mL) and EtOAc (50 mL). The solution was washed twice with water, followed by brine. The organic phase was dried over MgSO\(_4\), filtered and concentrated under reduced pressure. The crude mixture was purified by column chromatography (50% EtOAc/hexanes) to give \(5-[3,4\text{-difluorophenylcarbonyl}amino]-6-[5-(1-(phenethylaminocarbonyl)-piperidin-4-ylmethyl]-[1,2,4]oxadiazol-3-yl]-6-(tert-butyl-
dimethylsilyloxy)-hexyl]-carbamic acid tert-butyl ester (150 mg, 29% yield). LCMS (M+1)$^+$ 799.7.

**Step 5**

[0614] To a solution of [5-[(3,4-difluorophenylcarbonyl)amino]-6-{5-[1-(phenethylaminocarbonyl)-piperidin-4-ylmethyl]-[1,2,4]oxadiazol-3-yl]}-6-(tert-butyl-dimethylsilyloxy)-hexyl]-carbamic acid tert-butyl ester (150 mg, 0.29 mmol) and 3-[5-(sulfophenyl)-2-pyridyl]-1,2,4-triazin-5-ylbenzenesulfonic acid, disodium salt (PPTS) (5 mg, mmol) in THF (10 mL), 1 N TBAF in THF (0.28 mL, 0.28 mmol) was added. The mixture was stirred for 30 min. at room temperature, and diluted with EtOAc (60 mL). The solution was washed with sat. NaHCO$_3$ and brine. The organic phase was dried, filtered and concentrated under reduced pressure. To a solution of the crude product in CH$_2$Cl$_2$ (8 mL) chilled in an ice bath, Dess-Martin periodinane (199 mg, 0.47 mmol) was added. The mixture was stirred for 3 h, and diluted with ether (10 mL). To the mixture were added sat. NaHCO$_3$ (4 mL) and 20% Na$_2$S$_2$O$_3$ (4 mL). The mixture was stirred until the layers separated. The mixture was diluted with ether (30 mL) and washed with sat. NaHCO$_3$ and brine. The organic phase was dried over MgSO$_4$, filtered and concentrated under the reduced pressure. The crude mixture was purified by column chromatography (50% to 100% EtOAc/hexanes) to give [5-[(3,4-difluorophenylcarbonyl)amino]-6-{5-[1-(phenethylaminocarbonyl)-piperidin-4-ylmethyl]-[1,2,4]oxadiazol-3-yl]}-6-oxo-hexyl]-carbamic acid tert-butyl ester (78 mg, 67 % yield). LCMS (M+1)$^+$ 683.2; $^1$H NMR (400 MHz,CDCl$_3$): $\delta$ 7.78 (m, 1H), 7.60 (m, 1H), 7.36-7.18 (m, 8H), 5.58 (m, 1H), 4.80 (m, 1H), 3.90 (m, 2H), 3.48 (t, 2H), 3.12 (m, 2H), 2.93 (d, 2H), 2.81 (t, 2H), 2.75 (m, 2H), 2.11 (m, 2H), 1.92 (m, 1H), 1.75 (m, 2H), 1.55 (m, 4H), 1.50 (s, 9H), 1.28 (m, 2H).

**Step 6**

[0615] To a solution of [5-[(3,4-difluorophenylcarbonyl)amino]-6-{5-[1-(phenethylaminocarbonyl)-piperidin-4-ylmethyl]-[1,2,4]oxadiazol-3-yl]}-6-oxo-hexyl]-carbamic acid tert-butyl ester (78 mg, 0.12 mmol) in acetonitrile (5 mL) was added 4 N HCl in dioxane (0.5 mL, mmol). The mixture was stirred for 30 min, and concentrated under reduced pressure. The crude mixture was purified by reverse-phase HPLC, and further lyophilized to give [5-[(3,4-difluorophenylcarbonyl)amino]-6-{5-[1-(phenethylaminocarbonyl)-piperidin-4-ylmethyl]-[1,2,4]oxadiazol-3-yl]}-6-oxo-hexyl]-amine hydrochloride as an off-white solid. LCMS (M+1)$^+$ 583.6.
Biological Examples

Example 1
Inhibitory Activity Against Human Tryptase

[0616] The following protocol represents an assay for determination of inhibition of tryptase under physiological conditions (pH 7.4). Human skin Beta-1 tryptase can be purchased from Promega. Tosyl-Gly-Pro-Lys-para-nitroanilide (tos-GPK-pNa) can be purchased from Centerchem, Inc. Inhibitor profiles were generated by incubating each enzyme in the presence of inhibitor (various concentrations) or 10% DMSO (vehicle control) for 30 minutes in 96 well clear polystyrene plates at room temperature prior to the addition of substrate. Specifically, 400 μM tos-GPK-pNa was added to 1 nM enzyme in 50 mM Tris (7.4), 150 mM NaCl, 0.02% Tween-20, 1 mM EDTA, 50 μg/ml heparin. Enzyme activity can be measured by monitoring the hydrolysis of the synthetic substrate tos-GPK-pNa at 405 nM over 5 minutes using a UV/Max kinetic plate reader (Molecular Devices). The apparent inhibition constants (Ki, app) can be calculated from the progress curves using the software package BatchKi (BioKin, Ltd.). BatchKi uses nonlinear least-squares regression to fit experimental data to the Morrison equation for tight binding inhibitors.

Example 2
Identification of Compounds with Anti-inflammatory Efficacy

[0617] The efficacy of the compounds of the present invention for the treatment of immunomediately inflammatory disorders can be evaluated by either in vitro or in vivo procedures. Thus, the antiinflammatory efficacy of the compounds of the present invention can be demonstrated by assays well known in the art, for example, the Reversed Passive Arthus Reaction technique (see US Patent 5,126,352).

Example 3
Identification of Compounds with Efficacy in Treatment of Skin Diseases

[0618] Assays for determining the therapeutic value of compounds in the treatment of various skin conditions, such as hyperproliferative skin disease, are well known in the art, for example, the Arachidonic Acid Mouse ear Test.
Example 4
Primate Acute Asthma Model

A primate acute asthma model may be employed for the in vivo evaluation of the compounds of the invention as antiasthmatics.

Example 5
Identification of Compounds with Anti-ulcer Efficacy

The compounds of the present invention can be evaluated for their antiulcer activity according to the procedures described in Chiu, *Archives Internationales de Pharmacodynamie et de Therapie*, 1984, 270, 128-140.

Example 6
Identification of Compounds with Activity Against Syncytial Virus Infection

The efficacy of the compounds of the present invention in blocking cell fusion caused by a syncytial virus infection can be evaluated by the methods generally set forth in Tidwell, *J. Med. Chem.*, 1983, 26, 294-298.

Pharmaceutical Composition Examples

The following are representative pharmaceutical formulations containing a compound of Formula I.

**Tablet Formulation**

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Quantity per tablet, mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>compound of this invention</td>
<td>400</td>
</tr>
<tr>
<td>cornstarch</td>
<td>50</td>
</tr>
<tr>
<td>croscarmellose sodium</td>
<td>25</td>
</tr>
<tr>
<td>lactose</td>
<td>120</td>
</tr>
<tr>
<td>magnesium stearate</td>
<td>5</td>
</tr>
</tbody>
</table>

**Capsule Formulation**

The following ingredients are mixed intimately and loaded into a hard-shell gelatin capsule.

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Quantity per tablet, mg</th>
</tr>
</thead>
</table>

compound of this invention 200  
lactose, spray-dried 148  
magnesium stearate 2

Suspension Formulation

[0625] The following ingredients are mixed to form a suspension for oral administration.

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>compound of this invention</td>
<td>1.0 g</td>
</tr>
<tr>
<td>fumaric acid</td>
<td>0.5 g</td>
</tr>
<tr>
<td>sodium chloride</td>
<td>2.0 g</td>
</tr>
<tr>
<td>methyl paraben</td>
<td>0.15 g</td>
</tr>
<tr>
<td>propyl paraben</td>
<td>0.05 g</td>
</tr>
<tr>
<td>granulated sugar</td>
<td>25.5 g</td>
</tr>
<tr>
<td>sorbitol (70% solution)</td>
<td>12.85 g</td>
</tr>
<tr>
<td>Veegum K (Vanderbilt Co.)</td>
<td>1.0 g</td>
</tr>
<tr>
<td>flavoring</td>
<td>0.035 mL</td>
</tr>
<tr>
<td>colorings</td>
<td>0.5 mg</td>
</tr>
<tr>
<td>distilled water</td>
<td>q.s. to 100 mL</td>
</tr>
</tbody>
</table>

Injectable Formulation

[0626] The following ingredients are mixed to form an injectable formulation.

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>compound of this invention</td>
<td>1.2 g</td>
</tr>
<tr>
<td>sodium acetate buffer solution</td>
<td>0.4 M 2.0 mL</td>
</tr>
<tr>
<td>HCl (1 N) or NaOH (1 M)</td>
<td>q.s. to suitable pH</td>
</tr>
<tr>
<td>water (distilled, sterile)</td>
<td>q.s. to 20 mL</td>
</tr>
</tbody>
</table>

[0627] All of the above ingredients, except water, are combined and heated to 60-70 degree C. with stirring. A sufficient quantity of water at 60 degree C. is then added with vigorous stirring to emulsify the ingredients, and water then added q.s. to 100 g.

