OMEGA-CARBOXY ARYL SUBSTITUTED DIPHENYL UREAS AS P38 KINASE INHIBITORS

Inventors: Bernd Riedl, Wupperral (DE); Jacques Dumas, Orange, CT (US); Uday Khire, Hamden, CT (US); Timothy B. Lowinger, Nishinomiya City (JP); William J. Scott, Guilford, CT (US); Roger A. Smith, Madison, CT (US); Jill E. Wood, Hamden, CT (US); Mary-Katherine Monahan, Hamden, CT (US); Reina Latero, Hamden, CT (US); Joel Renick, Milford, CT (US); Robert N. Sibley, North Haven, CT (US)

Correspondence Address: MILLEN, WHITE, ZELANO & BRANIGAN, P.C., 2200 CLARENDON BLVD., SUITE 1400 ARLINGTON, VA 22201 (US)

Appl. No.: 12/249,386
Filed: Oct. 10, 2008

Related U.S. Application Data
Continuation of application No. 11/845,597, filed on Aug. 27, 2007, which is a division of application No. 10/086,417, filed on Mar. 4, 2002, now abandoned, which is a continuation of application No. 09/425,229, filed on Oct. 22, 1999, now abandoned, which is a continuation-in-part of application No. 09/257,265, filed on Feb. 25, 1999, now abandoned.

Provisional application No. 60/115,878, filed on Jan. 13, 1999.

Publication Classification
Int. Cl.
A61K 31/17  (2006.01)
A61K 31/4035  (2006.01)
A61K 31/4412  (2006.01)
A61K 31/5375  (2006.01)
A61K 31/495  (2006.01)
A61K 31/496  (2006.01)
A61K 31/4453  (2006.01)
A61K 31/341  (2006.01)
A61K 31/4930  (2006.01)
A61P 35/00  (2006.01)
A61P 19/00  (2006.01)

U.S. Cl. 514/231.2, 514/597; 514/598; 514/417; 514/416; 514/349; 514/350; 514/237.8; 514/255.01; 514/253.01; 514/331; 514/471; 514/428

ABSTRACT
This invention relates to the use of a group of aryl ureas in treating p38 mediated diseases, and pharmaceutical compositions for use in such therapy.
OMEGA-CARBOXY ARYL SUBSTITUTED DIPHENYL UREAS AS P38 KINASE INHIBITORS

CROSS-REFERENCE TO RELATED APPLICATIONS

This is a continuation-in-part of Ser. No. 09/257,265 filed Feb. 25, 1999 and a continuation-in-part of Ser. No. 60/115,878 filed Jan. 13, 1999.

FIELD OF THE INVENTION

This invention relates to the use of a group of aryl urreas in treating cytokine mediated diseases and proteolytic enzyme mediated diseases, and pharmaceutical compositions for use in such therapy.

BACKGROUND OF THE INVENTION

Two classes of effector molecules which are critical for the progression of rheumatoid arthritis are pro-inflammatory cytokines and tissue degrading proteases. Recently, a family of kinases was described which is instrumental in controlling the transcription and translation of the structural genes coding for these effector molecules.

The mitogen-activated protein (MAP) kinase family is made up of a series of structurally related proline-directed serine/threonine kinases which are activated either by growth factors (such as EGF) and phorbol esters (ERK), or by IL-1, TNFα or stress (p38, JNK). The MAP kinases are responsible for the activation of a wide variety of transcription factors and proteins involved in transcriptional control of cytokine production. A pair of novel protein kinases involved in the regulation of cytokine synthesis was recently described by a group from SmithKline Beecham (Lee et al. Nature 1994, 372, 739).

These enzymes were isolated based on their affinity to bond to a class of compounds, named CSAILDs (cytokine suppressive anti-inflammatory drugs) by SKB. The CSAILDs, bicyclic pyridyl imidazole, have been shown to have cytokine inhibitory activity both in vitro and in vivo. The isolated enzymes, CSBP-1 and -2 (CSAILD binding protein 1 and 2) have been cloned and expressed. A murine homologue for CSBP-2 has also been reported (Han et al. Science 1994, 265, 808).

Early studies suggested that CSAILDs function by interfering with mRNA translational events during cytokine biosynthesis. Inhibition of p38 has been shown to inhibit both cytokine production (e.g., TNFα, IL-1, IL-6, IL-8) and proteolytic enzyme production (e.g., MMP-1, MMP-3) in vitro and/or in vivo.


TNFα levels have also been related to host-versus-graft reactions (Piguet et al. Immunol. Ser. 1992, 56, 409) including ischemia reperfusion injury (Colletti et al. J. Clin.


Because inhibition of p38 leads to inhibition of TNFα production, p38 inhibitors will be useful in treatment of the above listed diseases.


Because inhibition of p38 leads to inhibition of MMP production, p38 inhibitors will be useful in treatment of the above diseases.

Inhibitors of p38 are active in animal models of TNFα production, including a murine lipo polysaccharide (LPS) model of TNFα production. Inhibitors of p38 are active in a number of standard animal models of inflammatory diseases, including carrageenan-induced edema in the rat paw, an arachidonic acid-induced edema in the rat paw, an arachidonic acid-induced peritonitis in the mouse, fetal rat bone resorption, murine type II collagen-induced arthritis, and Freund’s adjuvant-induced arthritis in the rat. Thus, inhibitors of p38 will be useful in treating diseases mediated by one or more of the above-mentioned cytokines and/or proteolytic enzymes.

The need for new therapies is especially important in the case of arthritic diseases. The primary disabling effect of osteoarthritis, rheumatoid arthritis, and septic arthritis is the progressive loss of articular cartilage and thereby normal joint function. No marketed pharmaceutical agent is able to prevent or slow this cartilage loss, although nonsteroidal anti-inflammatory drugs (NSAIDs) have been given to control pain and swelling. The end result of these diseases is total loss of joint function which is only treatable by joint replacement surgery. P38 inhibitors will halt or reverse the progression of cartilage loss and obviate or delay surgical intervention.

Several patents have appeared claiming polyaryluminolizes and/or compounds containing polyaryluminolizes as inhibitors of p38 for example, Lee et al. WO 95/07922; Adams et al. WO 95/02591; Adams et al. WO 95/13067; Adams et al. WO 95/31451. It has been reported that aryluminolizes complex to the ferric form of cytochrome P450iso (Harris et al. Mol. Eng. 1995, 5, 143, and references therein), causing concern that these compounds may display structure-related toxicity (Howard-Martin et al. Toxicol. Pathol. 1987, 15, 569). Therefore, there remains a need for improved p38 inhibitors.

SUMMARY OF THE INVENTION

This invention provides compounds, generally described as aryl ureas, including both aryl and heteroaryl analogues, which inhibit p38 mediated events and thus inhibit the production of cytokines (such as TNFα, IL-1 and IL-8) and proteolytic enzymes (such as MMP-1 and MMP-3). The invention also provides a method of treating a cytokine mediated disease state in humans or mammals, wherein the cytokine is one whose production is affected by p38. Examples of such cytokines include, but are not limited to TNFα, IL-1 and IL-8. The invention also provides a method of treating a protease mediated disease state in humans or mammals, wherein the protease is one whose production is affected by p38. Examples of such proteases include, but are not limited to collagenase (MMP-1) and stromelysin (MMP-3).

Accordingly, these compounds are useful therapeutic agents for such acute and chronic inflammatory and/or immunomodulatory diseases such as rheumatoid arthritis, osteoarthritis, septic arthritis, rheumatic fever, bone resorption, postmenopausal osteoporosis, sepsis, gram negative sepsis, septic shock, endotoxic shock, toxic shock syndrome, systemic inflammatory response syndrome, inflammatory bowel diseases including Crohn’s disease and ulcerative colitis, Jarisch-Herxheimer reactions, asthma, adult respiratory distress syndrome, acute pulmonary fibrotic diseases, pulmonary sarcoidosis, allergic respiratory diseases, silicosis, coal worker’s pneumoconiosis, alveolar injury, hepatic failure, liver disease during acute inflammation, severe alcoholic hepatitis, malaria including Plasmodium falciparum malaria.
and cerebral malaria, non-insulin-dependent diabetes mellitus (NIDDM), congestive heart failure, damage following heart disease, atherosclerosis, Alzheimer’s disease, acute encephalitis, brain injury, multiple sclerosis including demyelination and oligoden-drocyte loss in multiple sclerosis, advanced cancer, lymphoid malignancies, tumor metastasis, pancreatitis, including systemic complications in acute pancreatitis, impaired wound healing in infection, inflammation and cancer, periodontal diseases, corneal ulceration, proteinuria, myelodysplastic syndromes, systemic lupus erythematous, biliary cirrhosis, bowel necrosis, psoriasis, radiation injury, toxicity following administration of monoclonal antibodies such as OKT3, host-versus-graft reactions including ischemia reperfusion injury and allograft rejections including kidney, liver, heart, and skin allograft rejections, lung allograft rejection including chronic lung allograft rejection (obiterative bronchitis) as well as complications due to total hip replacement, and infectious diseases including tuberculosis, Helicobacter pylori infection during peptic ulcer disease, Chaga’s disease resulting from Trypanosoma cruzi infection, effects of Shiga-like toxin resulting from E. coli infection, effects of enterotoxin A resulting from Staphylococ- cus infection, meningococcal infection, and infections from Borrelia burgdorferi, Treponema pallidum, cytomegalo-virus, influenza virus, Theiler’s encephalomyelitis virus, and the human immunodeficiency virus (HIV).

[0015] The present invention, therefore, provides compounds generally described as aryl ureas, including both aryl and heteroaryl analogues, which inhibit the p38 pathway. The invention also provides a method for treatment of p38-mediated disease states in humans or mammals, e.g., disease states mediated by one or more cytokines or proteolytic enzymes produced and/or activated by a p38 mediated process. Thus, the invention is directed to compounds, compositions, and methods for the treatment of diseases mediated by p38 kinase wherein a compound of Formula I is administered or a pharmaceutically acceptable salt thereof.

A-D-B

[0016] A is a substituted moiety of up to 40 carbon atoms of the formula: -L-M-L', where L is a 5 or 6 membered cyclic structure bound directly to D, L' comprises a substituted cyclic moiety having at least 5 members, M is a bridging group having at least one atom, q is an integer of from 1-3; and each cyclic structure of L and L' contains 0-4 members of the group consisting of nitrogen, oxygen, and sulfur, and

[0017] B is a substituted or unsubstituted, up to tricyclic aryl or heteroaryl moiety of up to 30 carbon atoms with at least one 6-member cyclic structure bound directly to D containing 0-4 members of the group consisting of nitrogen, oxygen and sulfur,

[0018] wherein L is substituted by at least one substituent selected from the group consisting of: −SO3R, −CO(O)R, and −CN(R)R.

[0019] R is hydrogen or a carbon based moiety of up to 24 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally halogen substituted, up to per halo,

[0020] R is hydrogen or a carbon based moiety of up to 30 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen, hydroxy and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen;

[0021] R is R or NR, where R and R are independently hydrogen,

[0023] a) a carbon based moiety of up to 30 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen, hydroxy and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen, or

[0024] −OSi(R)3, where R is hydrogen or a carbon based moiety of up to 24 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen, hydroxy and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen; or

[0025] b) R and R together form a 5-7 member heterocyclic structure of 1-3 heteroatoms selected from N, S and O, or a substituted 5-7 member heterocyclic structure of 1-3 heteroatoms selected from N, S and O substituted by halogen, hydroxy or carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen; or

[0026] c) one of R or R is −C(O)−, a C1-C6 divalent alkylen group or a substituted C1-C6 divalent alkylen group bound to the moiety L to form a cyclic structure with at least 5 members, wherein the substituents of the substituted C1-C6 divalent alkylen group are selected from the group consisting of halogen, hydroxy, and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen;

[0027] wherein B is substituted, L is substituted or L' is additionally substituted, the substituents are selected from the group consisting of halogen, up to per halio, and W, where n is 0-3;

[0028] wherein each W is independently selected from the group consisting of: −CN, −CO(R)2, −CO(NR)2, −C(O)−R, −NO2, −OR, −SR, −NR2, −NR(C(O) OR)2, −NR(C(O))OR2, −Q-Ar, and carbon based moieties of up to 24 carbon atoms, optionally containing heteroatoms selected from N, S and O and optionally substituted by one or more substituents independently selected from the group consisting of: −CN, −CO(R)2, −C(O)OR, −CO(NR)2, −OR, −SR, −NR2, −NO2, −NR(C(O)OR)2, −NR(C(O))OR2 and halogen up to per halo; with each R' independently selected from H or a carbon based moiety of up to 24 carbon atoms, optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen;

[0029] wherein Q is −O−, −S−, −N(R')−, −(CH2)m−, −C(O)−, −CH(OH)−, −(CH2)nO−, −(CH2)n−, −(CH2)n(NR)−, −(O(CH2)n)−, −CHX2−, −SR−, −(CH2)n−, −N(R')(CH2)m−, where m = 1-3, and X' is halogen; and

[0030] wherein R is a 5- or 6-member aromatic structure containing 0-2 members selected from the group consisting of nitrogen, oxygen and sulfur, which is optionally substituted by halogen, up to per halo, and optionally substituted by Z, wherein Z is independently selected from the group consisting of: −CN, −CO(R)2, −CO(NR)2, −C(O)−R, −NO2, −OR, −SR, −NR2, −NR(C(O))OR2, −NR(C(O))OR2, and a carbon based moiety of up to 24 carbon atoms, optionally containing heteroatoms selected from N, S
and O and optionally substituted by one or more substituents selected from the group consisting of —CN, —CONR₂, —COR₂, —CO(NR₂)₃, —OR₂, —SR₂, —NO₂, —NR₁R₂, —NRC(O)R₂, and —NR₂C(O)OR₂, with R² as defined above.

[0031] In formula 1, suitable hetero groups include, but are not limited to, 5-12 carbon-atom aromatic rings or ring systems containing 1-3 rings, at least one of which is aromatic, in which one or more, e.g., 1-4 carbon atoms in one or more of the rings can be replaced by oxygen, nitrogen or sulfur atoms. Each ring typically has 3-7 atoms. For example, B can be 2- or 3-furyl, 2- or 3-thienyl, 2- or 4-triazinyl, 1-, 2- or 3-pyrydyl, 1-, 2-, 4-, or 5-imidazolyl, 1-, 3-, 4-, or 5-pyrazolyl, 2-, 4-, or 5-pyridyl, 1-, 2-, or 4-pyrazolyl, 2-, 4-, 5-, or 6-pyrimidinyl, 1,2,3-triazol-1-, 4- or 5-yl, 1,2,4-triazol-1-, 3- or 5-yl, 1- or 5-tetrazolyl, 1,2,3-oxidiazol-4- or 5-yl, 1,2,4-oxidazol-3- or 5-yl, 1,3,4-thiadiazol-2-, 3-, 4-, or 5-yl, 1,2,4-oxadiazol-3-, 5-, 1,3,4-thiadiazol-2-, 4- or 5-yl, 1,2,4-oxadiazol-3-, 5-, 1,3,4-thiadiazol-2-, 4-, 5-, 6-, 7-, 8-, 9-quinolizino, 1-, 3- or 5-quinolizino, 1-, 3-, 4-, or 5-thienyl, 2-, 3-, 4-, 5-, 6-, 7-, 8-, 9-, 10-phenyl, or 1- or 2-naphthyl, pyrazinyl, 2-, 3-, 4-, 5-, 6-, 7-benzofuranyl, 2-, 3-, 4-, 5-, 6- or 7-benzothienyl, 1-, 2-, 3-, 4-, 5-, 6- or 7-indolyl, 1-, 2-, 4- or 5-benzimidazolyl, 1-, 3-, 4-, 5-, 6-, or 7-benzopyrazolyl, 2-, 4-, 5-, 6- or 7-benzoxazolyl, 3-, 4-, 5-, 6- or 7-benzoxazolyl, 1-, 3-, 4-, 5-, 6- or 7-benzothiazolyl, 2-, 4-, 5-, 6- or 7-benzisothiazolyl, 2-, 4-, 5-, 6- or 7-benzisoxazolyl, 2-, 3-, 4-, 5-, 6- or 7-benzisoxazolyl, 1-, 2-, 3-, 4-, 5-, 6-, 7-, 8-, 9-quinoxalinyl, 1-, 2-, 3-, 4- or 9-carbazolyl, 1-, 2-, 3-, 4-, 5-, 6-, 7-, 8- or 9-acridinyl, or 2-, 4-, 5-, 6-, 7- or 8-quinazolinyl, or additionally optionally substituted phenyl, 2- or 3-thienyl, 1,3,4-thiadiazolyl, 3-pyrrol, 3-pyrazolyl, 2-thiazolyl or 5-thiazoil, etc. For example, B can be 4-methylphenyl, 5-methyl-2-thienyl, 4-methyl-2-thienyl, 1-methyl-3-pyrryl, 1-methyl-3-pyrazolyl, 5-methyl-2-thiazolyl or 5-methyl-1,2,4-thia diazol-2-yl.