Suppository Formulation

[0628] A suppository of total weight 2.5 g is prepared by mixing the compound of the invention with Witepsol. H-15 (triglycerides of saturated vegetable fatty acid; Riches-Nelson, Inc., New York), and has the following composition:
[0629] The foregoing invention has been described in some detail by way of illustration and
example, for purposes of clarity and understanding. It will be obvious to one of skill in the art that
changes and modifications may be practiced within the scope of the appended claims. Therefore, it
is to be understood that the above description is intended to be illustrative and not restrictive. The
scope of the invention should, therefore, be determined not with reference to the above
description, but should instead be determined with reference to the following appended claims,
along with the full scope of equivalents to which such claims are entitled. All patents, patent
applications and publications cited in this application are hereby incorporated by reference in their
entirety for all purposes to the same extent as if each individual patent, patent application or
publication were so individually denoted.
WE CLAIM:

1. A Compound of Formula I

\[
\begin{align*}
\text{Ar}^1 & \quad \text{W} \quad \text{Ar}^2 \\
\text{R}^2 & \text{R}^1 \\
\text{R}^3 & \text{R}^{3a}
\end{align*}
\]

where:

\( \text{Ar}^1 \) is activating heteroarylene or activating phenylene;

\( \text{W} \) is \(-\text{A}^1-\text{D}-\text{A}^2-\); where \( \text{D} \) is \(-\text{O}-, -\text{NR}^4-, -\text{C(O)}-, -\text{C(O)}\text{O}-, -\text{OC(O)}-, -\text{C(O)}\text{NR}^4-, -\text{NR}^4\text{C(O)}-, -\text{S(O)}_n- \) (where \( n \) is 0, 1, or 2), \(-\text{NR}^4\text{S(O)}_2-, -\text{S(O)}_2\text{NR}^4-, -\text{NR}^4\text{C(O)}\text{O}-, -\text{OC(O)}\text{NR}^4-, -\text{NR}^4\text{C(O)}\text{NR}^5-, -\text{CR'\text{R}''-} \) (where \( \text{R'} \) and \( \text{R''} \) together with the carbon to which they are attached form cycloalkyne), or a bond and where \( \text{R}^4 \) and \( \text{R}^5 \) are independently hydrogen, alkyl, alkylcarbonyl, or haloalkylcarbonyl; where \( \text{A}^1 \) and \( \text{A}^2 \) are independently a bond, alkylene, alkenylene, alkynylene, haloalkylene, haloalkenylene, or haloalkynylene; and where at least one of \( \text{A}^1, \text{D}, \text{or} \text{A}^2 \) is not a bond;

\( \text{R}^1 \) is hydrogen, alkyl, or substituted alkyl;

\( \text{R}^2 \) is heteroarylalkyl, alkylaminoalkyloxyalkyl, dialkylaminoalkyloxyalkyl, heterocycloalkylalkyl, \( \text{R}^a\text{R}^b\text{NC(=NH)}\text{NH-S(O)}_2\text{alkyl}, \text{R}^a\text{R}^b\text{NC(=NH)}\text{NH-C(O)}\text{alkyl}, \text{R}^a\text{R}^b\text{NC(=NH)}\text{OH-alkyl}, \text{R}^a\text{R}^b\text{NC(=NH)}\text{Nalkyl}, \text{R}^a\text{R}^b\text{NC(=NH)}\text{alkyl}, \text{alkyl-S(O)}_n\text{alkyl}, \text{aminocarbylalkyl}, \text{alkylaminocarbylalkyl}, \text{dialkylaminocarbylalkyl}, \text{alkylcarbylalkyl}, \text{alkoxyalkylalkyl}, \text{acyloxyalkyl}, \text{aminocarbylalkyl}, \text{alkyl-NR}^a\text{-carbylalkyl, hydroxyalkyl, alkoxycarbylamin}, \text{alkyl-NR}^a\text{-sulfonylalkyl, heteroaryl, heteroaralkyl, heteroaralkenyl, heteroaralkylaminocarbylalkyl, heteroaralkyloxyalkylalkyl, heteroaralkyloxyalkylalkyl, arylalkyl, aralkyl, aralkenyl, aralkyloxyalkyl, aryloxyalkyl, heteroaryloxyalkyl, heteroaralkyl-NR}^a\text{-carbylalkylalkyl, heteroaralkyl-NR}^a\text{-sulfonylalkyl, heterocyloalkylalkyloxyalkyl, heterocyloalkylalkyloxyalkylalkyl, heterocyloalkylalkyl-NR}^a\text{-carbylalkylalkyl, heterocyloalkylalkyl-NR}^a\text{-sulfonylalkyl, R}^a\text{R}^7\text{Nalkyl (where alkyl is optionally substituted with halo), or R}^a\text{R}^7\text{Nalkenyl (where alkenyl is optionally substituted with halo),}}

30
wherein R^6 and R^7 are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, aryl, acyl, aminoalkylcarbonyl, alkylationoalkylcarbonyl, dialkylationoalkylcarbonyl, alkylcyanocarbonyl, alkylcyanonitrile, dialkylcyanonitrile, alkylcarbonyloxyalkylcyanoxy carbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, aminocarbonyl, alkoxycarbonyl, alkylsulfonylethoxyalkylcarbonyl, heteroaralkyl-NR^6-carbonyl, heteroaryl, heteroarylcarbonyl, heteroaralkyl, heteroaralkylcarbonyl, heteroaralkylcarbonyl, heterocycloalkylalkylcarbonyl, heterocycloalkylalkylcarbonyl, heterocycloalkylalkyl-NR^6-carbonyl, heterocycloalkylalkylcarbonyl, and heterocycloalkylalkylsulfonylethoxyalkylcarbonyl.

wherein n is 0, 1, or 2 and wherein R^8 and R^b are independently hydrogen or alkyl;

R^3 is hydroxy or -OSiR^{24a}R^{24b}R^{24c} (where R^{24a}, R^{24b}, and R^{24c} are independently alkyl or aryl) and R^{3a} is hydrogen, hydroxy, or -OSiR^{24a}R^{24b}R^{24c} (where R^{24a}, R^{24b}, and R^{24c} are independently alkyl or aryl); or R^3 and R^{3a} together with the carbon to which they are attached form carbonyl;

Q is

i) -OR^8 wherein R^8 is hydrogen, alkyl, substituted alkyl, acyl, aralkyl, aralkenyl, heteroaralkyl, aryl, heteroaryl, or -C(O)NR^9R^{10} (wherein R^9 and R^{10} are independently hydrogen, alkyl, aryl, heteroaryl, aralkyl, aralkenyl, heterocycloalkyl, heterocycloalkylalkyl, or heteroaralkyl);

ii) -S(O)_rR^{11} where r is 0, 1, or 2 and R^{11} is alkyl, substituted alkyl, aryl, heteroaryl, heteroaralkyl, aralkyl, or aralkenyl; or -S(O)_rR^{11} where r is 2 and R^{11} is -N R^{12}R^{13} (wherein R^{12} and R^{13} are alkyl, substituted alkyl, aryl, heteroaryl, heteroaralkyl, aralkyl, or aralkenyl);

iii) -NR^{14}R^{15} wherein each R^{14} and R^{15} are independently hydrogen, alkyl, substituted alkyl, alkenyl, alkenyloxyalkylcarbonyl, haloalkylcarbonyl, haloalkoxy carbonyl, alkenyloxy carbonyl, alkoxy carbonyl, alkoxyalkylcarbonyl, alkoxyalkylaminocarbonyl, cycloalkylcarbonyl, cycloalkylalkylcarbonyl, arylcarbonyl, aralkylcarbonyl, heteroarylcarbonyl, heterocycloalkylcarbonyl, aryloxycarbonyl, heterocycloalkylalkylcarbonyl, cycloalkylcarbonyl, heteroarylalkylcarbonyl, aralkylcarbonyl, aralkyloxy carbonyl, heterocycloalkylalkylcarbonyl, heteroaralkenyloxy carbonyl, aryl, aralkyl, aralkenyl,
heteroaryl, heteroaralkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, (R₁⁸R₁⁷N=)R₁⁶C⁻ (wherein R₁⁶, R₁⁷, and R₁⁸ are independently hydrogen, alkyl, or substituted alkyl), R₁⁹R₂⁰NC(O)⁻, R₂¹S(O)₂⁻, or R₁⁹R₂⁰NS(O)₂⁻, wherein R₁⁹, R₂⁰, and R₂¹ are independently hydrogen, alkyl, substituted alkyl, aralkenyl, aralkyl, heteroaryl, heterocycloalkyl, cycloalkyl, aralkyl, aralkenyl, heterocycloalkylalkyl, heteroaralkyl, cycloalkylalkyl, or heteroaralkenyl, or R₁⁴ and R₁⁵ together with the nitrogen to which they are attached form heterocycloalkyl or heteroaryl;

iv) heterocycloalkylalkylcarbonylamino;

v) fused-heterocycloalkylalkylcarbonylamino;

vi) heteroaralkylcarbonylamino; or

vii) hydrogen; and

Ar² is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl where Ar² is further substituted with E where E is selected from the group consisting of

i) -Y¹⁻X¹⁻Y²⁻Z¹⁻Y³⁻Ar³, wherein X¹ and Z¹ are independently -O⁻, -NR²²⁻, -C(O)⁻, -C(O)O⁻, -OC(O)⁻, -C(O)NR²²⁻, -NR²²C(O)⁻, -S(O)ₙ⁻ (where n is 0, 1, or 2), -NR²²S(O)₂⁻, -S(O)₂NR²²⁻, -S(O)₂C(O)O⁻, -OC(O)NR²²⁻, or -NR²²C(O)NR²²⁻; and Y¹, Y², Y³, and Ar³ are as defined below;

ii) -X¹⁻Z¹⁻Y³⁻Ar³, wherein X¹ is -O⁻, -NR²²⁻, -C(O)⁻, -C(O)O⁻, -OC(O)⁻, -C(O)NR²²⁻, -NR²²C(O)⁻, -S(O)ₙ⁻ (where n is 0, 1, or 2), -NR²²S(O)₂⁻, -S(O)₂NR²²⁻, -S(O)₂C(O)O⁻, -OC(O)NR²²⁻, or -NR²²C(O)NR²²⁻; Z¹ is cycloalkylene or heterocycloalkylene; and Y³ and Ar³ are as defined below;

iii) -X¹⁻Y²⁻Ar³, wherein X¹ is -O⁻, -NR²²⁻, -C(O)⁻, -C(O)O⁻, -OC(O)⁻, -C(O)NR²²⁻, -NR²²C(O)⁻, -S(O)ₙ⁻ (where n is 0, 1, or 2), -NR²²S(O)₂⁻, -S(O)₂NR²²⁻, -NR²²C(O)O⁻, -OC(O)NR²²⁻, or -NR²²C(O)NR²²⁻; and Y² and Ar³ are as defined below;

iv) -X²⁻Ar³⁺, wherein X² is -O⁻, -C(O)NR²²⁻, or -NR²²C(O)⁻; and Ar³⁺ is substituted aryl, heteroaryl, cycloalkyl, or heterocycloalkyl;

v) -X³⁻Ar³, wherein X³ is -NR²²⁻, -C(O)⁻, -C(O)O⁻, -OC(O)⁻, -S(O)ₙ⁻ (where n is 0, 1, or 2), -NR²²S(O)₂⁻, -S(O)₂NR²²⁻, -NR²²C(O)O⁻, -OC(O)NR²²⁻, or -NR²²C(O)NR²²⁻; and Ar³ is as defined below;

vi) -X¹⁻Y²⁻Z¹⁻Ar³, wherein X¹ and Z¹ are independently -O⁻, -NR²²⁻, -C(O)⁻,
-C(O)O-, -OC(O)-, -C(O)NR22-, -NR22C(O)-, -S(O)n- (where n is 0, 1, or 2),
-NR22S(O)2-, -S(O)2NR22-, -NR22C(O)O-, -OC(O)NR22-, or -NR22C(O)NR23-, and Y1 and Ar3 are as defined below;

vii) \(-Y1^1\)-Ar3 where Y1^1 and Ar3 are as defined below;

viii) \(-Y1^1\)-X1^1-Y2^2-Ar3, wherein X1^1 is -O-, -NR22-, -C(O)-, -C(O)O-, -OC(O)-, -C(O)NR22-, -NR22C(O)-, -S(O)n- (where n is 0, 1, or 2), -NR22S(O)2-, -S(O)2NR22-, -NR22C(O)O-, -OC(O)NR22-, or -NR22C(O)NR23-, and Y1^1, Y2^2, and Ar3 are as defined below;

ix) \(-X1\)-Y2^1-\(\text{Ar}^3\), wherein X1 is -O-, -NR22-, -C(O)-, -C(O)O-, -OC(O)-, -C(O)NR22-, -NR22C(O)-, -S(O)n- (where n is 0, 1, or 2), -NR22S(O)2-, -S(O)2NR22-, -NR22C(O)O-, -OC(O)NR22-, or -NR22C(O)NR23-, and Y1, Y2, and Ar3 are as defined below; and

x) \(-X1\)-Y2^1-Z1^1-\(\text{Ar}^3\), wherein X1 and Z1 are independently -O-, -NR22-, -C(O)-, -C(O)O-, -OC(O)-, -C(O)NR22-, -NR22C(O)-, -S(O)n- (where n is 0, 1, or 2), -NR22S(O)2-, -S(O)2NR22-, -NR22C(O)O-, -OC(O)NR22-, or -NR22C(O)NR23-, and Y1, Y2, and Ar3 are as defined below; and

wherein R22 and R23 are independently hydrogen, alkyl, substituted alkyl, or acyl; wherein Y1, Y2, and Y3 are independently alkylene, alkenylene, alkynylene, haloalkylene, haloalkenylene, haloalkynylene, carboxyalkylene, or -CR^6R^4 (where R^6 and R^4 together with the carbon to which they are attached form cycloalkylene); and wherein Ar3 is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl; or

a pharmaceutically acceptable salt thereof.

2. A compound of Formula I

\[
\text{Ar}^1 \quad \text{W} \quad \text{Ar}^2
\]

30 wherein
Ar$^1$ is activating heteroarylene;

$W$ is $-A^1$-D-$A^2$-; where $D$ is -C(O)-, -CR’$R''$- (where $R'$ and $R''$ together with the carbon to which they are attached form cycloalkylene), or a bond; where $A^1$ and $A^2$ are independently a bond or alkylene; and where at least one of $A^1$, $D$, or $A^2$ is not a bond;

$R^1$ is hydrogen;

$R^2$ is heteroarylalkyl, $R^6R^7$NC(=NH)NH-C(O)-alkyl, aralkyl, $R^6R^7$Nalkyl (where alkyl is optionally substituted with halo), or $R^6R^7$Nalkenyl (where alkenyl is optionally substituted with halo), wherein $R^6$ and $R^7$ are independently hydrogen or alkoxycarbonyl, wherein $R^6$ and $R^7$ are independently selected from hydrogen and alkyl;

$R^3$ is hydroxy or -OSiR$^{24a}$R$^{24b}$R$^{24c}$ (where $R^{24a}$, $R^{24b}$, and $R^{24c}$ are independently alkyl or aryl) and $R^{3a}$ is hydrogen; or $R^3$ and $R^{3a}$ together with the carbon to which they are attached form carboxyl;

$Q$ is fused-heterocycloalkylalkylcarbonylamino; hydrogen; or -NR$^{14}$R$^{15}$ wherein each $R^{14}$ and $R^{15}$ are independently hydrogen, alkyl, substituted alkyl, alkylicarbonyl, haloalkylcarbonyl, haloalkoxy carbonyl, alkenyl oxy carbonyl, alkoxy carbonyl, alkoxy alkyl oxy carbonyl, alkoxy carbonyl amino carbonyl, cyclo alkyl carbonyl, aryl carbonyl, hetero aryl carbonyl, hetero cyclo alkyl carbonyl, alkoxy carbonyl, hetero cyclo alkyl alkyl oxy carbonyl, $R^{19}R^{20}$NC(O)-, $R^{19}S(O)_{2}$-, $R^{19}R^{20}$NS(O)(O)$_2$, wherein $R^{19}$, $R^{20}$, and $R^{21}$ are independently hydrogen, alkyl, aryl, hetero aryl, hetero cyclo alkyl, aralkyl, or hetero aralkyl; or $R^{14}$ and $R^{15}$ together with the nitrogen to which they are attached form heterocyclo alkyl or hetero aryl; and

Ar$^2$ is aryl, hetero aryl, or heterocyclo alkyl where Ar$^2$ is further substituted with E where E is selected from the group consisting of

i) $-X^1$-$Z^2$-$Y^3$-Ar$^3$, where $X^1$ is -C(O)-; $Z^2$ is heterocyclo alkylene; $Y^3$ is alkylene; and $Ar^3$ is aryl;

ii) $-X^1$-$Y^2$-$Ar^3$, where $X^1$ is -O-, -NR$^{22}$-, -C(O)-, -C(O)O-, -OC(O)-, -C(O)NR$^{22}$-, -NR$^{22}$C(O)-, -S(O)$_n$- (where n is 0, 1, or 2), -NR$^{22}$S(O)$_2$-, -S(O)$_2$NR$^{22}$-, -NR$^{22}$C(O)O-, -OC(O)NR$^{22}$-, or -NR$^{22}$C(O)NR$^{22}$-; $Y^2$ is alkenylene, alkenylene, or carboxy alkylene; and $Ar^3$ is aryl, hetero aryl, or cyclo alkyl;

iii) $-X^1$-$Y^2$-$Ar^3$, where $X^1$ is -OC(O)NR$^{22}$-, -S(O)$_2$-, or -C(O)-; and $Ar^3$ is aryl;

iv) $-X^1$-$Y^2$-$Z^1$-$Ar^3$, where $X^1$ is -O- or -C(O)NR$^{22}$-; $Y^2$ is alkylene; $Z^1$ is -O- or -C(O)-; and $Ar^3$ is aryl or hetero aryl;

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v) $-Y^1\text{-Ar}^3$ where $Y^1$ is alkyne and $\text{Ar}^3$ is aryl;

vi) $-Y^1\text{-X}^1\text{-Ar}^3$, where $Y^1$ is alkyne; $X^1$ is $-\text{C(O)}$; and $\text{Ar}^3$ is heterocycloalkyl; and

vii) $-X^1\text{-Y}^2\text{-Y}^3\text{-Ar}^3$, where $X^1$ is $-\text{O}$; $Y^2$ is alkyne; $Y^3$ is $-\text{CR}^6\text{R}^7$ (where $\text{R}^6$ and $\text{R}^7$ are independently hydrogen, alkyl, substituted alkyl, or acyl; or a pharmaceutically acceptable salt thereof).