[0032] Suitable alkyl groups and alkyl portions of groups, e.g., alkoxy, etc. throughout include methyl, ethyl, propyl, butyl, etc., including all straight-chain and branched isomers such as isopropyl, isobutyl, sec-butyl, tert-butyl, etc.

[0033] Suitable ary1 groups which do not contain heteroatoms include, for example, phenyl and 1- and 2-naphthyl.

[0034] The term “cycoalkyl”, as used herein, refers to cyclic structures with or without alkyl substituents such that, for example, C₄ cycloalkyl” includes methyl substituted cyclopropyl groups as well as cyclobutyl groups. The term “cycoalkyl”, as used herein also includes saturated heterocyclic groups.

[0035] Suitable halogen groups include F, Cl, Br, and/or I, from one to per substitution (i.e. all H atoms on a group replaced by a halogen atom) being possible where an alkyl group is substituted by halogen, mixed substitution of halogen atoms also being possible on a given moiety.

[0036] The invention also relates to compounds per se, of formula 1.

[0037] The present invention is also directed to pharmaceutically acceptable salts of formula 1. Suitable pharmaceutically acceptable salts include salts of inorganic and organic acids, such as hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, methanesulfonic acid, trifluoromethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, 1-naphthalenesulfonic acid, 2-naphthalenesulfonic acid, acetic acid, trichloroacetic acid, malic acid, tartaric acid, citric acid, lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylacetic acid, and mandelic acid. In addition, pharmaceutically acceptable salts include acid salts of inorganic bases, such as salts containing alkaline cations (e.g., Li⁺, Na⁺ or K⁺), alkaline earth cations (e.g., Mg²⁺, Ca²⁺ or Ba²⁺), the ammonium cation, as well as acid salts of organic bases, including aliphatic and aromatic substituted ammonium, and quaternary ammonium cations, such as those arising from protonation or deprotonation of triethanolamine, N,N-dietanolamine, N,N-dicyclohexylamine, lysine, pyridine, N,N-dimethylaminoxypridine (DMA), 1,4-diazabicolo[2.2.2]octane (DABCO), 1,5-diazabicolo[4.3.4]non-5-ene (DBN) and 1,8-diazabicolo[5.4.0]octa-7-ene (DBU).

[0038] A number of the compounds of Formula 1 possess asymmetric carbons and can therefore exist in racemic and optically active forms. Methods of separation of enantiomeric and diastereomeric mixtures are well known to one skilled in the art. The present invention encompasses all isolated racemic or optically active form of compounds described in Formula 1 which possess p38 kinase inhibitory activity.

General Preparative Methods

[0039] The compounds of Formula 1 may be prepared by use of known chemical reactions and procedures, some from starting materials which are commercially available. Nevertheless, the following general preparative methods are presented to aid one of skill in the art in synthesizing these compounds, with more detailed particular examples being presented in the experimental section describing the working examples.

[0040] Substituted anilines may be generated using standard methods (March. Advanced Organic Chemistry, 3rd Ed.; John Wiley: New York (1985)). Larock. Comprehensive Organic Transformations; VCH Publishers: New York (1989). As shown in Scheme I, aryl amines are commonly synthesized by reduction of nitroaroyls using a metal catalyst, such as Ni, Pd, or Pt, and H₂ or a hydride transfer agent, such as formate, cyclohexadiene, or a borohydride (Rylander. Hydrogenation Methods; Academic Press: London, UK (1985)). Nitroaroyls may also be directly reduced using a strong hydride source, such as LiAlH₄ (Seydah-Penne. Reductions by the Alumino- and Borohydrides in Organic Synthesis; VCH Publishers: New York (1991)), or using a zero valent metal, such as Fe, Sn or Cu, often in acidic media. Many methods exist for the synthesis of nitroaroyls (March. Advanced Organic Chemistry, 3rd Ed.; John Wiley: New York (1985)). Larock. Comprehensive Organic Transformations; VCH Publishers: New York (1989)). As shown in Scheme 1, aryl amines are commonly synthesized by reduction of nitroaroyls using a metal catalyst, such as Ni, Pd, or Pt, and H₂ or a hydride transfer agent, such as formate, cyclohexadiene, or a borohydride (Rylander. Hydrogenation Methods; Academic Press: London, UK (1985)). Nitroaroyls may also be directly reduced using a strong hydride source, such as LiAlH₄ (Seydah-Penne. Reductions by the Alumino- and Borohydrides in Organic Synthesis; VCH Publishers: New York (1991)), or using a zero valent metal, such as Fe, Sn or Cu, often in acidic media. Many methods exist for the synthesis of nitroaroyls (March. Advanced Organic Chemistry, 3rd Ed.; John Wiley: New York (1985)).
Nitroaryls are commonly formed by electrophilic aromatic nitration using HNO₂, or an alternative NO₂⁻ source. Nitroaryls may be further elaborated prior to reduction. Thus, nitroaryls substituted with potential leaving groups (e.g., F, Cl, Br, etc.) may undergo substitution reactions on treatment with nucleophiles, such as thiolate (enamplified in Scheme II) or phenoxide. Nitroaryls may also undergo Ullman-type coupling reactions (Scheme II).

[0041] Nitroaryls may also undergo transition metal mediated cross coupling reactions. For example, nitroaryl electrophiles, such as nitroaryl bromides, iodides or triflates, undergo palladium mediated cross coupling reactions with aryl nucleophiles, such as arylboronic acids (Suzuki reactions, exemplified below), arylthins (Stille reactions) or arylzincs (Negishi reaction) to afford the biaryl (5).

[0042] Either nitroaryl or anilines may be converted into the corresponding arenesulfonyl chloride (7) on treatment with chlorosulphonic acid. Reaction of the sulfonfyl chloride with a fluoride source, such as KF, then affords the sulfonfyl fluoride (8). Reaction of sulfonfyl fluoride 8 with trimethylsilyl trifluoromethanesulphonium hexafluorophosphate (TASF) leads to the corresponding trifluoromethylsulfone (9). Alternatively, sulfonfyl chloride 7 may be reduced to the arenethiol (10), for example with zinc amalgam. Reaction of thiol 10 with CHClF₂ in the presence of base gives the difluoromethyl mercaptan (11), which may be oxidized to the sulfone (12) with any of a variety of oxidants, including CrO₃-acetic anhydride (Sedova et al. Zh. Org. Khim. 1970, 6, 568).

[0043] As shown in Scheme IV, non-symmetrical urea formation may involve reaction of an aryl isocyanate (14) with an aryl amine (13). The heteroaryl isocyanate may be synthesized from a heteroaryl amine by treatment with phosgene or...
a phosphine equivalent, such as trichloromethyl chloroformate (diphosphine), bis(trichloromethyl) carbonate (triphosgene), or N,N'-carbonylphosphoryl azide (CDI). The isocyanate may also be derived from a heterocyclic carboxylic acid derivative, such as an ester, an acid halide or an anhydride by a Curtius-type rearrangement. Thus, reaction of acid derivative 16 with an azide source, followed by rearrangement affords the isocyanate. The corresponding carboxylic acid (17) may also be subjected to Curtius-type rearrangements using diphenylphosphoryl azide (DPPA) or a similar reagent.

![Scheme IV](image)

[0044] Finally, ureas may be further manipulated using methods familiar to those skilled in the art.

[0045] The invention also includes pharmaceutical compositions including a compound of Formula I, and a pharmaceutically acceptable carrier.

[0046] The compounds may be administered orally, topically, parenterally, by inhalation or spray, vaginally, rectally or sublingually in dosage unit formulations. The term “administration by injection” includes intravenous, intramuscular, subcutaneous and parenteral injections, as well as use of infusion techniques. Dermal administration may include topical application or transdermal administration. One or more compounds may be present in association with one or more non-toxic pharmaceutically acceptable carriers and if desired other active ingredients.

[0047] Compositions intended for oral use may be prepared according to any suitable method known to the art for the manufacture of pharmaceutical compositions. Such compositions may contain one or more agents selected from the group consisting of diluents, sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be, for example: inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; and binding agents, for example magnesium stearate, stearic acid or tale. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and adsorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. These compounds may also be prepared in solid, rapidly released form.

[0048] Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin or olive oil.

[0049] Aqueous suspensions containing the active materials in admixture with excipients suitable for use in aqueous suspensions may also be used. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example, lecithin, or condensation products of an alkyene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethylenoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example, ethyl, or n-propyl, p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

[0050] Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example, sweetening, flavoring and coloring agents, may also be present.

[0051] The compounds may also be in the form of non-aqueous liquid formulations, e.g., oily suspensions which may be formulated by suspending the active ingredients in a vegetable oil, for example arachis oil, olive oil, sesame oil or peanut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide palatable oral preparations. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

[0052] Compounds of the invention may also be administered transdermally using methods known to those skilled in the art (see, for example: Chien; “Transdermal Controlled Systemic Medications”; Marcel Dokker, Inc.; 1987. Lipp et al, WO04/041577 3 Mar. 1994). For example, a solution or suspension of a compound of Formula I in a suitable volatile solvent optionally containing penetration enhancing agents can be combined with additional additives known to those skilled in the art, such as matrix materials and bactericides. After sterilization, the resulting mixture can be formulated following known procedures into dosage forms. In addition,
on treatment with emulsifying agents and water, a solution or suspension of a compound of Formula I may be formulated into a lotion or saline.

[0053] Suitable solvents for processing transdermal delivery systems are known to those skilled in the art, and include lower alcohols such as ethanol or isopropyl alcohol, lower ketones such as acetone, lower carboxylic acid esters such as ethyl acetate, polar ethers such as tetrahydrofuran, lower hydrocarbons such as hexane, cyclohexane or benzene, or halogenated hydrocarbons such as dichloromethane, chloroform, trichloro trifluoroethane, or trichloro trifluoroethane. Suitable solvents may also include mixtures of one or more materials selected from lower alcohols, lower ketones, lower carboxylic acid esters, polar ethers, lower hydrocarbons, halogenated hydrocarbons.

[0054] Suitable penetration enhancing materials for transdermal delivery system are known to those skilled in the art, and include, for example, monohydrorxy or polyhydroxy alcohols such as ethanol, propylene glycol or benzyl alcohol, saturated or unsaturated C₃-C₆ fatty acids such as stearic acid, saturated or unsaturated fatty esters with up to 24 carbons such as methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl isobutyl tertbutyl or monoglycerin esters of acetic acid, caprylic acid, lauric acid, myristic acid, stearic acid, or palmitic acid, or diesters of saturated or unsaturated dicarboxylic acids with a total of up to 24 carbons such as diisopropyl adipate, diisobutyl adipate, diisopropyl sebacate, diisopropyl malate, or diisopropyl fumarate. Additional penetration enhancing materials include phosphatidyl derivatives such as lecithin or cephalin, terpenes, amides, ketones, ureas and their derivatives, and ethers such as dimethyl isosorbid and diethylene glycol monoethyl ether. Suitable penetration enhancing formulations may also include mixtures of one or more materials selected from monohydrorxy or polyhydroxy alcohols, saturated or unsaturated C₃-C₆ fatty acids, saturated or unsaturated C₆-C₁₈ fatty esters with up to 24 carbons, diesters of saturated or unsaturated dicarboxylic acids with a total of up to 24 carbons, phosphatidyl derivatives, terpenes, amides, ketones, ureas and their derivatives, and ethers.

[0055] Suitable binding materials for transdermal delivery systems are known to those skilled in the art and include polyacrylates, silicones, polyurethanes, block polymers, styrenebutadiene copolymers, and natural and synthetic rubbers. Cellulose ethers, derivatized polyethylene, and silicones may also be used as matrix components. Additional additives, such as viscosity agents or oils may be added to increase the viscosity of the matrix.

[0056] Pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oil phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soybean, lecithin, and esters or partial esters derived from fatty acids and hexanol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

[0057] Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents.

[0058] The compounds may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal or vaginal temperature and will therefore melt in the rectum or vagina to release the drug. Such materials include cocoa butter and polyethylene glycols.

[0059] For all regimens of use disclosed herein for compounds of Formula I, the daily oral dosage regimen will preferably be from 0.01 to 200 mg/Kg of total body weight. The daily dosage for administration by injection, including intravenous, intramuscular, subcutaneous and parenteral injections, and use of infusion techniques will preferably be from 0.01 to 200 mg/Kg of total body weight. The daily oral dosage regimen will preferably be from 0.01 to 200 mg/Kg of total body weight. The transdermal concentration will preferably be that required to maintain a daily dose of from 0.01 to 200 mg/Kg. The daily topical dosage regimen will preferably be from 0.1 to 200 mg administered between one to four times daily. The daily inhalation dosage regimen will preferably be from 0.01 to 10 mg/Kg of total body weight.

[0060] It will be appreciated by those skilled in the art that the particular method of administration will depend on a variety of factors, all of which are considered routinely when administering therapeutics. It will also be understood, however, that the specific dose level for a given patient depends on a variety of factors, including specific activity of the compound administered, the age of the patient, the body weight of the patient, the general health of the patient, the gender of the patient, the diet of the patient, time of administration, route of administration, the severity of the condition undergoing therapy, etc. It will be further appreciated by one skilled in the art that the optimal course of treatment, i.e., the mode of treatment and the daily number of doses of a compound of Formula I or a pharmaceutically acceptable salt thereof given for a defined number of days, can be ascertained by those skilled in the art using conventional course of treatment tests.

[0061] The compounds of FIG. 1 are producible from known compounds (or from starting materials which, in turn, are producible from known compounds), e.g., through the general preparative methods shown above. The activity of a given compound to inhibitraf kinase can be routinely assayed, e.g., according to procedures disclosed below. The following examples are for illustrative purposes only and are not intended, nor should they be construed to limit the invention in any way.


[0063] The following examples are for illustrative purposes only and are not intended, nor should they be construed to limit the invention in any way.

EXAMPLES

[0064] All reactions were performed in flame-dried or oven-dried glassware under a positive pressure of dry argon
or dry nitrogen, and were stirred magnetically unless otherwise indicated. Sensitive liquids and solutions were transferred via syringe or cannula, and introduced into reaction vessels through rubber septa. Unless otherwise stated, the term "concentration under reduced pressure" refers to use of a Buchi rotary evaporator at approximately 15 mmHg. Unless otherwise stated, the term "under high vacuum" refers to a vacuum of 0.01-0.10 mmHg.

[0065] All temperatures are reported uncorrected in degrees Celsius (°C). Unless otherwise indicated, all parts and percentages are by weight.