3. The compound of Claim 1 wherein:

$\text{Ar}^1$ is oxadiazol-diyli;

$R^3$ and $R^{3a}$ together with the carbon to which they are attached form carbonyl;

$R^1$ is hydrogen;

$R^2$ is $R^6R^7$-alkyl; and

$Q$ is $-\text{NR}^{14}\text{R}^{15}$.

4. The Compound of Claim 3 wherein $\text{Ar}^2$ is heterocycloalkyl.

5. The Compound of Claim 3 wherein $\text{Ar}^2$ is aryl.

6. The Compound of Claim 3 wherein $\text{Ar}^2$ is heteroaryl.

7. The compound of Claim 5 wherein $\text{Ar}^2$ is 6-membered aryl.

8. The compound of Claim 1 wherein $\text{Ar}^2$ is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl where $\text{Ar}^2$ is further substituted with $E$ where $E$ is in a 1,4-relationship with $W$ and $E$ is selected from the group consisting of

i) $-Y^1\text{-X}^1\text{-Y}^2\text{-Z}^1\text{-Y}^3\text{-Ar}^3$, wherein $X^1$ and $Z^1$ are independently $-\text{O}$, $-\text{NR}^{22}$, $-\text{C(O)}$, $-\text{C(O)}\text{O}$, $-\text{OC(O)}$, $-\text{C(O)}\text{NR}^{22}$, $-\text{NR}^{22}\text{C(O)}$, $-\text{S(O)}_n^-$ (where $n$ is 0, 1, or 2), $-\text{NR}^{22}\text{S(O)}_2^-$, $-\text{S(O)}_2\text{NR}^{22}$, $-\text{NR}^{22}\text{C(O)}\text{O}$, $-\text{OC(O)}\text{NR}^{22}$, or $-\text{NR}^{22}\text{C(O)}\text{NR}^{23}$; and $Y^1$, $Y^2$, $Y^3$, and $\text{Ar}^3$ are as defined below;

ii) $-X^1\text{-Z}^2\text{-Y}^3\text{-Ar}^3$, wherein $X^1$ is $-\text{O}$, $-\text{NR}^{22}$, $-\text{C(O)}$, $-\text{C(O)}\text{O}$, $-\text{OC(O)}$, $-\text{C(O)}\text{NR}^{22}$, $-\text{NR}^{22}\text{C(O)}$, $-\text{S(O)}_n^-$ (where $n$ is 0, 1, or 2), $-\text{NR}^{22}\text{S(O)}_2^-$, $-\text{S(O)}_2\text{NR}^{22}$, $-\text{NR}^{22}\text{C(O)}\text{O}$, $-\text{OC(O)}\text{NR}^{22}$, or $-\text{NR}^{22}\text{C(O)}\text{NR}^{23}$; $Z^2$ is cycloalkylene or heterocycloalkylene; and $Y^3$ and $\text{Ar}^3$ are as defined below;

iii) $-X^1\text{-Y}^2\text{-Ar}^3$, wherein $X^1$ is $-\text{O}$, $-\text{NR}^{22}$, $-\text{C(O)}$, $-\text{C(O)}\text{O}$, $-\text{OC(O)}$, $-\text{C(O)}\text{NR}^{22}$, $-\text{NR}^{22}\text{C(O)}$, $-\text{S(O)}_n^-$ (where $n$ is 0, 1, or 2), $-\text{NR}^{22}\text{S(O)}_2^-$, $-\text{S(O)}_2\text{NR}^{22}$, $-\text{NR}^{22}\text{C(O)}\text{O}$, $-\text{OC(O)}\text{NR}^{22}$, or $-\text{NR}^{22}\text{C(O)}\text{NR}^{23}$; and $Y^2$ and $\text{Ar}^3$ are as defined below;
iv) $-X^2\cdot Ar^3$, wherein $X^2$ is $-O\cdot$, $-C(O)NR^{22\prime}$, or $-NR^{22\prime\prime}C(O)\cdot$; and $Ar^3$ is substituted aryl, heteroaryl, cycloalkyl, or heterocycloalkyl;

v) $-X^3\cdot Ar^3$, wherein $X^3$ is $-NR^{22\prime\prime\prime}$, $-C(O)\cdot$, $-C(O)O\cdot$, $-OC(O)\cdot$, $-S(O)_n\cdot$ (where $n$ is 0, 1, or 2), $-NR^{22\prime\prime\prime}S(O)_2\cdot$, $-S(O)_2NR^{22\prime\prime\prime}$, $-NR^{22\prime\prime\prime}C(O)O\cdot$, $-OC(O)NR^{22\prime\prime\prime}$, or $-NR^{22\prime\prime\prime}C(O)NR^{23\prime}$; and $Ar^3$ is as defined below;

vi) $-X^1\cdot Y^2\cdot Z^1\cdot Ar^3$, wherein $X^1$ and $Z^1$ are independently $-O\cdot$, $-NR^{22\prime\prime\prime}$, $-C(O)\cdot$, $-C(O)O\cdot$, $-OC(O)\cdot$, $-S(O)_n\cdot$ (where $n$ is 0, 1, or 2), $-NR^{22\prime\prime\prime}S(O)_2\cdot$, $-S(O)_2NR^{22\prime\prime\prime}$, $-NR^{22\prime\prime\prime}C(O)O\cdot$, $-OC(O)NR^{22\prime\prime\prime}$, or $-NR^{22\prime\prime\prime}C(O)NR^{23\prime}$; and $Y^2$ and $Ar^3$ are as defined below;

vii) $-Y^1\cdot Ar^3$ where $Y^1$ and $Ar^3$ are as defined below;

viii) $-Y^1\cdot X^1\cdot Y^2\cdot Ar^3$, wherein $X^1$ is $-O\cdot$, $-NR^{22\prime\prime\prime}$, $-C(O)\cdot$, $-C(O)O\cdot$, $-OC(O)\cdot$, $-C(O)NR^{22\prime\prime\prime}$, $-NR^{22\prime\prime\prime}C(O)\cdot$, $-S(O)_n\cdot$ (where $n$ is 0, 1, or 2), $-NR^{22\prime\prime\prime}S(O)_2\cdot$, $-S(O)_2NR^{22\prime\prime\prime}$, $-NR^{22\prime\prime\prime}C(O)O\cdot$, $-OC(O)NR^{22\prime\prime\prime}$, or $-NR^{22\prime\prime\prime}C(O)NR^{23\prime}$; and $Y^1$, $Y^2$, and $Ar^3$ are as defined below;

ix) $-Y^1\cdot X^1\cdot Y^3\cdot Ar^3$, wherein $X^1$ is $-O\cdot$, $-NR^{22\prime\prime\prime}$, $-C(O)\cdot$, $-C(O)O\cdot$, $-OC(O)\cdot$, $-C(O)NR^{22\prime\prime\prime}$, $-NR^{22\prime\prime\prime}C(O)\cdot$, $-S(O)_n\cdot$ (where $n$ is 0, 1, or 2), $-NR^{22\prime\prime\prime}S(O)_2\cdot$, $-S(O)_2NR^{22\prime\prime\prime}$, $-NR^{22\prime\prime\prime}C(O)O\cdot$, $-OC(O)NR^{22\prime\prime\prime}$, or $-NR^{22\prime\prime\prime}C(O)NR^{23\prime}$; and $Y^1$ and $Ar^3$ are as defined below;

i) $-X^1\cdot Y^2\cdot Z^1\cdot Ar^3$, wherein $X^1$ is $-O\cdot$, $-NR^{22\prime\prime\prime}$, $-C(O)\cdot$, $-C(O)O\cdot$, $-OC(O)\cdot$, $-C(O)NR^{22\prime\prime\prime}$, $-NR^{22\prime\prime\prime}C(O)\cdot$, $-S(O)_n\cdot$ (where $n$ is 0, 1, or 2), $-NR^{22\prime\prime\prime}S(O)_2\cdot$, $-S(O)_2NR^{22\prime\prime\prime}$, $-NR^{22\prime\prime\prime}C(O)O\cdot$, $-OC(O)NR^{22\prime\prime\prime}$, or $-NR^{22\prime\prime\prime}C(O)NR^{23\prime}$; and $Y^2$, $Y^3$, and $Ar^3$ are as defined below; and