[0066] Commercial grade reagents and solvents were used without further purification. N-cyclohexyl-N′-(methylpoly-styrene)carbodiimide was purchased from Calbiochem-Novabiochem Corp. 3-tert-Butylalanine, 3-tert-butyl-2-methoxyaniline, 4-bromo-3-(trifluoromethyl)aniline, 4-chloro-3-(trifluoromethyl)aniline 2-methoxy-5-(trifluoromethyl) aniline, 4-tert-butyl-2-nitroaniline, 3-aminomethanethiol, ethyl 4-isocyanatobenzoate, N-acetyl-4-chloro-2-methoxy-5-(trifluoromethyl)aniline and 4-chloro-3-(trifluoromethyl) phenyl isoacylate were purchased and used without further purification. Syntheses of 3-aminomethoxyquinoline (E. Cho et al. WO 98/00400), A. Cordi et al. EP 542,600, IBID Bioorg. Med. Chem. 3, 1995, 129), 4-(3-carboxypropylenoxy)-1-nitrobenzene (K. Iwakyo Kagaku Zasshi 79, 1959, 760; Chem. Abstr. 53, 1959, 2761b), 3-tert-butylphenyl isoacylate (O. Rohr et al. DE 2,436,108) and 2-methoxy-5-(trifluoromethyl)phenyl isoacylate (K. Iwakyo Kagaku Zasshi 70, 1967, 491) have previously been described.

[0067] Thin-layer chromatography (TLC) was performed using Whatman® pre-coated glass-backed silica gel 60A F-254 250 μ plates. Visualization of plates was effected by one or more of the following techniques: (a) ultraviolet illumination, (b) exposure to iodine vapor, (c) immersion of the plate in a 10% solution of phosphomolybdc acid in ethanol followed by heating, (d) immersion of the plate in a ceric sulfate solution followed by heating, and/or (e) immersion of the plate in an acidic ethanol solution of 2,4-dinitrophenylhydrazine followed by heating. Column chromatography (flash chromatography) was performed using 230-400 mesh EM Science® silica gel.

[0068] Melting points (mp) were determined using a Thomas-Hoover melting point apparatus or a Mettler FP66 automated melting point apparatus and are uncorrected. Fourier transform infrared spectra were obtained using a Mattson 4020 Galaxy Series spectrophotometer. Proton (1H) nuclear magnetic resonance (NMR) spectra were measured with a General Electric GN-Omega 300 (300 MHz) spectrometer with either Me₄Si (δ 0.00) or residual protiated solvent (CHCl₃, δ 7.46; MeOD δ 3.30; DMSO δ 2.49) as standard. Carbon (13C) NMR spectra were measured with a General Electric GN-Omega 300 (75 MHz) spectrometer with solvent (CDCl₃, δ 77.0; MeOD-d₄; δ 49.0; DMSO-d₆ δ 39.5) as standard. Low resolution mass spectra (MS) and high resolution mass spectra (HRMS) were either obtained as electron impact mass spectra (EI-MS) or as fast atom bombardment (FAB) mass spectra. Electron impact mass spectra (EI-MS) were obtained with a Hewlett Packard 5989A mass spectrometer equipped with a Vacumetrics Desorption Chemical Ionization Probe for sample introduction. The ion source was maintained at 250°C. Electron impact ionization was performed with electron energies of 70 eV and a trap current of 300 μA. Liquid-cerium secondary ion mass spectra (FAB-MS), an updated version of fast atom bombardment were obtained using a Kratos Concept 1-1H spectrometer. Chemical ionization mass spectra (CI-MS) were obtained using a Hewlett Packard 5973A-Engine (5989A) with methane or ammonia as the reagent gas (1×10⁻⁴ torr to 2.5×10⁻⁸ torr). The direct insertion desorption chemical ionization (DCl) probe (Vacumetrics, Inc.) was ramped from 0-1.5 amps in 10 sec and held at 10 amps until all traces of the sample disappeared (~1-2 min). Spectra were scanned from 50-800 amu at 2 sec per scan. HPLC-electrospray mass spectra (EIPLC ES-MS) were obtained using a Hewlett-Packard 1100 HPLC equipped with a quaternary pump, a variable wavelength detector, a C18 column, and a Finnigan LCQ ion trap mass spectrometer with electrospray ionization. Spectra were scanned from 120-800 amu using a variable ion time according to the number of ions in the source. Gas chromatography-ion selective mass spectra (GC-MS) were obtained with a Hewlett Packard 5890 gas chromatograph equipped with an HPI-1 methyl silicone column (0.33 mm coating; 25 ms/0.2 mm) and a Hewlett Packard 5971 Mass Selective Detector (ionization energy 70 eV). Elemental analyses are conducted by Petrobank Microlit Labs, Madison N.J.

[0069] All compounds displayed NMR spectra, IRMS and either elemental analysis or HRMS consistent with assigned structures.

List of Abbreviations and Acronyms:

[0070] AcOH acetic acid
anhydrous
atm atmosphere(s)
BOC tert-butoxycarbonyl
CDI 1,1-diisocyanodiisocyanate
coc concentrated
d day(s)
dec decomposition
DMAC N,N-dimethylacetamide
[0071] DMFU 1,3-dimethyl-3,4,5,6-tetrahydro-2H-pyrimidinone
DMF N,N-dimethylformamide
[0072] DMSO dimethylsulfoxide
DPPA diphenylphosphoryl azide
EDCI 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide
EtOAc ethyl acetate
EtOH ethanol (100%)
Et₂O diethyl ether
Et₃N triethylamine
h hour(s)
HOBr 1-hydroxybromotriazolone
mCPBA 3-chloroperbenzoic acid
MeOH methanol
pet. ether petroleum ether (boiling range 30-60°C)
temp. temperature
THF tetrahydrofuran
TFA trifluoroacetic acid
Tf trifluoromethanesulfonfyl
A. General Methods for Synthesis of Substituted Anilines


Step 1. Methyl 3-methoxy-2-naphthoate

A solution of methyl 3-hydroxy-2-naphthoate (10.1 g, 50.1 mmol) and K₂CO₃ (7.96 g, 57.6 mmol) in DMF (200 mL) was stirred at room temp. for 15 min., then treated with iodomethane (3.43 mL, 55.1 mmol). The mixture was allowed to stir at room temp. overnight, then was treated with water (200 mL). The resulting mixture was extracted with EtOAc (2x200 mL). The combined organic layers were washed with a saturated NaCl solution (100 mL), dried (MgSO₄), concentrated under reduced pressure (approximately 0.4 mmHg overnight) to give methyl 3-methoxy-2-naphthoate as an amber oil (10.30 g): 1H-NMR (DMSO-d₆) δ 2.70 (s, 3H), 2.85 (s, 3H), 3.78 (app t, J=8.09 Hz, 1H), 7.44 (s, 1H), 7.53 (app t, J=8.09 Hz, 1H), 7.84 (d, J=8.09 Hz, 1H), 7.90 (s, 1H), 8.21 (s, 1H).

Step 2. 3-Methoxy-2-naphthoic Acid

A solution of methyl 3-methoxy-2-naphthoate (6.28 g, 29.10 mmol) and water (10 mL) in MeOH (100 mL) at room temp. was treated with 1 N NaOH solution (33.4 mL, 33.4 mmol). The mixture was heated at the reflux temp. for 3 h, cooled to room temp., and made acidic with a 10% citric acid solution. The resulting solution was extracted with EtOAc (2x100 mL). The combined organic layers were washed with a saturated NaCl solution, dried (MgSO₄) and concentrated under reduced pressure. The residue was triturated with hexane then washed several times with hexane to give 3-methoxy-2-naphthoic acid as a white solid (5.40 g, 92%): 1H-NMR (DMSO-d₆) δ 3.88 (s, 3H), 7.34-7.41 (m, 2H), 7.49-7.54 (m, 1H), 7.83 (d, J=8.09 Hz, 1H), 7.91 (d, J=8.09 Hz, 1H), 8.19 (s, 1H), 12.83 (br s, 1H).

Step 3. 2-(N-(Carboxbenzyloxy)amino)-3-methoxyphthalene

A solution of 3-methoxy-2-naphthoic acid (3.36 g, 16.6 mmol) and Et₃N (2.59 mL, 18.6 mmol) in anh toluene (70 mL) was stirred at room temp. for 15 min., then treated with a solution of DPPA (5.12 g, 18.6 mmol) in toluene (10 mL) via pipette. The resulting mixture was heated at 80°C for 2 h. After cooling the mixture to room temp., benzyl alcohol (2.06 mL, 20 mmol) was added via syringe. The mixture was then warmed to 80°C overnight. The resulting mixture was cooled to room temp., quenched with a 10% citric acid solution, and extracted with EtOAc (2x100 mL). The combined organic layers were washed with a saturated NaCl solution, dried (MgSO₄) and concentrated under reduced pressure. The residue was purified by column chromatography (14% EtOAc/86% hexane) to give 2-(N-carboxbenzyloxy)amino-3-methoxyphthalene as a pale yellow oil (5.1 g, 100%): 1H-NMR (DMSO-d₆) δ 3.89 (s, 3H), 5.17 (s, 2H), 7.27-7.44 (m, 8H), 7.72-7.75 (m, 2H), 8.20 (s, 1H), 8.76 (s, 1H).

Step 4. 2-Amino-3-methoxyphthalene

A solution of 2-(N-(carboxbenzyloxy)amino-3-methoxyphthalene (5.0 g, 16.3 mmol) and 10% Pd/C (0.5 g) in EtOAc (70 mL) was maintained under a H₂ atm (balloon) at room temp. overnight. The resulting mixture was filtered through Celite® and concentrated under reduced pressure to give 2-amino-3-methoxyphthalene as a pale pink powder (2.40 g, 85%): 1H-NMR (DMSO-d₆) δ 3.86 (s, 3H), 6.86 (s, 2H), 7.04-7.16 (m, 2H), 7.43 (d, J=8.0 Hz, 1H), 7.56 (d, J=8.0 Hz, 1H); EI-MS m/z 173 (M⁺).

Step 1a. Synthesis of 4-chloro-N-methyl-2-pyridinecarboxamide Via the Menisci Reaction

[0078] Caution: this is a highly hazardous, potentially explosive reaction. To a stirring solution of 4-chloropyridine (10.0 g) in N-methylformamide (250 mL) at room temp. was added cone. H₂SO₄ (3.55 mL) to generate an exotherm. To this mixture was added H₂O₂ (30% wt in H₂O, 17 mL) followed by FeSO₄·7H₂O (0.56 g) to generate another exotherm. The resulting mixture was stirred in the dark at room temp. for 1 h, then warmed slowly over 4 h to 45°C. When bubbling had subsided, the reaction was heated at 60°C for 16 h. The resulting opaque brown solution was diluted with H₂O (700 mL) followed by a 10% NaOH solution (250 mL). The resulting mixture was extracted with EtOAc (3×500 mL). The organic phases were washed separately with a saturated NaCl solution (3×150 mL), then they were combined, dried (MgSO₄) and filtered through a pad of silica gel with the aid of EtOAc. The resulting brown oil was purified by column chromatography (gradient from 50% EtOAc/50% hexane to 80% EtOAc/20% hexane). The resulting yellow oil crystallized at 0°C over 72 h to give 4-chloro-N-methyl-2-pyridinecarboxamide (0.61 g, 5.3%); TLC (50% EtOAc/50% hexane) Rₚ 0.50; ¹H NMR (CDCl₃) δ 7.04 (d, J= 5.1 Hz, 3H), 7.43 (dd, J= 5.4, 2.4 Hz, 1H), 7.96 (br s, 1H), 8.21 (s, 1H), 8.44 (d, J= 5.1 Hz, 1H); CI-MS m/z 171 [(M+H)+].

Step 1b. Synthesis of 4-chloropyridine-2-carbonyl chloride HCl Salt Via Picolinic Acid

[0079] Anhydrous DMF (6.0 mL) was slowly added to SOCl₂ (180 mL) between 40° and 50°C. The solution was stirred in that temperature range for 10 min. then picolinic acid (60.0 g, 487 mmol) was added in portions over 30 min. The resulting solution was heated at 72°C. (vigorous SO₂ evolution) for 16 h to generate a yellow solid precipitate. The resulting mixture was cooled to room temp., diluted with toluene (500 mL) and concentrated to 200 mL. The toluene addition/concentration process was repeated twice. The resulting nearly dry residue was filtered and the solids were washed with toluene (2×200 mL) and dried under high vacuum for 4 h to afford 4-chloropyridine-2-carbonyl chloride HCl salt as a yellow-orange solid (92.0 g, 89%).

Step 2a. Synthesis of methyl 4-chloropyridine-2-carboxylate HCl Salt

[0080] Anh DMF (10.0 mL) was slowly added to SOCl₂ (300 mL) at 40-48°C. The solution was stirred at that temp. for 10 min., then picolinic acid (100 g, 812 mmol) was added over 30 min. The resulting solution was heated at 72°C (vigorous SO₂ evolution) for 16 h to generate a yellow solid. The resulting mixture was cooled to room temp., diluted with toluene (500 mL) and concentrated to 200 mL. The toluene addition/concentration process was repeated twice. The resulting nearly dry residue was filtered, and the solids were washed with toluene (50 mL) and dried under high vacuum for 4 hours to afford 4-chloropyridine-2-carbonyl chloride HCl salt as an off-white solid (27.2 g, 16%). This material was set aside.

[0081] The red filtrate was added to MeOH (200 mL) at a rate which kept the internal temperature below 55°C. The contents were stirred at room temp. for 45 min., cooled to 5°C, and treated with Et₂O (200 mL) dropwise. The resulting solids were filtered, washed with Et₂O (200 mL) and dried under reduced pressure at 35°C to 40°C. To provide methyl 4-chloropyridine-2-carboxylate HCl salt as a white solid (110 g, 65%); mp 108-112°C; ¹H NMR (DMSO-d₆) δ 3.83 (s, 3H); 7.82 (dd, J= 5.5, 2.2 Hz, 1H); 8.08 (d, J= 2.2 Hz, 1H); 8.68 (d, J= 5.5 Hz, 1H); 10.68 (br s, 1H); HPLC ES-MS m/z 172 ((M+H)+).

Step 3a. Synthesis of 4-chloro-N-methyl-2-pyridinecarboxamide from methyl 4-chloropyridine-2-carboxylate

[0082] A suspension of methyl 4-chloropyridine-2-carboxylate HCl salt (89.0 g, 428 mmol) in MeOH (75 mL) at 0°C was treated with a 2.0 M methylamine solution in THF (1 L) at a rate which kept the internal temp. below 5°C. The resulting mixture was stored at 3°C for 5 h, then concentrated under reduced pressure. The resulting solids were suspended in EtOAc (1 L) and filtered. The filtrate was washed with a saturated NaCl solution (500 mL), dried (Na₂SO₄) and concentrated under reduced pressure to afford 4-chloro-N-methyl-2-pyridinecarboxamide as pale-yellow crystals (71.2 g, 97%); mp 41-43°C; ¹H NMR (DMSO-d₆) δ 2.81 (s, 3H), 7.74 (dd, J= 5.1, 2.2 Hz, 1H), 8.00 (d, J= 2.2, 1H), 8.61 (d, J= 5.1 Hz, 1H), 8.85 (br d, 1H); CI-MS m/z 171 ((M+H)+).

Step 1. Synthesis of 5-hydroxyisoindoline-1,3-dione

[0085] To a mixture of ammonium carbonate (5.28 g, 54.9 mmol) in cone. AcOH (25 mL) was slowly added 4-hydroxyxiphosphoric acid (5.0 g, 27.45 mmol). The resulting mixture was heated at 120º C. for 45 min., then the clear, bright yellow mixture was heated at 160º C. for 2 h. The resulting mixture was maintained at 160º C. and was concentrated to approximately 15 mL., then was cooled to room temp. and adjusted pH 10 with a 1N NaOH solution. This mixture was cooled to 0º C. and slowly acidified to pH 5 using a 1N HCl solution. The resultant precipitate was collected by filtration and dried under reduced pressure to yield 5-hydroxyisoindoline-1,3-dione as a pale yellow powder as product (3.24 g, 72%): 1H NMR (DMSO-d6) δ 7.00-7.03 (m, 2H), 7.56 (d, J=9.1 Hz, 1H).