xi) $-Y^1\cdot X^1\cdot Y^2\cdot Z^1\cdot Ar^3$, wherein $X^1$ and $Z^1$ are independently $-O\cdot$, $-NR^{22\prime\prime\prime}$, $-C(O)\cdot$, $-C(O)O\cdot$, $-OC(O)\cdot$, $-S(O)_n\cdot$ (where $n$ is 0, 1, or 2), $-NR^{22\prime\prime\prime}S(O)_2\cdot$, $-S(O)_2NR^{22\prime\prime\prime}$, $-NR^{22\prime\prime\prime}C(O)O\cdot$, $-OC(O)NR^{22\prime\prime\prime}$, or $-NR^{22\prime\prime\prime}C(O)NR^{23\prime}$; and $Y^1$, $Y^2$, and $Ar^3$ are as defined below; and

wherein $R^{22}$ and $R^{23}$ are independently hydrogen, alkyl, substituted alkyl, or acyl; wherein $Y^1$, $Y^2$, and $Y^3$ are independently alkylene, alkenylene, alkynylene, haloalkylene, haloalkynylene, carboxyalkylene, or $-CR^6R^7$ (where $R^6$ and $R^7$ together with the carbon to which they are attached form cycloalkylene); and wherein $Ar^3$ is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl.

9. The compound of Claim 1 wherein $Ar^1$ is activating heteroarylene.
10. The compound of Claim 1 wherein R³ and R³₃ together with the carbon to which they are attached form carbonyl.

11. The compound of Claim 3 wherein Ar² is 6-membered aryl further substituted with E where E is in a 1,4-relationship with W and E is -X¹⁻Y²⁻Z¹⁻Ar³.

12. The compound of Claim 3 wherein Ar² is 6-membered aryl further substituted with E in the 4-position where E is -X¹⁻Y²⁻Z¹⁻Ar³.

13. The compound of Claim 3 wherein Ar² is 6-membered aryl further substituted with E in the 4-position where E is -X³⁻Ar³ and W is in the 1-position.

14. The compound of Claim 3 wherein Ar² is 6-membered aryl further substituted with E in the 4-position where E is -X¹⁻Y²⁻Y³⁻Ar³.

15. The compound of Claim 3 wherein Ar² is 6-membered aryl further substituted with E in the 4-position where E is -X¹⁻Z²⁻Y³⁻Ar³.

16. The compound of Claim 3 wherein Ar² is piperazin-1-yl further substituted with E where E is in a 1,4-relationship with W and E is -Y¹⁻Ar³ or -X¹⁻Y²⁻Ar³.

17. The compound of Claim 1 wherein
   Ar¹ is oxadiazol-diyl;
   R³ and R³₃ together with the carbon to which they are attached form carbonyl;
   R¹ is hydrogen;
   R² is heteroaryl, R⁶R⁷Nalkenyl, R⁶R⁷NC(=NH)NH-C(O)alkyl, or aralkyl; and
   Q is -NR¹⁴R¹⁵.

18. The compound of Claim 3 wherein R¹⁴ is hydrogen and R¹⁵ is phenylmethyloxycarbonyl.

19. The compound of Claim 3 wherein R¹⁴ is hydrogen and R¹⁵ is arylcarbonyl.

20. The compound of Claim 3 wherein R¹⁴ is hydrogen and R¹⁵ is alkylcarbonyl.

21. The compound of Claim 3 wherein R¹⁴ is hydrogen and R¹⁵ is alkoxyalkylcarbonyl.

22. The compound of Claim 3 wherein R¹⁴ is hydrogen and R¹⁵ is heteroalkylcarbonyl.

23. The compound of Claim 3 wherein R¹⁴ and R¹⁵ together with the nitrogen to which they are attached form heteroaryl.

24. The compound of Claim 3 wherein R¹⁴ is hydrogen and R¹⁵ is alkoxycarbonyl.

25. The compound of Claim 3 wherein R¹⁴ is hydrogen and R¹⁵ is heteroarylcarbonyl.

26. The compound of Claim 3 wherein R¹⁴ and R¹⁵ together with the nitrogen to which they are attached form heterocycloalkyl.