Step 2. Synthesis of 5-(4-nitrophenoxyl)isoindoline-1,3-dione

[0086] To a stirring slurry of NaH (1.1 g, 44.9 mmol) in DMF (40 mL) at 0º C. was added a solution of 5-hydroxyisoindoline-1,3-dione (3.2 g, 19.6 mmol) in DMF (40 mL) dropwise. The bright yellow-green mixture was allowed to return to room temp. and was stirred for 1 h, then 1-fluoro-4-nitrobenzene (2.67 g, 18.7 mmol) was added via syringe in 3-4 portions. The resulting mixture was heated at 70º C. overnight, then cooled to room temp. and diluted slowly with water (150 mL), and extracted with EtOAc (2×100 mL). The combined organic layers were dried (MgSO4) and concentrated under reduced pressure to give 5-(4-nitrophenoxyl)isoindoline-1,3-dione as a yellow solid (3.3 g, 62%): TLC (30% EtOAc/70% hexane) Rf 0.28; 1H NMR (DMSO-d6) δ 7.32 (d, J=12 Hz, 2H), 7.52-7.57 (m, 2H), 7.89 (d, J=7.8 Hz, 1H), 8.29 (d, J=9 Hz, 2H), 11.43 (br s, 1H); CI-MS m/z 285 ([M+H]+, 100%).

[0084] A solution of 4-aminophenol (9.60 g, 88.0 mmol) in anh. DMF (150 mL) was treated with potassium tert-butoxide (10.29 g, 91.7 mmol) and the reddish-brown mixture was stirred at room temp. for 2 h. The contents were treated with 4-chloro-N-methyl-2-pyridinecarboxamide (15.0 g, 87.9 mmol) and K2CO3 (6.50 g, 47.0 mmol) and then heated at 80º C. for 8 h. The mixture was cooled to room temp. and separated between EtOAc (500 mL) and a saturated NaCl solution (500 mL). The aqueous phase was back-extracted with EtOAc (300 mL). The combined organic layers were washed with a saturated NaCl solution (4×1000 mL), dried (Na2SO4) and concentrated under reduced pressure. The resulting solids were dried under reduced pressure at 35º C. for 3 h to afford 4-(2-(N-methylcarbamoyl)-4-pyridyloxy)aniline as a light-brown solid 17.9 g, 84%): 1H-NMR (DMSO-d6) δ 2.77 (d, J=4.8 Hz, 3H), 5.17 (br s, 2H), 6.64, 6.86 (AA'BB' quartet, J=8.4 Hz, 4H), 7.66 (dd, J=5.5, 2.5 Hz, 1H), 7.33 (d, J=2.5 Hz, 1H), 8.44 (d, J=5.5 Hz, 1H), 8.73 (br d, 1H); HPLC ES-MS m/z 244 ([M+H]+).
Step 3. Synthesis of 5-(4-aminophenoxysisoindoline-1,3-dione

A solution of 5-(4-nitrophenoxysisoindoline-1,3-dione (6.0 g, 2.11 mmol) in conc. AcOH (12 mL) and water (0.1 mL) was stirred under stream of argon while iron powder (0.59 g, 9.59 mmol) was added slowly. This mixture stirred at room temp for 72 h, then was diluted with water (25 mL) and extracted with EtOAc (3x30 mL). The combined organic layers were dried (MgSO$_4$) and concentrated under reduced pressure to give 5-(4-aminophenoxysisoindoline-1,3-dione as a brownish solid (0.4 g, 75%). TLC (50% EtOAc/50% hexane) R$_f$ 0.27; $^1$H NMR (DMSO-d$_6$) δ 8.14 (br s, 2H), 6.62 (d, J=8.7 Hz, 2H), 6.84 (d, J=8.7 Hz, 2H), 7.03 (d, J=2.1 Hz, 1H), 7.23 (dd, 1H), 7.75 (d, J=8.4 Hz, 1H), 11.02 (s, 1H); HPLC ES-MS m/z 255 (M+H)$^+$ 100%. A4. General Method for the Synthesis of Pyrrolylanilines. Synthesis of 5-tert-Butyl-2-(2,5-dimethylpyrrolyl)aniline

Step 1. Synthesis of 1-(4-tert-butyl-2-nitrophenyl)-2,5-dimethylpyrrole

To a stirring solution of 2-nitro-4-tert-butylaniline (0.5 g, 2.57 mmol) in cyclohexane (10 mL) was added AcOH (0.1 mL) and acetonilidone (0.299 g, 2.63 mmol) via syringe. The reaction mixture was heated at 120°C for 72 h with azeotropic removal of volatiles. The reaction mixture was cooled to room temp, diluted with CH$_2$Cl$_2$ (10 mL) and sequentially washed with a 1N HCl solution (15 mL), a 1N NaOH solution (15 mL) and a saturated NaCl solution (15 mL), dried (MgSO$_4$) and concentrated under reduced pressure. The resulting orange-brown solids were purified via column chromatography (60 g SiO$_2$; gradient from 0% EtOAc/94% hexane to 25% EtOAc/75% hexane) to give 1-(4-tert-butyl-2-nitrophenyl)-2,5-dimethylpyrrole as an orange-yellow solid (0.34 g, 49%): TLC (15% EtOAc/85% hexane) R$_f$ 0.67; $^1$H NMR (CDCl$_3$) δ 1.34 (s, 9H), 1.89 (s, 6H), 5.84 (s, 2H), 7.19-7.24 (m, 1H), 7.62 (dd, 1H), 7.88 (d, J=2-4 Hz, 1H); CI-MS m/z 273 (M+H)$^+$ 50%. A5. General Method for the Synthesis of Anilines from Anilines by Nucleophilic Aromatic Substitution. Synthesis of 4-(2-N-Methylamnamide)-4-pyridyl)2-methylaniline HCl Salt

Step 2. Synthesis of 5-tert-Butyl-2-(2,5-dimethylpyrrolyl)aniline

A slurry of 1-(4-tert-butyl-2-nitrophenyl)-2,5-dimethylpyrrole (0.341 g, 1.25 mmol), 10% Pd/C (0.056 g) and EtOAc (50 mL) under an H$_2$ atmosphere (balloon) was stirred for 72 h, then filtered through a pad of Celite®. The filtrate was concentrated under reduced pressure to give 5-tert-butyl-2(2,5-dimethylpyrrolyl)aniline as yellowish solids (0.30 g, 99%): TLC (10% EtOAc/90% hexane) R$_f$ 0.43; $^1$H NMR (CDCl$_3$) δ 1.28 (s, 9H), 1.87-1.91 (m, 8H), 5.85 (br s, 2H), 6.73-6.96 (m, 3H), 7.28 (br s, 1H).

Step 3. Synthesis of 5-tert-Butyl-2-(2,5-dimethylpyrrolyl)aniline

A slurry of 4-amino-3-methylphenol (5.45 g, 44.25 mmol) in dry dimethylether (75 mL) was treated with potassium tert-butoxide (10.86 g, 96.77 mmol) and the black mixture was stirred at room temp. until the flask had reached room temp. The contents were then treated with 4-chloro-N-methyl-2-pyridine-carboxamide (Method A2, Step 3b; 7.52 g, 44.2 mmol) and heated at 110°C for 8 h. The mixture was cooled to room temp. and diluted with water (75 mL). The organic layer was extracted with EtOAc (5x100 mL). The combined organic layers were washed with a saturated NaCl solution (200 mL), dried (MgSO$_4$) and concentrated under reduced pressure. The residual black oil was treated with Et$_2$O (50 mL) and sonicated. The solution was then treated with HCl (1 M in Et$_2$O; 100 mL) and stirred at room temp. for 5 min. The resulting dark pink solid (7.04 g, 24.1 mmol) was removed by filtration from solution and stored under anaerobic conditions at 0°C. prior to use: $^1$H NMR (DMSO-d$_6$) δ 2.41 (s, 3H), 2.78 (d, J=4 Hz, 3H), 4.93 (br s, 2H), 7.19 (dd, J=8.5, 2.6 Hz, 1H), 7.23 (dd, J=5.5, 2.6 Hz, 1H), 7.26 (d, J=2.6 Hz, 1H), 7.55 (d, J=2.6 Hz, 1H), 7.64 (d, J=8.8 Hz, 1H), 8.55 (d, J=5.9 Hz, 1H), 8.99 (q, J=4.8 Hz, 1H).

![Chemical Structure]

Step 1: Synthesis of 3-Chloro-4-(2,2,2-trifluoracetamidino)phenol

[0091] Iron (3.24 g, 58.00 mmol) was added to stirring TFA (200 mL). To this slurry was added 2-chloro-4-nitrophenol (10.0 g, 58.0 mmol) and trifluoroacetic anhydride (20 mL). This gray slurry was stirred at room temp, for 6 d. The iron was filtered from solution and the remaining material was concentrated under reduced pressure. The resulting gray solid was dissolved in water (20 mL). To the resulting yellow solution was added a saturated NaHCO₃ solution (50 mL). The solid which precipitated from solution was removed. The filtrate was slowly quenched with the sodium bicarbonate solution until the product visibly separated from solution (determined was using a mini work-up vial). The slightly cloudy yellow solution was extracted with EtOAc (3x125 mL). The combined organic layers were washed with a saturated NaCl solution (125 mL), dried (MgSO₄) and concentrated under reduced pressure. The 1H NMR (DMSO-d₆) indicated a 1:1 ratio of the nitrophenol starting material and the intended product 3-chloro-4-(2,2,2-trifluoroacetamidino) phenol. The crude material was taken on to the next step without further purification.

![Chemical Structure]

Step 2: Synthesis of 4-(2-(N-Methylcarbamoyl)-4-pyridyloxy)-2-chlorophenyl (222-trifluoroacetamide)

[0092] A solution of crude 3-chloro-4-(2,2,2-trifluoracetamidino)phenol (5.62 g, 23.46 mmol) in dry dimethylacetamide (50 mL) was treated with potassium tert-butoxide (5.16. 45.98 mmol) and the brownish black mixture was stirred at room temp, until the flask had cooled to room temp. The resulting mixture was treated with 4-chloro-N-methyl-2-pyridinecarboxanide (Method A2, Step 3b, 1.99 g, 11.7 mmol) and heated at 100°C under argon for 4 d. The black reaction mixture was cooled to room temp, and then poured into cold water (100 mL). The mixture was extracted with EtOAc (3x75 mL) and the combined organic layers were concentrated under reduced pressure. The residual brown oil was purified by column chromatography (gradient from 20% EtOAc/pet. ether to 40% EtOAc/pet. ether) to yield 4-(2-(N-

Methylcarbamoyl)-4-pyridyloxy)-2-chlorophenyl (222-trifluoroacetamide) as a yellow solid (8.59 g, 23.0 mmol).

![Chemical Structure]

Step 3. Synthesis of 4-(2-(N-Methylcarbamoyl)-4-pyridyloxy)-2-chloroaniline

[0093] A solution of crude 4-(2-(N-Methylcarbamoyl)-4-pyridyloxy)-2-chlorophenyl (222-trifluoroacetamide) (8.59 g, 23.0 mmol) in dry Dioxane (20 mL) was treated with a N NaOH solution (20 mL). This brown solution was allowed to stir for 8 h. To this solution was added EtOAc (40 mL). The green organic layer was extracted with EtOAc (3x40 mL) and the solvent was concentrated to yield 4-(2(N-Methylcarbamoyl)-4-pyridyloxy)-2-chloroaniline as a green oil that solidified upon standing (2.86 g, 10.30 mmol); 1H NMR (DMSO-d₆) δ 8.77 (d, J=4.8 Hz, 1H), 7.51 (s, 2H), 6.60 (d, J=8.5, 2.6 Hz, 1H), 6.76 (d, J=2.6 Hz, 1H), 7.03 (d, J=8.5, 1H), 7.07 (dd, J=5.5, 2.6, 1H), 7.27 (d, J=2.6 Hz, 1H), 8.46 (d, J=5.5, 2.6 Hz, 1H), 8.75 (q, J=4.8, 1H).


![Chemical Structure]

[0094] A suspension of 3-chloro-6-(N-acetyl)-4-(trifluoro-etyl)anisole (4.00 g, 14.95 mmol) in a 6M HCl solution (24 mL) was heated at the reflux temp. for 1 h. The resulting solution was allowed to cool to room temp, during which time it solidified slightly. The resulting mixture was diluted with water (20 mL) then treated with a combination of solid NaOH and a saturated NaHCO₃ solution until the solution was basic. The organic layer was extracted with CH₂Cl₂ (3x50 mL). The combined organics were dried (MgSO₄) and concentrated under reduced pressure to yield 4-chloro-2-methoxy-5-(trifluoromethyl)aniline as a brown oil (3.20 g, 14.2 mmol); 1H NMR (DMSO-d₆) δ 3.84 (s, 3H), 5.30 (s, 2H), 7.01 (s, 2H).


![Chemical Structure]
Step 1. 4-(3-Methoxycarbonyl-4-methoxyphenoxo)-1-nitrobenzene

[0095] To a solution of 4-(3-carboxy-4-hydroxyphenoxo)-1-nitrobenzene (prepared from 2,5-dihydroxybenzoic acid in a manner analogous to that described in Method A13, Step 1, 12 mmol) in acetonitrile (50 mL) was added K₂CO₃ (5 g) and dimethyl sulfate (3.5 mL). The resulting mixture was heated at the reflux temp. overnight, then cooled to room temp. and filtered through a pad of Celite®. The resulting solution was concentrated under reduced pressure, absorbed onto SiO₂, and purified by column chromatography (50% EtOAc/50% hexane) to give 4-(3-methoxycarbonyl-4-methoxyphenoxo)-1-nitrobenzene as a yellow powder (3 g); mp 115-118° C.

Step 2.
4-(3-Carboxy-4-methoxyphenoxo)-1-nitrobenzene

[0096] A mixture of 4-(3-methoxycarbonyl-4-methoxyphenoxo)-1-nitrobenzene (1.2 g), KOH (0.33 g) and water (5 mL) in MeOH (45 mL) was stirred at room temp. overnight and then heated at the reflux temp. for 4 h. The resulting mixture was cooled to room temp. and concentrated under reduced pressure. The residue was dissolved in water (50 mL), and the aqueous mixture was made acidic with a 1N HCl solution. The resulting mixture was extracted with EtOAc (50 mL). The organic layer was dried (MgSO₄) and concentrated under reduced pressure to give 4-(3-carboxy-4-methoxyphenoxo)-1-nitrobenzene (1.04 g).

Step 3. 4-(3-(N-Methylcarbamoyl)-4-methoxyphenoxo)-1-nitrobenzene

[0097] To a solution of 4-(3-carboxy-4-methoxyphenoxo)-1-nitrobenzene (0.50 g, 1.75 mmol) in CH₂Cl₂ (12 mL) was added SOCl₂ (0.64 mL, 8.77 mmol) in portions. The resulting solution was heated at the reflux temp. for 18 h, cooled to room temp., and concentrated under reduced pressure. The resulting yellow solids were dissolved in CH₂Cl₂ (3 mL) then the resulting solution was treated with a methanolic solution (2.0 M in THF; 3.5 mL; 7.02 mmol) in portions (CAUTION: gas evolution), and stirred at room temp. for 4 h. The resulting mixture was treated with a 1N NaOH solution, then extracted with CH₂Cl₂ (25 mL). The organic layer was dried (Na₂SO₄) and concentrated under reduced pressure to give 4-(3-(N-methylcarbamoyl)-4-methoxyphenoxo)-1-nitrobenzene as a yellow solid (0.50 g, 95%).

Step 4. 4-(3-(N-Methylcarbamoyl)-4-methoxyphenoxo)aniline

[0098] A slurry of 4-(3-(N-methylcarbamoyl)-4-methoxyphenoxo)-1-nitrobenzene (0.78 g, 2.60 mmol) and 10% Pd/C (0.20 g) in EtOH (55 mL) was stirred under 1 atm of H₂ (balloon) for 2.5 d, then filtered through a pad of Celite®. The resulting solution was concentrated under reduced pressure to afford 4-(3-(N-methylcarbamoyl)-4-methoxyphenoxo)aniline as an off-white solid (0.68 g, 96%); TLC (0.1% Et,N/99.9% EtOAc) Rₖ 0.36.


Step 1. Synthesis of 5-(4-Nitrophenoxo)-2-methylisooindoline-1,3-dione

[0099] A slurry of 5-(4-nitrophenoxo)isooindoline-1,3-dione (A3 Step 2; 1.0 g, 3.52 mmol) and NaH (0.13 g, 5.27 mmol) in DMF (15 mL) was stirred at room temp. for 1 h, then treated with methyl iodide (0.3 mL, 4.57 mmol). The resulting mixture was stirred at room temp. overnight, then was cooled to 0° C and treated with water (10 mL). The resulting solids were collected and dried under reduced pressure to give 5-(4-nitrophenoxo)-2-methylisooindoline-1,3-dione as a bright yellow solid (0.87 g, 85%); TLC (35% EtOAc/65% hexane) Rₖ 0.61.

Step 2. Synthesis of 5-(4-Aminophenoxo)-2-methylisooindoline-1,3-dione

[0100] A slurry of nitrophenoxo)-2-methylisooindoline-1,3-dione (0.87 g, 2.78 mmol) and 10% Pd/C (0.10 g) in MeOH was stirred under 1 atm of H₂ (balloon) overnight. The resulting mixture was filtered through a pad of Celite® and concentrated under reduced pressure. The resulting yellow solids
were dissolved in EtOAc (3 mL) and filtered through a plug of SiO₂ (60% EtOAc/40% hexane) to afford 5-(4-aminophenoxy)-2-methylisoindoline-1,3-dione as a yellow solid (0.67 g, 86%); TLC (40% EtOAc/60% hexane) Rf 0.27.


Step 1. Synthesis of 4-Chloro-2-(N-(2-morpholin-4- yethyl)carbamoyl)pyridine

[0101] To a solution of methyl 4-chloropyrididine-2-carboxylate HCl salt (Method A2, Step 2: 1.01 g, 4.86 mmol) in THF (20 mL) was added 4-(2-aminoethyl)morpholine (2.55 mL, 19.4 mmol) dropwise and the resulting solution was heated at the reflux temp. for 20 h, cooled to room temp., and treated with water (50 mL). The resulting mixture was extracted with EtOAc (50 mL). The organic layer was dried (MgSO₄) and concentrated under reduced pressure to afford 4-chloro-2-(N-(2-morpholin-4-yl-ethyl)carbamoyl)pyridine as a yellow oil (1.25 g, 95%); TLC (10% MeOH/90% EtOAc) Rf 0.50.

Step 2. Synthesis of 4-(2-(N-(2-Morpholin-4-yl-ethyl) carbamoyl)pyridloxy)aniline

[0102] A solution of 4-aminophenol (0.49 g, 4.52 mmol) and potassium tert-butoxide (0.53 g, 4.75 mol) in DMF (8 mL) was stirred at room temp. for 2 h, then was sequentially treated with 4-chloro-2-(N-(2-morpholin-4-yl-ethyl)carbamoyl)pyridine (1.22 g, 4.52 mmol) and K₂CO₃ (0.31 g, 2.26 mmol). The resulting mixture was heated at 75°C overnight, cooled to room temp., and separated between EtOAc (25 mL) and a saturated NaCl solution (25 mL). The aqueous layer was back extracted with EtOAc (25 mL). The combined organic layers were washed with a saturated NaCl solution (3x25 mL) and concentrated under reduced pressure. The resulting brown solids were purified by column chromatography (58 g; gradient from 100% EtOAc to 25% MeOH/75% EtOAc) to afford 4-(2-(N-(2-morpholin-4-yl-ethyl)carbamoyl)pyridloxy)aniline (1.0 g, 65%); TLC (10% MeOH/90% EtOAc) Rf 0.32.


[0103] A slurry of 4-(3-carboxyphenoxo)-1-nitrobenzene (5.38 g, 20.7 mmol) and 10% Pd/C (0.50 g) in MeOH (120 mL) was stirred under an H₂ atmosphere (balloon) for 2 d. The resulting mixture was filtered through a pad of Celite®, then concentrated under reduced pressure to afford 4-(3-carboxyphenoxo)aniline as a brown solid (2.26 g, 48%); TLC (10% MeOH/90% CH₂Cl₂) Rf 0.44 (streaking).


[0104] To a solution of 5-hydroxyisoindolin-1-one in AcOH (300 mL) was slowly added zinc dust (47.6 g, 729 mmol) in portions, then the mixture was heated at the reflux temp. for 40 min., filtered hot, and concentrated under reduced pressure. The reaction was repeated on the same scale and the combined oily residue was purified by column chromatography (1.1 Kg SiO₂; gradient from 60% EtOAc/40% hexane to 25% MeOH/75% EtOAc) to give 5-hydroxyisoindolin-1-one (3.77 g); TLC (100% EtOAc) Rf 0.17; HPLC ES-MS m/z 150 ([M+H]+).

Step 2. Synthesis of 4-(1-isooindolin-5-yloxy)-1-nitrobenzene

[0105] To a slurry of NaH (0.39 g, 16.1 mmol) in DMF at 0°C was added 5-hydroxyisoindolin-1-one (2.6 g, 13.4 mmol) in portions. The resulting slurry was allowed to warm to room temp. and was stirred for 45 min., then 4-fluoro-1-nitrobenzene was added and then mixture was heated at 70°C for 3 h. The mixture was cooled to 0°C and treated with water dropwise until a precipitate formed. The resulting solids were collected to give 4-(1-isooindolin-5-yloxy)-1-nitrobenzene as a dark yellow solid (3.23 g, 89%); TLC (100% EtOAc) Rf 0.35.
Step 3. Synthesis of 4-(1-oxoisoindolin-5-yloxy)aniline

[0106] A slurry of 4-(1-isooindolin-5-yloxy)-1-nitrobenzene (2.12 g, 7.8 mmol) and 10% Pd/C (0.20 g) in EtOH (50 mL) was stirred under an H₂ atmosphere (balloon) for 4 h, then filtered through a pad of Celite®. The filtrate was concentrated under reduced pressure to afford 4-(1-oxoisoindolin-5-yloxy)aniline as a dark yellow solid: TLC (100% EtOAc) Rₓ 0.15.


Step 1. Synthesis of 4-(3-ethoxy carbonylphenoxo)-1-nitrobenzene

[0107] A mixture of 4-fluoro-1-nitrobenzene (16 mL, 150 mmol), ethyl 3-hydroxybenzoate (25 g, 150 mmol) and K₂CO₃ (41 g, 300 mmol) in DMF (125 mL) was heated at the reflux temp. overnight, cooled to room temp. and treated with water (250 mL). The resulting mixture was extracted with EtOAc (3x150 mL). The combined organic phases were sequentially washed with water (3x100 mL) and a saturated NaCl solution (2x100 mL), dried (Na₂SO₄) and concentrated under reduced pressure. The residue was purified by column chromatography (10% EtOAc/90% hexane) to afford 4-(3-ethoxy carbonyl phenoxo)-1-nitrobenzene as an oil (38 g).

Step 2. Synthesis of 4-(3-carboxyphenoxo)-1-nitrobenzene

[0108] To a vigorously stirred mixture of 4-(3-ethoxy carbonyl phenoxo)-1-nitrobenzene (5.14 g, 17.9 mmol) in a 3:1 THF/water solution (75 mL) was added a solution of LiOH·H₂O (1.50 g, 35.8 mmol) in water (36 mL). The resulting mixture was heated at 50°C overnight, then cooled to room temp., concentrated under reduced pressure and adjusted to pH 2 with a 1M HCl solution. The resulting bright yellow solids were removed by filtration and washed with hexane to give 4-(3-carboxyphenoxo)-1-nitrobenzene (4.40 g, 95%).

Step 3. Synthesis of 4-(3-(N-methylcarbamoyl)phenoxy)-1-nitrobenzene

[0109] A mixture of 4-(3-carboxyphenoxo)-1-nitrobenzene (3.72 g, 14.4 mmol), EDCI·HCl (3.63 g, 18.6 mmol), N-methylmorpholine (1.6 mL, 14.5 mmol) and methyamine (2.0 M in THF; 8 mL, 16 mmol) in CH₂Cl₂ (45 mL) was stirred at room temp. for 3 d, then concentrated under reduced pressure. The residue was dissolved in EtOAc (50 mL) and the resulting mixture was extracted with a 1M HCl solution (50 mL). The aqueous layer was back-extracted with EtOAc (2x50 mL). The combined organic phases were washed with a saturated NaCl solution (50 mL), dried (Na₂SO₄), and concentrated under reduced pressure to give 4-(3-(N-methylcarbamoyl)phenoxy)-1-nitrobenzene as an oil (1.89 g).

Step 4. Synthesis of 4-(3-(N-methylcarbamoyl)phenoxo)aniline

[0110] A slurry of 4-(3-(N-methylcarbamoylphenoxo)-1-nitrobenzene (1.89 g, 6.95 mmol) and 5% Pd/C (0.24 g) in EtOAc (20 mL) was stirred under an H₂ atm (balloon) overnight. The resulting mixture was filtered through a pad of Celite® and concentrated under reduced pressure. The residue was purified by column chromatography (5% MeOH/95% CH₂Cl₂). The resulting oil solidified under vacuum overnight to give 4-(3-(N-methylcarbamoyl)phenoxo)aniline as a yellow solid (0.95 g, 56%).

A. General Method for the Synthesis of α-Carbamoyl Anilines via EDCI-Mediated Amide Formation Followed by Nitroarene Reduction. Synthesis of 4-3-(5-Methylcarbamoyl)pyridoxy)aniline
Step 1. Synthesis of 4-(3-(5-methoxy-5-methyl)pyridyloxy)-1-nitrobenzene

[0111] To a slurry of NaH (0.63 g, 26.1 mmol) in DMF (20 mL) was added a solution of methyl 5-hydroxynicotinate (2.0 g, 13.1 mmol) in DMF (10 mL). The resulting mixture was heated to 70°C for 2 hours, cooled to room temp., and treated with MeOH (5 mL) followed by water (50 mL). The resulting mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (30% EtOAc/70% hexane) to afford 4-(3-(5-methoxy-5-methyl)pyridyloxy)-1-nitrobenzene (0.60 g).

[0112] A slurry of 4-(3-(5-methoxy-5-methyl)pyridyloxy)-1-nitrobenzene (0.60 g, 2.20 mmol) and 10% Pd/C in MeOH/EtOAc was stirred under an H₂ atmosphere (balloon) for 72 h. The resulting mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (gradient from 10% EtOAc/90% hexane to 30% EtOAc/70% hexane to 50% EtOAc/50% hexane) to afford 4-(3-(5-methoxy-5-methyl)pyridyloxy)aniline (0.28 g, 60%). ¹H NMR (CDCl₃) 8: 3.92 (s, 3H), 6.71 (d, 2H), 6.89 (d, 2H), 7.75 (s, 1H), 8.51 (d, 1H), 8.87 (d, 1H).

Step 2. Synthesis of 4-(3-(N-methylsulfamoyl)phenyloxy)benzene

[0114] To a slurry of phenol (1.9 g, 20 mmol), K₂CO₃ (6.0 g, 40 mmol), and Cul (4 g, 20 mmol) in DMF (25 mL) was added N-methyl-3-bromobenzensulfonamide (2.5 g, 10 mmol), and the resulting mixture was stirred at the reflux temp. overnight, cooled to room temp., and separated between EtOAc (50 mL) and a 1 N HCl solution (50 mL). The aqueous layer was back-extracted with EtOAc (2×50 mL). The combined organic phases were sequentially washed with water (2×50 mL) and a saturated NaCl solution (50 mL), dried (MgSO₄), and concentrated under reduced pressure. The residual oil was purified by column chromatography (30% EtOAc/70% hexane) to give 4-(3-(N-methylsulfamoyl)phenyloxy)benzene (0.30 g).

Step 3. Synthesis of 4-(3-(N-methylsulfamoyl)phenyloxy)-1-nitrobenzene

[0115] To a solution of 4-(3-(N-methylsulfamoyl)phenyloxy)benzene (0.30 g, 1.14 mmol) in TFA (6 mL) at -10°C, was added NaN₃O₂ (0.097 g, 1.14 mmol) in portions over 5 min. The resulting solution was stirred at -10°C for 1 h, then was allowed to warm to room temp., and was concentrated under reduced pressure. The residue was separated between EtOAc (10 mL) and water (10 mL). The organic phase was sequentially washed with water (10 mL) and a saturated NaCl solution (10 mL), dried (MgSO₄) and concentrated under reduced pressure to give 4-(3-(N-methylsulfamoyl)phenyloxy)-1-nitrobenzene (0.20 g). This material carried on to the next step without further purification.

Step 4. Synthesis of 4-(3-(N-methylsulfamoyl)phenyloxy)aniline

[0116] A slurry of 4-(3-(N-methylsulfamoyl)phenyloxy)-1-nitrobenzene (0.30 g) and 10% Pd/C (0.030 g) in EtOAc (20
ml) was stirred under an H₂ atmosphere (balloon) overnight. The resulting mixture was filtered through a pad of Celite®. The filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (30% EtOAc/70% hexane) to give 4-(3-(N-methylsulfamoyl)phenoxymethyl)methyleneoxyaniline (0.070 g).


[0117] To a slurry of 4-(4-acetylphenoxy)aniline HCl salt (prepared in a manner analogous to Method A13, step 4; 1.0 g, 3.39 mmol) in a mixture of EtOH (10 ml) and pyridine (1.0 ml) was added O-methylhydroxylamine HCl salt (0.65 g, 7.78 mmol, 2.0 equiv.). The resulting solution was heated at the reflux temperature for 30 min, cooled to room temperature and concentrated under reduced pressure. The resulting solids were triturated with water (10 ml) and washed with water to give 4-(4-(1-(N-methoxy)iminoethyl)phenoxy)aniline HCl salt as a yellow solid (0.85 g). TLC (50% EtOAc/50% pet. ether) Rf 0.78; 1H NMR (DMSO-d₆) δ 3.90 (s, 3H), 5.70 (s, 3H); HPLC-MS m/z 257 [(M+H)+].


[0118] To a solution of 4-chloro-N-(2-trimethylsilyloxlyoxy)ethylpyridine-2-carbonic acid (prepared in a manner analogous to Method A2, Step 3b; 1.5 g, 7.4 mmol) in anh DMF (7 ml) was added trimethylsilyl chloride (1.51 g, 9.2 mmol, 1.1 equiv.) and imidazole (1.12 g, 16.4 mmol, 2.2 equiv.). The resulting yellow solution was stirred for 3 h at room temp, then was concentrated under reduced pressure. The residue was separated between water (10 ml) and EtOAc (10 ml). The aqueous layer was extracted with EtOAc (3×10 ml). The combined organic phases were dried (MgSO₄), and concentrated under reduced pressure to afford 4-chloro-N-(2-trimethylsilyloxlyoxy)ethylpyridinecarboxamide as an orange oil (2.32 g, 88%). This material was used in the next step without further purification.

Step 2. 4-(4-(2-(N-(2-Trisopropylsilyl)oxlyoxy)ethylcarbamoyl)pyridyloxylamine.