27. A compound selected from the group consisting of:
[5-[(phenylmethyloxycarbonyl)amino]-6-{5-[4-(3-chlorophenethyl-aminocarbonyl)phenylmethyl]-[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine;
[5-[(phenylmethyloxycarbonyl)amino]-6-{5-[4-[2-(thien-2-yl)ethylaminocarbonyl]phenylmethyl]-[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine;
[5-[(phenylmethyloxycarbonyl)amino]-6-{5-[4-[3-(phenyl)prop-2-enyl-aminocarbonyl]phenylmethyl]-[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine;
[5-[(phenylmethyloxycarbonyl)amino]-6-{5-[4-[1(5)-carboxy-2-phenylethylaminocarbonyl]-phenylmethyl]-[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine;
[5-[(cyclopentylcarbonyl)amino]-6-{5-[4-[3-(phenyl)prop-2-enyl-aminocarbonyl]phenylmethyl]-[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine;
[5-[(n-pentylcarbonyl)amino]-6-{5-[4-(3,4-dichlorophenethoxy)-phenylmethyl]-[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine;
[5-[(2,4-difluorophenylcarbonyl)amino]-6-{5-[4-(3,4-dichlorophenethoxy)-phenylmethyl]-[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine;
[5-[(tert-butylicarbonyl)amino]-6-{5-[4-(3,4-dichlorophenethoxy)-phenylmethyl]-[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine;
[5-[(4-chlorophenylcarbonyl)amino]-6-{5-[4-(3,4-dichlorophenethoxy)-phenylmethyl]-[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine;
[5-[(3,4-difluorophenylcarbonyl)amino]-6-{5-[4-(3,4-dichlorophenethoxy)-phenylmethyl]-[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine;
[5-[(methylsulfonylarnino)-6-{5-[4-(3,4-dichlorophenethoxy)-phenylmethyl]-[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine;
[5-[(prop-1-en-3-yloxy carbonyl)amino]-6-{5-[4-(phenethoxy)-phenylmethyl]-[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine;
[5-[(phenylmethyloxycarbonyl)amino]-6-{5-[4-[1-(3,4-dichlorophenethyl)-aminocarbonyl]oxy]-phenylmethyl]-[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine;
[5-[(ethoxy carbonyl)arnino]-6-{5-[4-(3,4-dichlorophenethoxy)-phenylmethyl]-[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine;
[5-[(morpholinocarbonyl)amino]-6-{5-[4-(3,4-dichlorophenethoxy)-phenylmethyl]-[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine;
[5-[(bis-(morpholinocarbonyl)amino)-6-{5-[4-(3,4-dichlorophenethoxy)-phenylmethyl]-[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine;
[5-[(phenylmethyloxy carbonyl)amino]-6-5-[4-(3,4-difluorophenethyl oxy)-phenylmethyl]-
[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine;
[5-[(phenylmethyloxy carbonyl)amino]-6-5-[4-(phenethyloxy)-phenylmethyl]- [1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine;
[5-[(phenylmethyloxy carbonyl)amino]-6-5-[4-(thien-3-yl)ethyi oxy]-phenylmethyl]-
[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine;
[5-[(phenylmethyloxy carbonyl)amino]-6-5-[4-(phenethyloxy)-1-phenyl-1,1- dimethylmethyl]-[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine;
[5-[(phenylmethyloxy carbonyl)amino]-6-5-[4-(phenethyloxy)-1-phenyl-1-methylmethyl]-
[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine;
[5-[(phenylmethyloxy carbonyl)amino]-6-5-[4-(phenethyloxy)-phenylcycloprop-1-yl]- [1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine;
[5-[(ethylcarbonyl)amino]-6-5-[4-(3-chlorophenethylaminocarbonyl)-phenylmethyl]- [1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine;
[5-[(aromatic carbonyl)amino]-6-5-[4-(3,4-dichlorophenethyl oxy)-phenylmethyl]- [1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine;
[5-[(3-fluorophenethylcarbonyl)amino]-6-5-[4-(3,4-dichlorophenethyl oxy)-phenylmethyl]- [1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine;
[5-[(trifluoromethylcarbonyl)amino]-6-5-[4-(3,4-dichlorophenethyl oxy)-phenylmethyl]- [1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine;
[5-[(phenylmethyloxy carbonyl)amino]-6-5-[4-(3-phenylpropylaminocarbonyl)- phenylmethyl]-[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine;
[5-[(phenylmethyloxy carbonyl)amino]-6-5-[4-(phenethyloxyaminocarbonyl)-phenylmethyl]-[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine;
[5-[(isoproxy carbonyl)amino]-6-5-[4-(3,4-dichlorophenethyl oxy)-phenylmethyl]- [1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine;
[5-[(phenylmethyloxy carbonyl)amino]-6-5-[4-(3,5-difluorophenethylaminocarbonyl)- phenylmethyl]-[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine;
[5-[(methoxymethylcarbonyl)amino]-6-5-[4-(3,4-dichlorophenethyl oxy)-phenylmethyl]- [1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine;
[5-[(methoxyethyl)oxy carbonyl]amino]-6-{5-[4-(3,4-dichlorophenethoxy)-phenylmethyl]-1,2,4]oxadiazol-3-yl}-6-oxo-hexyl]-amine;
[5-[(3-fluorophenyl)carbonyl]amino]-6-{5-[4-(3,4-dichlorophenethoxy)-phenylmethyl]-1,2,4]oxadiazol-3-yl}-6-oxo-hexyl]-amine;
[5-[(2-fluorophenyl)carbonyl]amino]-6-{5-[4-(3,4-dichlorophenethoxy)-phenylmethyl]-1,2,4]oxadiazol-3-yl}-6-oxo-hexyl]-amine;
[5-[(isopropylcarbonyl]amino]-6-{5-[4-(3,4-dichlorophenethoxy)-phenylmethyl]-1,2,4]oxadiazol-3-yl}-6-oxo-hexyl]-amine;
[5-[(phenylmethoxy carbonyl)amino]-6-{5-[4-(4-bromophenethoxy)-phenylmethyl]-1,2,4]oxadiazol-3-yl}-6-oxo-hexyl]-amine;
[5-[(phenylmethoxy carbonyl)amino]-6-{5-[4-(3,4-dichlorophenethoxy)-phenylmethyl]-1,2,4]oxadiazol-3-yl}-6-oxo-hexyl]-amine;
[5-[(phenylmethoxy carbonyl)amino]-6-{5-[4-(3,4-dichlorophenethoxy)-phenylmethyl]-1,2,4]oxadiazol-3-yl}-6-oxo-hexyl]-amine;
[5-[(ethoxycarbonyl)amino]-6-{5-[4-(phenethoxy)-phenylmethyl]-[1,2,4]oxadiazol-3-yl}-6-oxo-hexyl]-amine;
[5-[(piperidin-1-ylcarbonyl]amino]-6-{5-[4-(3,4-dichlorophenethoxy)-phenylmethyl]-1,2,4]oxadiazol-3-yl}-6-oxo-hexyl]-amine;
[5-[(dimethylaminocarbonyl)amino]-6-{5-[4-(3,4-dichlorophenethoxy)-phenylmethyl]-1,2,4]oxadiazol-3-yl}-6-oxo-hexyl]-amine;
[5-((phenylmethylloxy carbonyl)amino)-6-{5-[4-(3,4-dichlorophenethylaminocarbonyl)phenylmethyl]-1,2,4]oxadiazol-3-yl}-6-oxo-hexyl]-amine;  
[5-((methoxy carbonyl) amino)-6-{5-[4-(3,4-dichlorophenethoxy)-phenylmethyl]-[1,2,4]oxadiazol-3-yl}-6-oxo-hexyl]-amine;  
[5-[(tetrahydrofuran-3-yl carbonyl) amino]-6-{5-[4-(3,4-dichlorophenethoxy)phenylmethyl]-[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine;  
[5-[(phenylmethylloxy carbonyl)amino]-6-{5-[4-(3,4-dimethoxyphenethoxy)phenylmethyl]-[1,2,4]oxadiazol-3-yl}-6-oxo-hexyl]-amine;  
[5-((phenylmethylloxy carbonyl)amino)-6-{5-[4-(thien-2-yl ethoxy) phenylmethyl]-[1,2,4]oxadiazol-3-yl}-6-oxo-hexyl]-amine;  
[5-[(phenylmethylloxy carbonyl) amino]-6-{5-[4-((napth-2-ylmethyl)oxy)-phenylmethyl]-[1,2,4]oxadiazol-3-yl}-6-oxo-hexyl]-amine;  
[5-[(pyrrolidin-1-yl carbonyl) amino]-6-{5-[4-(3,4-dichlorophenethoxy)phenylmethyl]-[1,2,4]oxadiazol-3-yl}-6-oxo-hexyl]-amine;  
[5-[(phenylmethylloxy carbonyl)amino]-6-{5-[4-(3,4-dimethylphenethyl)aminocarbonyl)-phenylmethyl]-[1,2,4]oxadiazol-3-yl}-6-oxo-hexyl]-amine;  
[5-[(phenylmethylloxy carbonyl) amino]-6-{5-[4-[(phenylmethyl)-aminocarbonyl)-phenylmethyl]-[1,2,4]oxadiazol-3-yl}-6-oxo-hexyl]-amine;  
[5-[(phenylmethylloxy carbonyl) amino]-6-{5-[4-[(phenylmethyl)-aminocarbonyl)-phenylmethyl]-[1,2,4]oxadiazol-3-yl}-6-oxo-hexyl]-amine;  
[5-[(phenylmethylloxy carbonyl) amino]-6-{5-[4-[(3,4-dimethylphenethyl)aminocarbonyl)-phenylmethyl]-[1,2,4]oxadiazol-3-yl}-6-oxo-hexyl]-amine;  
[5-[(2,5-dimethylfuran-3-yl carbonyl) amino]-6-{5-[4-(3,4-dichlorophenethoxy)-phenylmethyl]-[1,2,4]oxadiazol-3-yl}-6-oxo-hexyl]-amine;  
[5-[(phenylmethylloxy carbonyl) amino]-6-{5-[4-(3-trifluoromethoxyphenethoxy)phenylmethyl]-[1,2,4]oxadiazol-3-yl}-6-oxo-hexyl]-amine;  
[5-[(phenylmethylloxy carbonyl) amino]-6-{5-[4-(phenethylaminocarbonyl)phenylmethyl]-[1,2,4]oxadiazol-3-yl}-6-oxo-hexyl]-amine;  
[5-[(phenylmethylloxy carbonyl) amino]-6-{5-[4-[(4-phenylbutyl)-aminocarbonyl)-phenylmethyl]-[1,2,4]oxadiazol-3-yl}-6-oxo-hexyl]-amine;  
[5-[(phenylmethylloxy carbonyl) amino]-6-{5-[4-[(3-phenylpropyl)-oxy]-phenylcyclopropyl]-[1,2,4]oxadiazol-3-yl}-6-oxo-hexyl]-amine;
[5-[(phenylethoxy carbonyl)amino]-6-\{5-[(3-phenylpropyl)-oxy]-phenylmethyl]-
[1,2,4]oxadiazol-3-yl\}-6-oxo-hexyl]-amine;

[5-[(phenylethoxy carbonyl)amino]-6-\{5-4-[(R)-carboxy-2-phenylethyl-
aminocarboxyl]-phenylmethyl\}-[1,2,4]oxadiazol-3-yl\}-6-oxo-hexyl]-amine;

[5-[(phenylethoxy carbonyl)amino]-6-\{5-4-[(phenylmethyl)-oxy]-phenylmethyl]
[1,2,4]oxadiazol-3-yl\}-6-oxo-hexyl]-amine;

[5-[(phenylethoxy carbonyl)amino]-6-\{5-4-2-[4-(trifluoromethyl)-phenyl]-
ethylaminocarboxyl\}-phenylmethyl]-[1,2,4]oxadiazol-3-yl\}-6-oxo-hexyl]-amine;

[5-[(1-cyanocycloprop-1-ylcarbonyl)amino]-6-\{5-4-(3,4-dichlorophenethyl-oxy)-
phenylmethyl\}-[1,2,4]oxadiazol-3-yl\}-6-oxo-hexyl]-amine;

[5-[(phenylethoxy carbonyl)amino]-6-\{5-4-(4-chlorophenethyl-oxy)-phenylmethyl]
[1,2,4]oxadiazol-3-yl\}-6-oxo-hexyl]-amine;

[5-[(phenylethoxy carbonyl)amino]-6-\{5-4-(cyclohexylethoxy)-phenylmethyl]-
[1,2,4]oxadiazol-3-yl\}-6-oxo-hexyl]-amine;

[5-[(3,5-difluorophenylcarbonyl)amino]-6-\{5-4-(3-chlorophenethylaminocarboxyl)
phenylmethyl\}-[1,2,4]oxadiazol-3-yl\}-6-oxo-hexyl]-amine;

[5-[(3,4-difluorophenylcarbonyl)amino]-6-\{5-4-(3-chlorophenethylaminocarboxyl)
phenylmethyl\}-[1,2,4]oxadiazol-3-yl\}-6-oxo-hexyl]-amine;

[5-[(3-fluorophenylcarbonyl)amino]-6-\{5-4-(3-chlorophenethylaminocarboxyl)
phenylmethyl\}-[1,2,4]oxadiazol-3-yl\}-6-oxo-hexyl]-amine;

[5-[(4-fluorophenylcarbonyl)amino]-6-\{5-4-(3-chlorophenethylaminocarboxyl)
phenylmethyl\}-[1,2,4]oxadiazol-3-yl\}-6-oxo-hexyl]-amine;