[0119] To a solution of 4-hydroxyaniline (0.70 g, 6.0 mmol) in anh DMF (5 ml) was added potassium tert-butoxide (0.67 g, 6.0 mmol, 1.0 equiv.) in one portion causing an exotherm. When this mixture had cooled to room temperature, a solution of 4-chloro-2-(N-(2-trisopropylsilyloxlyoxy)ethyl)pyridinecarboxamide (2.32 g, 6 mmol, 1 equiv.) in DMF (4 ml) was added followed by K₂CO₃ (0.42 g, 3.0 mmol, 0.50 equiv.). The resulting mixture was heated to 80°C overnight. An additional portion of potassium tert-butoxide (0.34 g, 3 mmol, 0.50 equiv.) was then added and the mixture was stirred at 80°C for an additional 4 h. The mixture was cooled to 0°C with an ice/water bath, then water (approx. 1 ml) was slowly added dropwise. The organic layer was extracted with EtOAc (3×10 ml). The combined organic layers were washed with a saturated NaCl solution (20 ml), dried (MgSO₄) and concentrated under reduced pressure. The brown oily residue was purified by column chromatography (SiO₂; 30% EtOAc/70% pet ether) to afford 4-(4-(2-(N-(2-trisopropylsilyloxlyoxy)ethylcarbamoyl)pyridyloxylamine as a clear light brown oil (0.98 g, 38%).


Step 1. 4-(5-(2-Methyl)pyridyloxyl)-1-nitrobenzene.

[0120] A mixture of 5-hydroxy-2-methylpyridine (10.0 g, 91.6 mmol), 1-fluoro-4-nitrobenzene (9.8 ml, 91.6 mmol, 1.0 equiv.), K₂CO₃ (25 g, 183 mmol, 2.0 equiv.) in DMF (100 ml) was heated at the reflux temperature overnight. The resulting mixture was cooled to room temperature, treated with water (200 ml), and extracted with EtOAc (3×100 ml). The combined organic layers were sequentially washed with water (2×100 ml) and a saturated NaCl solution (100 ml), dried (MgSO₄) and concentrated under reduced pressure to give 4-(5-(2-methyl)pyridyloxyl)-1-nitrobenzene as a brown solid (12.3 g).
Step 2. Synthesis of 4-(5-(2-Methoxy carbonyl) pyridyl)oxy)-1-nitrobenzene

A mixture of 4-(5-(2-methyl) pyridyl)oxy)-1-nitrobenzene (1.70 g, 7.39 mmol) and selenium dioxide (2.50 g, 22.2 mmol, 3.0 equiv.) in pyridine (20 mL) was heated at the reflux temperature for 5 h, then cooled to room temperature. The resulting slurry was filtered, then concentrated under reduced pressure. The residue was dissolved in MeOH (100 mL). The solution was treated with a cone HCl solution (7 mL), then heated at the reflux temperature for 3 h, cooled to room temperature and concentrated under reduced pressure. The residue was separated between EtOAc (50 mL) and a 1N NaOH solution (50 mL). The aqueous layer was extracted with EtOAc (2×50 mL). The combined organic layers were sequentially washed with water (2×50 mL) and a saturated NaCl solution (50 mL), dried (MgSO₄) and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂; 50% EtOAc/50% hexane) to afford 4-(5-(2-methoxy carbonyl) pyridyl)oxy)-1-nitrobenzene (0.70 g).

Step 3. Synthesis of 4-(5-(2-Methoxy carbonyl) pyridyl)oxy)aniline

A slurry of 4-(5-(2-methoxy carbonyl) pyridyl)oxy)-1-nitrobenzene (0.50 g) and 10% Pd/C (0.050 g) in a mixture of EtOAc (20 mL) and MeOH (5 mL) was placed under a H₂ atmosphere (balloon) overnight. The resulting mixture was filtered through a pad of Celite®, and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂; 70% EtOAc/30% hexane) to give 4-(5-(2-methoxy carbonyl) pyridyl)oxy)aniline (0.40 g).


Step 1. 4-(4-Methylsulfonylphenoxy)-1-nitrobenzene

To a solution of 4-(4-methylthiophenoxy)1-nitrobenzene (2.0 g, 7.7 mmol) in CH₂Cl₂ (75 mL) at 0°C, was slowly added m-CPBA (57-86%, 4.0 g), and the reaction mixture was stirred at room temperature for 5 h. The reaction mixture was treated with a 1N NaOH solution (25 mL). The organic layer was sequentially washed with a 1N NaOH solution (25 mL), water (25 mL) and a saturated NaCl solution (25 mL), dried (MgSO₄), and concentrated under reduced pressure to give 4-(4-methylsulfonylphenoxy)-1-nitrobenzene as a solid (2.1 g).

Step 2. 4-(4-Methylsulfonylphenoxy)-1-aniline

4-(4-Methylsulfonylphenoxy)-1-nitrobenzene was reduced to the aniline in a manner analogous to that described in Method A18, step 3.

B. Synthesis of Urea Precursors


Step 1. Synthesis of 4-bromo-3-(trifluoromethyl)aniline HCl Salt

To a solution of 4-bromo-3-(trifluoromethyl)aniline (64 g, 267 mmol) in Et₂O (500 mL) was added an HCl solution (1 M in Et₂O; 300 mL) dropwise and the resulting mixture was stirred at room temp. for 16 h. The resulting pink-white precipitate was removed by filtration and washed with Et₂O (50 mL) to afford 4-bromo-3-(trifluoromethyl) aniline HCl salt (73 g, 98%).

Step 2. Synthesis of 4-bromo-3-(trifluoromethyl)phenyl isocyanate

A suspension of 4-bromo-3-(trifluoromethyl) aniline HCl salt (36.8 g, 133 mmol) in toluene (278 mL) was treated with trichloromethyl chloroformate dropwise and the resulting mixture was heated at the reflux temp. for 18 h. The resulting mixture was concentrated under reduced pressure. The residue was treated with toluene (500 mL), then concentrated under reduced pressure. The residue was treated with CH₂Cl₂ (500 mL), then concentrated under reduced pressure. The CH₂Cl₂ treatment/concentration protocol was repeated and resulting amber oil was stored at ~20°C. For 16 h, to afford 4-bromo-3-(trifluoromethyl)phenyl isocyanate as a tan solid (35.1 g, 86%): GC-MS m/z 265 (M⁺).
C. Methods of Urea Formation


\[
\text{Cl} - \text{CF}_3 - \text{N} = \text{O} - \text{NHMe}
\]

[0129] A solution of 4-chloro-3-(trifluoromethyl)phenyl isocyanate (14.60 g, 65.90 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (35 mL) was added dropwise to a suspension of 4-(2-(N-methylcarbamoyl)-4-pyridyloxy)aniline (Method A2, Step 4; 16.0 g, 65.77 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (55 mL) at 0°C. The resulting mixture was stirred at room temp. for 22 h. The resulting yellow solids were removed by filtration, then washed with CH\textsubscript{2}Cl\textsubscript{2} (2×30 mL) and dried under reduced pressure (approximately 1 mmHg) to afford N-(4-chloro-3-(trifluoromethyl)phenyl)-N'-(4-(2-(N-methylcarbamoyl)-4-pyridyloxy)phenyl)urea as an off-white solid (28.5 g, 93%): mp 207-209°C; H\textsuperscript{1}NMR (DMSO-d\textsubscript{6}) δ 2.77 (d, J = 4.8 Hz, 3H), 7.16 (m, 3H), 7.37 (d, J = 2.5 Hz, 1H), 7.62 (m, 4H), 8.11 (d, J = 2.5 Hz, 1H), 8.49 (d, J = 5.5 Hz, 1H), 8.77 (br d, 1H), 8.99 (s, 1H), 9.21 (s, 1H); HPLC ES-MS m/z 465 [(M+H)*].

C1b. General Method for the Synthesis of Ureas by Reaction of an Isocyanate with an Aniline. Synthesis of N-(4-Bromo-3-(trifluoromethyl)phenyl)-N'-(4-(2-(N-methylcarbamoyl)-4-pyridyloxy)phenyl) Urea

\[
\text{Br} - \text{CF}_3 - \text{N} = \text{O} - \text{NHMe}
\]

[0130] A solution of 4-bromo-3-(trifluoromethyl)phenyl isocyanate (Method H1, Step 2; 8.0 g, 30.1 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (80 mL) was added dropwise to a solution of 4-(2-(N-methylcarbamoyl)-4-pyridyloxy)aniline (Method A2, Step 4; 7.0 g, 28.8 mmol) in CH\textsubscript{2}Cl\textsubcript{2} (40 mL) at 0°C. The resulting mixture was stirred at room temp. for 16 h. The resulting yellow solids were removed by filtration, then washed with CH\textsubscript{2}Cl\textsubscript{2} (2×50 mL) and dried under reduced pressure (approximately 1 mmHg) at 40°C. To afford N-(4-bromo-3-(trifluoromethyl)phenyl)-N'-(4-(2-(N-methylcarbamoyl)-4-pyridyloxy)phenyl)urea as a pale-yellow solid (13.2 g, 90%): mp 203-205°C; H\textsuperscript{1}NMR (DMSO-d\textsubscript{6}) δ 2.77 (d, J = 4.8 Hz, 3H), 7.16 (m, 3H), 7.37 (d, J = 2.5 Hz, 1H), 7.58 (m, 3H), 7.77 (d, J = 8.8 Hz, 1H), 8.11 (d, J = 2.5 Hz, 1H), 8.49 (d, J = 5.5 Hz, 1H), 8.77 (br d, 1H), 8.99 (s, 1H), 9.21 (s, 1H); HPLC ES-MS m/z 505 [(M+H)*].

C1c. General Method for the Synthesis of Ureas by Reaction of an Isocyanate with an Aniline. Synthesis of N-(4-Chloro-3-(trifluoromethyl)phenyl)-N'-(2-methyl-4-(4-(N-methylcarbamoyl)-4-pyridyloxy)phenyl) Urea

[0131] A solution of 2-methyl-4-(4-(N-methylcarbamoyl)-4-pyridyloxy)aniline (Method A5; 0.11 g, 0.45 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (1 mL) was treated with Et\textsubscript{3}N (0.16 mL) and 4-chloro-3-(trifluoromethyl)phenyl isocyanate (0.16 g, 0.45 mmol). The resulting brown solution was stirred at room temp. for 6 d, then was treated with water (5 mL). The aqueous layer was back-extracted with EtOAc (3×5 mL). The combined organic layers were dried (MgSO\textsubscript{4}) and concentrated under reduced pressure to yield N-(4-chloro-3-(trifluoromethyl)phenyl)-N'-(2-methyl-4-(4-(N-methylcarbamoyl)-4-pyridyloxy)phenyl)urea as a brown oil (0.11 g, 0.22 mmol): H\textsuperscript{1}NMR (DMSO-d\textsubscript{6}) δ 2.27 (s, 3H), 2.77 (d, J = 4.8 Hz, 3H), 7.08 (m, 3H), 7.11 (d, J = 2.9 Hz, 1H), 7.15 (dd, J = 5.5, 2.6, Hz, 1H), 7.38 (d, J = 2.6 Hz, 1H), 7.62 (app d, J = 2.6 Hz, 2H), 7.84 (d, J = 8.8 Hz, 1H), 8.12 (s, 1H), 8.17 (s, 1H); HPLC ES-MS m/z 479 [(M+H)*].

C1d. General Method for the Synthesis of Ureas by Reaction of an Isocyanate with an Aniline. Synthesis of N-(4-Chloro-3-(trifluoromethyl)phenyl)-N'-(4-aminophenyl) Urea

\[
\text{Cl} - \text{CF}_3 - \text{N} = \text{O} - \text{NH}_2
\]

[0132] To a solution of 4-chloro-3-(trifluoromethyl)phenyl isocyanate (2.27 g, 10.3 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (308 mL) was added p-phenylenediamine (3.32 g, 30.7 mmol) in one part. The resulting mixture was stirred at room temp. for 1 h, treated with CH\textsubscript{2}Cl\textsubscript{2} (100 mL), and concentrated under reduced pressure. The resulting pink solids were dissolved in a mixture of EtOAc (110 mL) and MeOH (15 mL), and the clear solution was washed with a 0.05 N HCl solution. The organic layer was concentrated under reduced pressure to afford impure N-(4-chloro-3-(trifluoromethyl)phenyl)-N'-(4-aminophenyl)urea (3.3 g): TLC (100% EtOAc); Rf 0.72. General Method for the Synthesis of Ureas by Reaction of an Isocyanate with an Aniline. Synthesis of N-(4-Chloro-3-(trifluoromethyl)phenyl)-N'-(4-ethoxy carbamoylphenyl) Urea
[0133] To a solution of ethyl 4-isocyanatobenzoate (3.14 g, 16.4 mmol) in CH₂Cl₂ (30 mL) was added 4-chloro-3-(trifluoromethyl)aniline (3.21 g, 16.4 mmol), and the solution was stirred at room temp. overnight. The resulting slurry was diluted with CH₂Cl₂ (50 mL) and filtered to afford N-(4-chloro-3-(trifluoromethyl)phenyl)-N'-4-ethoxybenzylurea as a white solid (5.93 g, 97%): TLC (40% EtOAc/60% hexane) R₉ 0.44.

C1f. General Method for the Synthesis of Ureas by Reaction of an Isocyanate with an Aniline. Synthesis of N-(4-Chloro-3-(trifluoromethyl)phenyl)-N'-(3-carboxyphenyl) Urea

[0134] To a solution of 4-chloro-3-(trifluoromethyl)phenyl isocyanate (1.21 g, 5.46 mmol) in CH₂Cl₂ (8 mL) was added 4-(3-carboxyphenoxy)aniline (Method A11; 0.81 g, 5.76 mmol) and the resulting mixture was stirred at room temp. overnight, then treated with MeOH (8 mL), and stirred an additional 2 h. The resulting mixture was concentrated under reduced pressure. The resulting brown solids were triturated with a 1:1 EtOAc/hexane solution to give N-(4-chloro-3-(trifluoromethyl)phenyl)-N'-3(carboxyphenyl)urea as an off-white solid (1.21 g, 76%).

C2a. General Method for Urea Synthesis by Reaction of an Aniline with N,N'-Carbonyl Dimidazole Followed by Addition of a Second Aniline. Synthesis of N-(2-Methoxy-5-(trifluoromethyl)phenyl)-N'-4-(2-(N-methylcarbamoyl)-4-pyridyloxy)phenyl Urea

[0136] To a stirring solution of 3-amino-2-methoxyquinoline (0.14 g) in anhydrous CH₂Cl₂ (15 mL) at 0°C was added CDI (0.13 g). The resulting solution was allowed to warm to room temp. over 1 h then was stirred at room temp. for 16 h. The resulting mixture was treated with 4-(2-(N-methylcarbamoyl)-4-pyridyloxy)aniline (0.18 g). The resulting yellow solution stirred at room temp. for 72 h then was treated with water (125 mL). The resulting aqueous mixture was extracted with EtOAc (2×50 mL). The combined organic phases were washed with saturated NaCl solution (100 mL), dried (MgSO₄) and concentrated under reduced pressure. The residue was triturated (90% EtOAc/10% hexane). The resulting white solids were collected by filtration and washed with EtOAc. The filtrate was concentrated under reduced pressure and the residual oil purified by column chromatography (gradient from 33% EtOAc/67% hexane to 50% EtOAc/50% hexane to 100% EtOAc) to give N-(2-methoxy-5-(trifluoromethyl)phenyl)-N'-4-(2-(N-methylcarbamoyl)-4-pyridyloxy)phenylurea as a light tan solid (0.098 g, 30%): TLC (100% EtOAc) R₉ 0.62; ¹H NMR (DMSO-d₆) δ 7.26 (d, J=4.8 Hz, 3H), 3.96 (s, 3H), 7.1-7.6 and 8.4-8.6 (m, 11H), 8.75 (d, J=4.8 Hz, 1H), 9.55 (s, 1H); FAB-MS m/z 461 (M+H⁺).
[0138] To a stirring solution of 2-methoxy-5-(trifluoromethyl)phenyl isocyanate (0.10 g, 0.47 mmol) in CH₂Cl₂ (1.5 ml.) was added 5-(4-aminophenoxo)isoindoline-1,3-dione (Method A3, Step 3; 0.12 g, 0.47 mmol) in one portion. The resulting mixture was stirred for 12 h, then was treated with CH₂Cl₂ (10 ml.) and MeOH (5 ml). The resulting mixture was sequentially washed with a 1N HCl solution (15 ml.) and a saturated NaCl solution (15 ml.), dried (MgSO₄) and concentrated under reduced pressure to afford N-(2-methoxy-5-(trifluoromethyl)phenyl)-N⁴-(4-(1,3-dioxoisindolin-5-yloxy)phenyl)urea as a white solid (0.2 g, 96%): TLC (70% EtOAc/30% hexane) Rf 0.50; 'H NMR (DMSO-d₆) δ 3.95 (s, 3H), 7.51-7.10 (m, 6H), 7.57 (d, J=9.3 Hz, 2H), 7.80 (d, J=8.7 Hz, 1H), 8.55 (brs, 2H), 9.57 (s, 1H), 11.27 (brs, 1H); HPLC ES-MS 472.0 (M+H)⁺, 100%.