[5-[(4-chlorophenylcarbonyl)amino]-6-\{5-4-(3-chlorophenethylaminocarboxyl)
phenylmethyl\}-[1,2,4]oxadiazol-3-yl\}-6-oxo-hexyl]-amine;

[5-[(3,4-difluorophenylcarbonyl)amino]-6-\{5-4-(2-thien-2-yl)ethylaminocarboxyl)
phenylmethyl\}-[1,2,4]oxadiazol-3-yl\}-6-oxo-hexyl]-amine;

[5-[(4-fluorophenylsulfonyl)amino]-6-\{5-4-(3,4-dichlorophenethyl-oxy)-phenylmethyl]
[1,2,4]oxadiazol-3-yl\}-6-oxo-hexyl]-amine;

[5-[(3,4-difluorophenylcarbonyl)amino]-6-\{5-4-(phenethylaminocarboxyl)-
phenylcyclopropyl\}-[1,2,4]oxadiazol-3-yl\}-6-oxo-hexyl]-amine;
[5-[(4-fluorophenylcarbonyl)amino]-6-{{5-[4-(2-thien-2-yl)ethylaminocarbonyl]phenylmethyl}[1,2,4]oxadiazol-3-yl}-6-oxo-hexyl]-amine;

[5-[(tert-butylcarbonyl)amino]-6-{{5-[4-(3-chlorophenethylaminocarbonyl)phenylmethyl][1,2,4]oxadiazol-3-yl}-6-oxo-hexyl]-amine;

[5-[(tert-butylcarbonyl)amino]-6-{{5-[4-(2-thien-2-yl)ethylaminocarbonyl]phenylmethyl}[1,2,4]oxadiazol-3-yl}-6-oxo-hexyl]-amine;

[5-[(phenylmethoxy carbonyl)amino]-6-{{3-[4-(phenethyloxy)]-phenylmethyl}[1,2,4]oxadiazol-3-yl}-6-oxo-hexyl]-amine;

[5-[(phenylmethoxy carbonyl)amino]-6-{{5-[4-(thien-3-ylcarbonyl)phenylmethyl][1,2,4]oxadiazol-3-yl}-6-oxo-hexyl]-amine;

[5-[(phenylmethoxy carbonyl)amino]-6-{{5-[4-(3,4-dichloro phenylcarbonylmethoxy)]-phenylmethyl}[1,2,4]oxadiazol-3-yl}-6-oxo-hexyl]-amine;

[5-[(phenylmethoxy carbonyl)amino]-6-{{5-[4-(3,4-dichlorophenyl carbonyl methoxy)]-phenylmethyl}[1,2,4]oxadiazol-3-yl}-6-oxo-hexyl]-amine;

[5-[(phenylmethoxy carbonyl)amino]-6-{{5-[4-(2,3-dichlorothien-5-yl carbonylmethoxy)]-phenylmethyl}[1,2,4]oxadiazol-3-yl}-6-oxo-hexyl]-amine;

[5-[(phenylmethoxy carbonyl)amino]-6-{{5-[4-(4-cyanophenyl carbonylmethoxy)]-phenylmethyl}[1,2,4]oxadiazol-3-yl}-6-oxo-hexyl]-amine;

[5-[(phenylmethoxy carbonyl)amino]-6-{{5-[4-(2,3-dichlorothien-5-yl carbonylmethoxy)]-phenylmethyl}[1,2,4]oxadiazol-3-yl}-6-oxo-hexyl]-amine;

[5-[(phenylmethoxy carbonyl)amino]-6-{{5-[4-(3-phenylpropyl)piperazin-1-ylcarbonyl]phenylmethyl}[1,2,4]oxadiazol-3-yl}-6-oxo-hexyl]-amine;
[5-((phenylmethylloxycarbonyl)amino)-6-{5-[4-(4-phenylbutyl)-piperazin-1-ylmethyl]oxadiazol-3-yl}-6-oxo-hexyl]-amine;
[5-((phenylmethylloxycarbonyl)amino)-6-{5-[4-(3-phenylpropyl)-piperazin-1-ylmethyl]oxadiazol-3-yl}-6-oxo-hexyl]-amine;
[5-((ethoxycarbonyl)amino)-6-{5-[2-(phenylmethyl)-benzofuran-5-ylmethyl]oxadiazol-3-yl}-6-oxo-hexyl]-amine;
[5-((phenylmethylloxycarbonyl)amino)-6-{5-[4-(3-phenylpropyl)carbonyl]-piperazin-1-ylmethyl}-{1,2,4}oxadiazol-3-yl]-6-oxo-hexyl]-amine;
[5-((phenylmethylloxycarbonyl)amino)-6-{5-[4-(phenylethoxy)-(3-acetylphenyl)methyl]}{1,2,4}oxadiazol-3-yl]-6-oxo-hexyl]-amine;
[5-[(phenylmethylloxycarbonyl)amino]-6-{5-[4-(phenylethoxy)-(3-cyanophenyl)methyl]}{1,2,4}oxadiazol-3-yl]-6-oxo-hexyl]-amine;
[5-[(phenylmethylloxycarbonyl)amino]-6-{5-[4-(phenethylcarbonyl)piperazin-1-ylmethyl]}{1,2,4}oxadiazol-3-yl]-6-oxo-hexyl]-amine;
[5-[(phenylmethylloxycarbonyl)amino]-6-{5-[4-(phenethylcarbonyl)piperazin-1-ylmethyl]}{1,2,4}oxadiazol-3-yl]-6-oxo-hexyl]-amine;
[5-[(phenylmethylloxycarbonyl)amino]-6-{5-[(3-phenethylaminocarbonyloxy)phenylmethyl]}
{1,2,4}oxadiazol-3-yl]-6-oxo-hexyl]-amine;
[5-[(phenylmethylloxycarbonyl)amino]-6-{5-[3-(phenethylaminocarbonyloxy)-phenylmethyl]}{1,2,4}oxadiazol-3-yl]-6-oxo-hexyl]-amine;
[5-[(phenylmethylloxycarbonyl)amino]-6-{5-{3-[3-(phenethylaminocarbonyloxy)-phenylmethyl]oxadiazol-3-yl}-6-oxo-hexyl]-amine;
[5-[(phenylmethylloxycarbonyl)amino]-6-{5-{3-[3-(phenethylaminocarbonyloxy)-phenylmethyl]oxadiazol-3-yl}-6-oxo-hexyl]-amine;
[5-[(phenylmethylloxycarbonyl)amino]-6-{5-{4-(3,4-dichlorophenylethoxy)-phenylmethyl]oxadiazol-3-yl}-6-oxo-hexyl]-amine;
[5-[(phenylmethylloxycarbonyl)amino]-6-{5-{4-(3,4-dichlorophenylethoxy)-phenylmethyl]oxadiazol-3-yl}-6-oxo-hexyl]-amine;
[5-[(phenylmethylloxycarbonyl)amino]-6-{5-{4-(3,4-dichlorophenylethoxy)-phenylmethyl]oxadiazol-3-yl}-6-oxo-hexyl]-amine;
[5-[(4-fluorophenylcarbonyl)amino]-6-{5-[4-(phenethylaminocarbonyl)-piperazin-1-ylmethyl]}{1,2,4}oxadiazol-3-yl]-6-oxo-hexyl]-amine;}
ylmethyl}-[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine;

[5-{(phenylmethyloxy)carbonyl}amino]-6-{5-{4-(2-fluorophenylmethyl)-piperazin-1-yl}carbonyl}-[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine;

[5-{(phenylmethyloxy)carbonyl}amino]-6-{5-{4-(phenethoxy)-phenylmethyl}-[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine;

[5-{(phenylmethyloxy)carbonyl}amino]-6-{5-{4-(phenethoxy)-3-acetyl-phenylmethyl}-[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine;

2-[(phenethoxycarbonyl)amino]-3-{5-{4-(phenethoxy)-phenylmethyl}-[1,2,4]oxadiazol-3-yl]-3-oxo-1-(1H-pyrrolo[3,2-c]pyridin-2-yl) propane;

[5-{(phenylmethyloxy)carbonyl}amino]-6-{5-{4-(phenethoxy)-phenylmethyl}-[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine;

2-[(ethoxycarbonyl)amino]-3-{5-{4-(phenethyaminocarbonyl)-piperazinylmethyl}-[1,2,4]oxadiazol-3-yl]-3-oxo-1-[4-(aminomethyl)phenyl]-propane;

2-[(ethoxycarbonyl)amino]-3-{5-{4-(phenethylpropylcarbonyl)-piperazinylmethyl}-[1,2,4]oxadiazol-3-yl]-3-oxo-1-[4-(aminomethyl)phenyl]-propane;

[5-{(phenylmethyloxy)carbonyl}amino]-6-{5-{4-(3,4-dichloro-phenethoxy)-phenylmethyl}-[1,2,4]oxadiazol-3-yl]-4-oxo]-1-(guanidinocarbonyl)-butane;

[5-{(phenylmethyloxy)carbonyl}amino]-6-{5-{4-(1-(4-chlorophenyl)-cycloprop-1-ylmethyloxy)-phenylmethyl}-[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine; and

[5-{(4-fluorophenylcarbonyl)amino}-6-{5-{4-(morpholin-4-yl-carbonylmethyl)-piperazinylmethyl}-[1,2,4]oxadiazol-3-yl]-6-oxo-hexyl]-amine.