C2d. General Method for Urea Synthesis by Reaction of Aniline with N,N'-Carbonyl Diimidazole Followed by Addition of a Second Aniline. Synthesis of N-(5-(tert-Butyl)-2-(2,5-dimethylpyrrol-2-yl)phenyl)-N⁴-(4-(2-(N-methylcarbamoyl)-4-pyridyloxy)phenyl) Urea

[0141] To a stirring solution of phosgene (1.9 M in toluene; 2.07 ml, 0.37 mmol) in CH₂Cl₂ (20 ml) at 0°C was added anhyd pyridine (0.32 ml) followed by 2-methoxy-5-(trifluoromethyl)aniline (0.75 g). The yellow solution was allowed to warm to room temp during which a precipitate formed. The yellow mixture was stirred for 1 h, then concentrated under reduced pressure. The resulting solids were treated with anhyd toluene (20 ml) followed by 4-(2-(N-methylcarbamoyl)-4-pyridyloxy)aniline (prepared as described in Method A2; 0.30 g) and the resulting suspension was heated at 80°C for 20 h, then allowed to cool to room temp. The resulting mixture was diluted with water (100 ml), then was made basic with a saturated Na₂CO₃ solution (2-3 ml). The basic solution was extracted with EtOAc (2x250 ml). The organic layers were then washed with a saturated NaCl solution, combined, dried (MgSO₄), and concentrated under reduced pressure. The resulting yellowish residue was dissolved in MeOH and absorbed onto SiO₂ (100 g). Column chromatography (300 g SiO₂; gradient from 1% Et₃N/33% EtOAc/66% hexane to 1% Et₃N/99% EtOAc to 1% Et₃N/20% MeOH/79% EtOAc) followed by concentration under reduced pressure at 45°C gave a warn concentrated EtOAc solution, which was treated with hexane (10 ml) to slowy form crystals of N-(5-(tert-Butyl)-2-(2,5-dimethylpyrrol-2-yl)phenyl)-N⁴-(4-(2-(N-methylcarbamoyl)-4-pyridyloxy)phenyl)urea (0.44 g): TLC (1% Et₃N/99% EtOAc) Rf 0.40.

D. Interconversion of Ureas

[0142] D. Conversion of α-Aminophenyl Ureas into α-(Arylamino)phenyl Ureas. Synthesis of N-(4-Chloro-3-((trifluoromethyl)phenyl)-N⁴-(4-(3-methoxyacarbonyl)phenyl)carboxyaminophenyl) Urea

[0140] One of the anilines to be coupled was dissolved in dichlorothene (0.10 M). This solution was added to a 8 ml vial (0.5 ml) containing dichlorothene (1 ml). To this was added a bis(trichloromethyl) carbonate solution (0.12 M in dichlorothene, 0.2 ml, 0.4 equiv.), followed by disopropyllethylamine (0.35 M in dichlorothene, 0.2 ml, 1.2 equiv.). The vial was capped and heat at 80°C for 5 h, then allowed to cool to room temp for approximately 10 h. The second aniline was added (0.10 M in dichlorothene, 0.5 ml, 1.0 equiv.) followed by disopropylethylamine (0.35 M in dichlorothene, 0.2 ml, 1.2 equiv.). The resulting mixture was heated at 80°C for 4 h, cooled to room temperature and treated with MeOH (0.5 ml). The resulting mixture was concentrated under reduced pressure and the products were purified by reverse phase HPLC.

mmol), mono-methyl isophthalate (0.25 g, 1.38 mmol), 
HOBT.H₂O (0.41 g, 3.03 mmol) and N-methylmorpholine 
(0.33 mL, 3.03 mmol) in DMF (8 mL) was added EDCI.HCl 
(0.29 g, 1.52 mmol). The resulting mixture was stirred 
at room temp. overnight, diluted with EtOAc (25 mL) and 
sequentially washed with water (25 mL) and a saturated 
NaCl solution (25 mL). The organic layer was dried 
(Na₂SO₄) and concentrated under reduced pressure. The 
resulting solids were triturated with an EtOAc solution (80% 
EtOAc/20% hexane) to give N-(4-chloro-3-((trifluoromethyl)phenyl)-N'-(4-(3-methoxy carbonylphenyl)carboxamidinophenyl)urea (0.27 g, 43%): mp 121-122; TLC 
(80% EtOAc/20% hexane) Rₖ 0.75.

D1b. Conversion of o-Carboxyphenyl Ureas into o-(Arylcarbamoyl)phenyl Ureas. Synthesis of N-(4-chloro-3-((trifluoromethyl)phenyl)-N'-(4-(3-methylcarbamoylphenyl)carbamoyl)phenyl) Urea

[0145] A mixture of N-(4-chloro-3-((trifluoromethyl)phenyl)-N'-(3-cyclohexylphenyl)urea (Method C1e; 0.030 g, 0.067 mmol) and N-cyclohexyl-N'-(methylpolystyrene) carbodiimide (55 mg) in 1,2-dichloroethane (1 mL) was treated with a solution of 3-aminopyridine in CH₂Cl₂ (1 M; 0.074 mL, 0.074 mmol). (In cases of insolubility or turbidity, a small amount of DMSO was also added.) The resulting mixture was heated at 35°C. overnight. Turbid reactions were then treated with THF (1 mL) and heating was continued for 18 h. The resulting mixtures were treated with poly(4-(isocyanatomethyl)styrene) (0.040 g) and the resulting mixture was stirred at 36°C for 72 h, then cooled to room temp. and filtered. The resulting solution was filtered through a plug of silica gel (1 g). Concentration under reduced pressure afforded N-(4-chloro-3-((trifluoromethyl)phenyl)-N'-(4-(N-(3-(N-(3-pyridyl)carbamoyl)phenyl)carbamoyl)phenyl)urea (0.024 g, 59%); TLC (70% EtOAc/30% hexane) Rₖ 0.42.

D2. Conversion of o-Carboxyphenyl Ureas into o-(Carbamoylaryl)phenyl Ureas. Synthesis of N-(4-chloro-3-((trifluoromethyl)phenyl)-N'-(4-(3-methylcarbamoylphenyl)carboxamidinophenyl) Urea

[0146] To a sample of N-(4-chloro-3-((trifluoromethyl)phenyl)-N'-(4-(3-carboxyethoxyphenyl)carboxamidinophenyl)urea (0.17 g, 0.34 mmol) was added methanolic HCl (2 M in THF; 1 mL; 1.7 mmol) and the resulting mixture was stirred at room temp. overnight, then concentrated under reduced pressure to give N-(4-chloro-3-((trifluoromethyl)phenyl)-N'-(4-(3-methylcarbamoyl)phenyl)carboxamidinophenyl)urea as a white solid: mp 247; TLC (100% EtOAc) Rₖ 0.35.

D3. Conversion of o-Carboxyaryl Ureas into o-(Carboxyaryl) Ureas. Synthesis of N-(4-chloro-3-((trifluoromethyl)phenyl)-N'-(4-(3-carboxyphenyl) Urea

[0147] To a slurry of N-(4-chloro-3-((trifluoromethyl)phenyl)-N'-(4-(3-hydroxyphenyl)urea (Method C1e; 5.93 g, 15.3 mmol) in MeOH (75 mL) was added an aqueous KOH solution (2.5 N, 10 mL; 23 mmol). The resulting mixture was heated at the reflux temp. for 12 h, cooled to room temp., and concentrated under reduced pressure. The residue was diluted with water (50 mL), then treated with a 1 N HCl solution to adjust the pH to 2 to 3. The resulting solids were collected and dried under reduced pressure to give N-(4-chloro-3-((trifluoromethyl)phenyl)-N'-(4-(3-carboxyphenyl)urea as a white solid (5.05 g, 92%).
Step 1. Synthesis of N-(4-Chloro-3-(trifluoromethyl)phenyl)-N'-(4-(3-(5-carboxypyridyl)oxyphenyl)urea

and 4-(3-(5-methoxycarbonylpyridyl)oxyanilines (Method A14, Step 2) in a manner analogous to Method C1a. A suspension of N-(4-chloro-3-(trifluoromethyl)phenyl)-N'-(4-(3-(5-methoxycarbonylpyridyl)oxyphenyl)urea (0.26 g, 0.56 mmol) in MeOH (10 mL) was treated with a solution of KOH (0.14 g, 2.5 mmol) in water (1 mL) and was stirred at room temp. for 1 h. The resulting mixture was adjusted to pH 5 with a 1 N HCl solution. The resulting precipitate was removed by filtration and washed with water. The resulting solids were dissolved in filtered EtOH (10 mL) and the resulting solution was concentrated under reduced pressure. The EtOH/concentration procedure was repeated twice to give N-(4-chloro-3-(trifluoromethyl)phenyl)-N'-(4-(3-(5-carboxyphenyl)oxyphenyl)urea (0.18 g, 71%).

Step 2. Synthesis of N-(4-chloro-3-(trifluoromethyl)phenyl)-N'-(4-(3-(5-(2-dimethylaminoethyl)carbamoyl)pyridyl)oxyphenyl)urea

[0149] A mixture of N-(4-chloro-3-(trifluoromethyl)phenyl)-N'-(4-(3-(5-carboxyphenyl)oxyphenyl)urea (0.050 g, 0.011 mmol), N,N-dimethylformamide (0.22 mg, 0.17 mmol), HOBT (0.028 g, 0.17 mmol), N-methylisopropylamine (0.035 g, 0.28 mmol), and EDCl.HCl (0.032 g, 0.17 mmol) in DMF (2.5 mL) was stirred at room temp. overnight. The resulting solution was separated between EtOAc (50 mL) and water (50 mL). The organic phase was washed with water (35 mL), dried (MgSO₄) and concentrated under reduced pressure. The residue was dissolved in a minimal amount of CH₂Cl₂ (approximately 2 mL). The resulting solution was treated with Et₂O dropwise to give N-(4-chloro-3-(trifluoromethyl)phenyl)-N'-(4-(3-(5-(2-dimethylaminoethyl)carbamoyl)pyridyl)oxyphenyl)urea as a white precipitate (0.48 g, 84%). ¹H NMR (DMSO-d₆) δ 2.10 s (6H), 3.26 (s, 1H), 7.03 (d, 2H), 7.52 (d, 2H), 7.60 (m, 3H), 8.05 (s, 1H), 8.43 (s, 1H), 8.58 (t, 1H), 8.69 (s, 1H), 8.90 (s, 1H), 9.14 (s, 1H); HPLC ES-MS m/z 522 ([M+H]+).

D5. General Method for the Deprotection of N-(o-Silyloxyalkyl)amides. Synthesis of N-(4-Chloro-3-(trifluoromethyl)phenyl)-N'-(4-(4-(2-(N-(2-hydroxyethyl)carbamoyl)pyridyloxyphenyl)urea.

[0150] To a solution of N-(4-chloro-3-(trifluoromethyl)phenyl)-N'-(4-(4-(2-(N-(2-hydroxyethyl)carbamoyl)pyridyloxyphenyl)urea (prepared in a manner analogous to Method C1a; 0.25 g, 0.37 mmol) in anh THF (2 mL) was tetraethylammonium fluoride (1.0 M in THF; 2 mL). The mixture was stirred at room temperature for 5 min, then was treated with water (10 mL). The aqueous mixture was extracted with EtOAc (3×10 mL). The combined organic layers were dried (MgSO₄) and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂; gradient from 100% hexane to 40% EtOAc/60% hexane) to give N-(4-chloro-3-(trifluoromethyl)phenyl)-N'-(4-(4-(2-(N-(2-hydroxyethyl)carbamoyl)pyridyloxyphenyl)urea as a white solid (0.019 g, 10%).

[0151] Listed below are compounds listed in the Tables below which have been synthesized according to the Detailed Experimental Procedures given above:

Syntheses of Exemplified Compounds
See Tables for Compound Characterization

[0152] Entry 1: 4-(3-N-Methylcarbamoylphenoxo)aniline was prepared according to Method A13. According to Method C3, 3-tert-butylinilene was reacted with bis(trichloromethyl) carbonate followed by 4-(3-N-Methylcarbamoylphenoxo)aniline to afford the urea.

[0153] Entry 2: 4-Fluoro-1-nitrobenzene and p-hydroxycetophenone were reacted according to Method A13, Step 1 to afford the 4-(4-acetophenonyl)-1-nitrobenzene. 4-(4-Acetylphenonyl)-1-nitrobenzene was reduced according to Method A13, Step 2 to afford 4-(4-acetyloxyphenonyl)aniline. According to Method C3, 3,3-tert-butylinilene was reacted with bis(trichloromethyl) carbonate followed by 4-(4-acetyloxyphenonyl)aniline to afford the urea.

[0154] Entry 3: According to Method C2d, 3-tert-butylinilene was treated with CDI, followed by 4-(3-N-methylcarbamoyl)-4-(methoxyphenyl)aniline, which had been prepared according to Method A8, to afford the urea.

[0155] Entry 4: 5-tert-Butyl-2-methoxyaniline was converted to 5-tert-butyl-2-methoxyphenyl isocyanate according to Method B1. 4-(3-N-Methylcarbamoylphenoxo)aniline, prepared according to Method A13, was reacted with the isocyanate according to Method C1a to afford the urea.

[0156] Entry 5: According to Method C2d, 5-tert-butyl-2-methoxyaniline was reacted with CDI followed by 4-(3-N-
methylcarbamoyl)-4-methoxyphenoxy) aniline, which had been prepared according to Method A8, to afford the urea. [0157] Entry 6: 5-(4-Aminophenoxy)isoindoline-1,3-dione was prepared according to Method A3. According to Method 2d, 5-tert-butyl-2-methoxyaniline was reacted with CDI followed by 5-(4-aminophenoxy)isoindoline-1,3-dione to afford the urea.

[0158] Entry 7: 4-(1-Oxoisodolin-5-yl)oxo)aniline was synthesized according to Method A12. According to Method 2d, 5-tert-butyl-2-methoxyaniline was reacted with CDI followed by 4-(1-oxoisodolin-5-yl)oxo)aniline to afford the urea.

[0159] Entry 8: 4-(3-N-Methylcarbamoylphenoxo) aniline was synthesized according to Method A13. According to Method C2a, 2-methoxy-5-(3-fluoromethyl)aniline was reacted with CDI followed by 4-(3-N-methylcarbamoylphenoxo)aniline to afford the urea.

[0160] Entry 9: 4-Hydroxyacetophenone was reacted with 2-chloro-5-nitropyridine to give 4-(4-acetylphenoxy)-5-nitropyridine according to Method A3. Step 2. According to Method A8, Step 4, 4-(4-acetylphenoxy)-5-nitropyridine was reduced to 4-(4-acetylphenoxy)-5-nitroaniline. 2-Methoxy-5-(3-fluoromethyl)aniline was converted to 2-methoxy-5-(3-fluoromethyl)phenyl isocyanate according to Method B1. The isocyanate was reacted with 4-(4-acetylphenoxy)-5-nitroaniline according to Method C1a to afford the urea.