28. A pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula I and a pharmaceutically acceptable excipient.

29. A process of preparing a Compound of Formula I comprising:

(a) reacting an intermediate of Formula 7:

\[
\begin{align*}
\text{PG}^2 \text{HN} & , \\
\text{N} & , \\
\text{O} & , \\
W & , \\
\text{Ar}^2 \text{OH} & , \\
\text{NHPG}^1 & 
\end{align*}
\]
where PG\(^1\) is a N-protecting group, such as tert-butoxycarbonyl (Boc) or 9-fluorenlymethoxycarbonyl (Fmoc), and the like; PG\(^2\) is N-protecting group, such as benzyloxy carbonyl (CBz), and the like; and W and Ar\(^2\) are as defined above for a compound of Formula I, including preferred embodiments; with an alcohol of the formula Ar\(^3\)-Y\(^2\)-OH or an isocyanate of formula Ar\(^3\)-Y\(^2\)-NCO where Y\(^2\) and Ar\(^3\) are as defined above, including preferred embodiments; optionally oxidizing the hydroxy; optionally removing the protecting group(s); and optionally further modifying the deprotected amine(s) to yield a compound of Formula I;

(b) reacting an intermediate of formula 16:

\[
\begin{align*}
\text{PG}^2\text{HN} & \quad \text{N} \quad \text{N} \quad \text{O} \\
\text{W} & \quad \text{Ar}^2 \\
\text{LG} & \\
\text{NHPG}^1
\end{align*}
\]

where PG\(^1\) is a N-protecting group, such as tert-butoxycarbonyl (Boc) or 9-fluorenlymethoxycarbonyl (Fmoc), and the like; PG\(^2\) is N-protecting group, such as benzyloxy carbonyl (CBz), and the like; and W and Ar\(^2\) are as defined above for a compound of Formula I, including preferred embodiments; and LG is a leaving group under acylating conditions, e.g., LG is -OH in the presence of a coupling agent or LG is halo; with an amine of formula Ar\(^3\)-Y\(^2\)-NHR\(^{22}\), where Y\(^2\), R\(^{22}\), and Ar\(^3\) are as defined above, including preferred embodiments; optionally oxidizing the hydroxy; optionally removing the protecting group(s); and optionally further modifying the deprotected amine(s) to yield a compound of Formula I;

(c) reacting an intermediate of formula 27:

\[
\begin{align*}
\text{H}_2\text{N} & \quad \text{OPG}^3 \\
\text{N} & \quad \text{N} \quad \text{O} \\
\text{NHPG}^1 \\
\text{O} & \quad \text{Y}^2\cdot\text{Ar}^3
\end{align*}
\]

where PG\(^1\) is a N-protecting group, such as tert-butoxycarbonyl (Boc) or 9-fluorenlymethoxycarbonyl (Fmoc), and the like; PG\(^3\) is an O-protecting group, such as tert-butyldimethylsilyl (TBDMS), and the like; and Y\(^2\) and Ar\(^3\) are as defined above for a
compound of Formula I, including preferred embodiments; with

(1) an intermediate of formula $\text{R}^{14}\text{X}$ where $X$ is halo and $\text{R}^{14}$ is alkyl, substituted alkyl, aryl, aralkyl, aralkenyl, heteroaryl, heteroaralkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, or heterocycloalkylalkyl; optionally removing the O-protecting group; optionally oxidizing the deprotected hydroxy; optionally removing the N-protecting group; and optionally further modifying the deprotected amine to yield a compound of Formula I;

(2) an intermediate of formula $\text{RC(O)LG}$ where LG is a leaving group under acylating conditions, e.g., -OH in the presence of a coupling agent or halo, and $\text{R}$ is alkyl, cyanoalkyl, haloalkyl, haloalkoxy, alkenyloxy, alkoxy, alkoxyalkyl, alkoxyalkyloxy, alkoxy carbonylamino, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, heterocycloalkyl, aryloxy, heteroaryloxy, cycloalkyloxy, heterocycloalkyloxy, aralkyloxy, aralkenyloxy, heterocycloalkylalkyloxy, heteroaralkyloxy, or heteroaralkenyloxy; optionally removing the O-protecting group; optionally oxidizing the deprotected hydroxy; optionally removing the N-protecting group; and optionally further modifying the deprotected amine to yield a compound of Formula I;

(3) an intermediate of formula $\text{R}^{21}\text{S(O)}_{2}\text{LG}$ where LG is a leaving group under sulfonylating reaction conditions; optionally removing the O-protecting group; optionally oxidizing the deprotected hydroxy; optionally removing the N-protecting group; and optionally further modifying the deprotected amine to yield a compound of Formula I;

(4) an intermediate of formula $\text{R}^{19}\text{R}^{20}\text{NC(O)LG}$ where LG a leaving group under acylating reaction conditions; optionally removing the O-protecting group; optionally oxidizing the deprotected hydroxy; optionally removing the N-protecting group; and optionally further modifying the deprotected amine to yield a compound of Formula I; or

(5) an intermediate of formula $\text{R}^{19}\text{R}^{20}\text{NS(O)}_{2}\text{LG}$ where LG is a leaving group under sulfonylating reaction conditions; optionally removing the O-protecting group; optionally oxidizing the deprotected hydroxy; optionally removing the N-protecting group; and optionally further modifying the deprotected amine to yield a compound of Formula I;
(d) reacting an intermediate of formula 30:

\[
\begin{array}{c}
\text{PG}^2\text{HN} \\
\text{N-O} \\
\text{Cl} \\
\text{NHPG}^1
\end{array}
\]

where PG\(^1\) is a N-protecting group, such as tert-butoxycarbonyl (Boc) or 9-fluorenylethoxycarbonyl (Fmoc), and the like, and PG\(^2\) is N-protecting group, such as benzylxycarbonyl (CBz), and the like; with an amine of formula 31:

\[
\begin{array}{c}
\text{HN} \\
\text{N-E}
\end{array}
\]

where E is as defined above for a compound of Formula I, including preferred embodiments; optionally oxidizing the hydroxy; optionally removing the protecting group(s); and optionally further modifying the deprotected amine(s) to yield a compound of Formula I;

(e) reacting an intermediate of formula 36:

\[
\begin{array}{c}
\text{PG}^2\text{HN} \\
\text{N-O} \\
\text{N} \\
\text{NH}
\end{array}
\]

where PG\(^1\) is a N-protecting group, such as tert-butoxycarbonyl (Boc) or 9-fluorenylethoxycarbonyl (Fmoc), and the like, and PG\(^2\) is N-protecting group, such as benzylxycarbonyl (CBz), and the like; with a halide of formula halo-\(\text{Y}^2\)-Ar\(^3\) and \(\text{Y}^2\) and Ar\(^3\) are as defined above for a compound of Formula I, including preferred embodiments; optionally oxidizing the hydroxy; optionally removing the protecting group(s); and optionally further modifying the deprotected amine(s) to yield a compound of Formula I;

(f) optionally modifying any of the R\(^1\), R\(^2\), W, Ar\(^1\), Ar\(^2\), and Ar\(^3\) groups in the product(s) from Methods (a)-(e); or

(g) optionally separating individual isomers yielded in Methods (a)-(f).

30. Use of a compound of any of the Claims 1-28 for the manufacture of a medicament for the
31. The use of Claim 30 where the animal is human.

32. Use of a compound of any of the Claims 1-28 for the manufacture of a medicament for the treatment, in an animal, of an immunomeditated respiratory disease independently selected from the group consisting of asthma, COPD, and allergic rhinitis.

33. The use of Claim 32 wherein the syndrome is asthma.

34. Use of a compound of any of the Claims 1-28 for the manufacture of a medicament for the treatment, in an animal, of an immunomeditated respiratory disease independently selected from the group consisting of asthma, COPD, and allergic rhinitis, in an animal which method comprises administering to said animal a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula I and a pharmaceutically acceptable excipient in combination with one or more compound(s) independently selected from the group consisting of a β-2 adrenoreceptor agonist, corticosteroid, leukotriene antagonist, phosphodiesterase 4 inhibitor, and antihistamine.

35. The method of Claim 34 wherein the β-2 adrenoreceptor agonist is salmeterol or levalbuterol, the corticosteroid is budesonide or fluticasone, the leukotriene D4 antagonist is montelukast, and the phosphodiesterase 4 inhibitor is roflumilast.
## INTERNATIONAL SEARCH REPORT

### A. CLASSIFICATION OF SUBJECT MATTER

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<th>C07D271/06</th>
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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 A61P

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, CHEM ABS Data, WPI Data, BEILSTEIN Data

### C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Further documents are listed in the continuation of Box C.

| X | See patent family annex. |

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Date of the actual completion of the international search: 10 March 2006

Date of mailing of the international search report: 16/03/2006

Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel: (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016

Authorized officer: Usuelli, A
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