[0161] Entry 10: 4-Fluoro-1-nitrobenzene and p-hydroxyacetophenone were reacted according to Method A13, Step 1 to afford the 4-(4-acetylphenoxy)-1-nitrobenzene. 4-(4-Acetylphenoxy)-1-nitrobenzene was reduced according to Method A13, Step 4 to afford 4-(4-acetylphenoxy)aniline. According to Method C3, 5-(3-fluoromethyl)-2-methoxybutylaniline was reacted with bis(trichloromethyl) carbonate followed by 4-(4-acetylphenoxy)aniline to afford the urea.

[0162] Entry 11: 4-Chloro-N-methyl-2-pyridinecarboxamide, which was synthesized according to Method A2, Step 3a, was reacted with 3-aminophenol according to Method A2, Step 4 using DMAC in place of DMF to give 3-(2-N-methylcarbamoyl)-4-pyridylxoy aniline. According to Method C4, 2-methoxy-5-(3-fluoromethyl)aniline was reacted with phosgene followed by 3-(2-N-methylcarbamoyl)-4-pyridylxoy aniline to afford the urea.

[0163] Entry 12: 4-Chloropyridine-2-carbonyl chloride HCl salt was reacted with ammonia according to Method A2, Step 3b to form 4-chloro-2-pyridinecarboxamide. 4-Chloro-2-pyridinecarboxamide was reacted with 3-aminophenol according to Method A2, Step 4 using DMAC in place of DMF to give 4-2-carbonyl-4-pyridylxoy aniline. According to Method C2a, 2-methoxy-5-(3-fluoromethyl)aniline was reacted with phosgene followed by 3-(2-N-methylcarbamoyl)-4-pyridylxoy aniline to afford the urea.

[0164] Entry 13: 4-Chloro-N-methyl-2-pyridinecarboxamide was synthesized according to Method A2, Step 3b. 4-Chloro-N-methyl-2-pyridinecarboxamide was reacted with 4-aminophenol according to Method A2, Step 4 using DMAC in place of DMF to give 4-2-(N-methylcarbamoyl)-4-pyridylxoy aniline. According to Method C2a, 2-methoxy-5-(3-fluoromethyl)aniline was reacted with CDI followed by 4-2-(N-methylcarbamoyl)-4-pyridylxoy aniline to afford the urea.

[0165] Entry 14: 4-Chloropyridine-2-carbonyl chloride HCl salt was reacted with ammonia according to Method A2, Step 3b to form 4-chloro-2-pyridinecarboxamide. 4-Chloro-2-pyridinecarboxamide was reacted with 4-aminophenol according to Method A2, Step 4 using DMAC in place of DMF to give 4-2-carbonyl-4-pyridylxoy aniline. According to Method C4, 2-methoxy-5-(3-fluoromethyl)aniline was reacted with phosgene followed by 4-(2-carbamoyl-4-pyridylxoy) aniline to afford the urea.

[0166] Entry 15: According to Method C2d, 5-(trifluoromethyl)-2-methoxyaniline was reacted with CDI followed by 4-(3-N-methylcarbamoyl)-4-methoxyphenoxy)aniline, which had been prepared according to Method A8, to afford the urea.

[0167] Entry 16: 4-(2-N-Methylcarbamoyl)-4-pyridylxoy)-2-methylaniline was synthesized according to Method A5. 5-(Trifluoromethyl)-2-methoxyaniline was converted into 5-(trifluoromethyl)-2-methoxyphenyl isocyanate according to Method B1. The isocyanate was reacted with 4-(2-N-methylcarbamoyl)-4-pyridylxoy)-2-methylaniline according to Method C1c to afford the urea.

[0168] Entry 17: 4-(2-N-Methylcarbamoyl)-4-pyridylxoy)-2-chloroaniline was synthesized according to Method A6. 5-(Trifluoromethyl)-2-methoxyaniline was converted into 5-(trifluoromethyl)-2-methoxyphenyl isocyanate according to Method B1. 5-(Trifluoromethyl)-2-methoxyphenyl isocyanate was reacted with 4-(2-N-methylcarbamoyl)-4-pyridylxoy)-2-chloroaniline according to Method C1a to afford the urea.

[0169] Entry 18: According to Method A2, Step 4, 5-amino-2-methylenol was reacted with 4-chloro-N-methyl-2-pyridinecarboxamide, which had been synthesized according to Method A2, Step 3b, to give 3-(2-N-methylcarbamoyl)-4-pyridylxoy)-4-methylaniline, 5-(Trifluoromethyl)-2-methoxyphenyl isocyanate was reacted with 3-(2-N-methylcarbamoyl)-4-pyridylxoy)-4-methylaniline according to Method C1a to afford the urea.

[0170] Entry 19: 4-Chloropyridine-2-carbonyl chloride was reacted with ethylamine according to Method A2, Step 3b. The resulting 4-chloro-N-ethyl-2-pyridinecarboxamide was reacted with 4-aminophenol according to Method A2, Step 4 to give 4-(2-N-ethylcarbamoyl)-4-pyridylxoy aniline. 5-(Trifluoromethyl)-2-methoxyaniline was converted into 5-(trifluoromethyl)-2-methoxyphenyl isocyanate according to Method B1. 5-(Trifluoromethyl)-2-methoxyphenyl isocyanate was reacted with 4-(2-N-ethylcarbamoyl)-4-pyridylxoy aniline according to Method C1a to afford the urea.

[0171] Entry 20: According to Method A2, Step 4, 4-amino-2-chloroanisol was reacted with 4-chloro-N-methyl-2-pyridinecarboxamide, which had been synthesized according to Method A2, Step 3b, to give 4-(2-N-methylcarbamoyl)-4-pyridylxoy)-3-chloroaniline. 5-(Trifluoromethyl)-2-methoxyphenyl isocyanate was reacted with 4-(2-N-methylcarbamoyl)-4-pyridylxoy)-3-chloroaniline according to Method C1a to afford the urea.

[0172] Entry 21: 4-(4-Methylthiophenoxo)-1-nitrobenzene was oxidized according to Method A19, Step 1 to give 4-(4-methylsulfonylphenoxo)-1-nitrobenzene. The nitrobenzene was reduced according to Method A19, Step 2 to give 4-(4-methylsulfonylphenoxo)-1-aniline. According to Method C1a, 5-(trifluoromethyl)-2-methoxyphenyl isocyanate was reacted with 4-(4-methylsulfonylphenoxo)-1-aniline to afford the urea.

[0173] Entry 22: 4-(3-Carboxamophenoxo)-1-nitrobenzene was reduced to 4-(3-carboxamophenoxo)aniline according to Method A5, Step 4. According to Method C1a, 5-(trifluoromethyl)-2-methoxyphenyl isocyanate was reacted with 4-(3-carboxamophenoxo)aniline to afford the urea.
[0174] Entry 23: 5-(4-Aminophenoxo)isoindoline-1,3-dione was synthesized according to Method A3. 5-(Trifluoromethyl)-2-methoxyaniline was converted into 5-(trifluoromethyl)-2-methoxynaphthalene isocyanate according to Method B1. 5-(Trifluoromethyl)-2-methoxynaphthalene isocyanate was reacted with 5-(4-aminophenoxo)isoindoline-1,3-dione according to Method C1a to afford the amine.

[0175] Entry 24: 4-Chloropyridine-2-carbonyl chloride was reacted with dimethylamine according to Method A2, Step 3b. The resulting 4-chloro-N,N-dimethyl-2-pyridinecarboxamide was reacted with 4-aminophenol according to Method A2, Step 4 to give 4-(2-(N,N-dimethylcarbamoyl)-4-pyridyloxy)aniline. 5-(Trifluoromethyl)-2-methoxyaniline was converted into 5-(trifluoromethyl)-2-methoxynaphthalene isocyanate according to Method B1. 5-(Trifluoromethyl)-2-methoxynaphthalene isocyanate was reacted with 4-(2-(N,N-dimethylcarbamoyl)-4-pyridyloxy)aniline according to Method C1a to afford the amine.

[0176] Entry 25: 4-(1-Oxooxindolin-5-yl)oxoaniline was synthesized according to Method A12. 5-(Trifluoromethyl)-2-methoxyaniline was treated with CDI, followed by 4-(1-oxooxindolin-5-yl)oxoaniline according to Method C2d to afford the amine.

[0177] Entry 26: 4-Hydroxyacetophenone was reacted with 4-fluorobenzene according to Method A13, Step 1 to give 4-(4-acetylphenoxo)nitrobenzene. The nitrobenzene was reduced according to Method A13, Step 4 to afford 4-(4-acetylphenoxo)aniline, which was converted into the 4-(4-(1-(N-methoxy)iminomethyl)phenoxo)aniline HCl salt according to Method A16. 5-(Trifluoromethyl)-2-methoxyaniline was converted into 5-(trifluoromethyl)-2-methoxynaphthalene isocyanate according to Method B1. 5-(Trifluoromethyl)-2-methoxynaphthalene isocyanate was reacted with 4-(4-(1-(N-methoxy)iminomethyl)phenoxo)aniline HCl salt to Method C1a to afford the amine.

[0178] Entry 27: 4-Chloro-N-methylpyridinecarboxamide was synthesized as described in Method A2, Step 3b. The chloropyridine was reacted with 4-aminophenol according to Method A2, Step 4 to give 4-(4-(2-(N-methylcarbamoyl)phenyl)ethynyl)aniline. 5-(Trifluoromethyl)-2-methoxyaniline was converted into 5-(trifluoromethyl)-2-methoxynaphthalene isocyanate according to Method B1. 5-(Trifluoromethyl)-2-methoxynaphthalene isocyanate was reacted with 4-(4-(2-(N-methylcarbamoyl)phenyl)ethynyl)aniline according to Method C1a to afford the amine.

[0179] Entry 28: 5-(4-Aminophenoxy)-2-methylisoindoline-1,3-dione was synthesized according to Method A9. 5-(Trifluoromethyl)-2-methoxyaniline was converted into 5-(trifluoromethyl)-2-methoxynaphthalene isocyanate according to Method B1. 5-(Trifluoromethyl)-2-methoxynaphthalene isocyanate was reacted with 5-(4-aminophenoxy)-2-methylisoindoline-1,3-dione according to Method C1a to afford the amine.

[0180] Entry 29: 4-Chloro-N-methylpyridinecarboxamide was synthesized as described in Method A2, Step 3b. The chloropyridine was reacted with 3-aminophenol according to Method A2, Step 4 to give 3-(4-(2-(N-methylcarbamoyl)phenyl)ethynyl)aniline. 5-(Trifluoromethyl)-2-methoxyaniline was converted into 5-(trifluoromethyl)-2-methoxynaphthalene isocyanate according to Method B1. 5-(Trifluoromethyl)-2-methoxynaphthalene isocyanate was reacted with 3-(4-(2-(N-methylcarbamoyl)phenyl)ethynyl)aniline according to Method C1a to afford the amine.

[0181] Entry 30: 4-Chloropyridine-2-carbonyl chloride was reacted with isopropylamine according to Method A2, Step 3b. The resulting 4-chloro-N-isopropyl-2-pyridinecarboxamide was reacted with 4-aminophenol according to Method A2, Step 4 to give 4-(2-(N-isopropylcarbamoyl)-4-pyridyloxy)aniline. 5-(Trifluoromethyl)-2-methoxyaniline was converted into 5-(trifluoromethyl)-2-methoxynaphthalene isocyanate according to Method B1. 5-(Trifluoromethyl)-2-methoxynaphthalene isocyanate was reacted with 4-(2-(N-isopropylcarbamoyl)-4-pyridyloxy)aniline according to Method C1a to afford the amine.

[0182] Entry 31: 4-(3-(5-Methoxycarbonyl)pyridyl)oxyaniline was synthesized according to Method A14. 5-(Trifluoromethyl)-2-methoxynaphthalene was converted into 5-(trifluoromethyl)-2-methoxynaphthalene isocyanate according to Method B1. 5-(Trifluoromethyl)-2-methoxynaphthalene isocyanate was reacted with 4-(3-(5-methoxycarbonyl)pyridyl)oxyaniline according to Method C1a to afford the amine. N-(5-(Trifluoromethyl)-2-methoxynaphthalene)-N'-4-(4-(3-(5-methoxycarbonyl)pyridyl)oxy)phenylurea was saponified according to Method D4, Step 1, and the corresponding acid was coupled with 4-(2-aminoethyl)aminomethane to afford the amide according to Method D4, Step 2.

[0183] Entry 32: 4-(3-(5-Methoxycarbonyl)pyridyl)oxyaniline was synthesized according to Method A14. 5-(Trifluoromethyl)-2-methoxynaphthalene was converted into 5-(trifluoromethyl)-2-methoxynaphthalene isocyanate according to Method B1. 5-(Trifluoromethyl)-2-methoxynaphthalene isocyanate was reacted with 4-(3-(5-methoxycarbonyl)pyridyl)oxyaniline according to Method C1a to afford the amine. N-(5-(Trifluoromethyl)-2-methoxynaphthalene)-N'-4-(4-(3-(5-methoxycarbonyl)pyridyl)oxy)phenylurea was saponified according to Method D4, Step 1, and the corresponding acid was coupled with methylamine according to Method D4, Step 2 to afford the amide.

[0184] Entry 33: 4-(3-(5-Methoxycarbonyl)pyridyl)oxyaniline was synthesized according to Method A14. 5-(Trifluoromethyl)-2-methoxynaphthalene was converted into 5-(trifluoromethyl)-2-methoxynaphthalene isocyanate according to Method B1. 5-(Trifluoromethyl)-2-methoxynaphthalene isocyanate was reacted with 4-(3-(5-methoxycarbonyl)pyridyl)oxyaniline according to Method C1a to afford the amine. N-(5-(Trifluoromethyl)-2-methoxynaphthalene)-N'-4-(4-(3-(5-methoxycarbonyl)pyridyl)oxy)phenylurea was saponified according to Method D4, Step 1, and the corresponding acid was coupled with N,N-dimethylethlenediammine according to Method D4, Step 2 to afford the amide.

[0185] Entry 34: 4-(3-Carboxyphenoxo)aniline was synthesized according to Method A11. 5-(Trifluoromethyl)-2-methoxynaphthalene was converted into 5-(trifluoromethyl)-2-methoxynaphthalene isocyanate according to Method B1. 4-(3-Carboxyphenoxo)aniline was reacted with 5-(trifluoromethyl)-2-methoxynaphthalene isocyanate according to Method C1f to afford N-(5-(trifluoromethyl)-2-methoxynaphthalene)-N'-3-(3-carboxyphenyl)urea, which was coupled with 3-amino-propylamine according to Method D1c.

[0186] Entry 35: 4-(3-Carboxyphenoxo)aniline was synthesized according to Method A11. 5-(Trifluoromethyl)-2-methoxynaphthalene was converted into 5-(trifluoromethyl)-2-methoxynaphthalene isocyanate according to Method B1. 4-(3-Carboxyphenoxo)aniline was reacted with 5-(trifluoromethyl)-2-methoxynaphthalene isocyanate according to Method C1f to afford N-(5-(trifluoromethyl)-2-methoxynaphthalene)-N'-3-(3-carboxyphenyl)urea, which was coupled with N-(4-fluorophenyl)perazaine according to Method D1c.

[0187] Entry 36: 4-(3-Carboxyphenoxo)aniline was synthesized according to Method A11. 5-(Trifluoromethyl)-2-methoxynaphthalene was converted into 5-(trifluoromethyl)-2-methoxynaphthalene isocyanate according to Method B1. 4-(3-Carboxyphenoxo)aniline was reacted with 5-(trifluoromethyl)-2-methoxynaphthalene isocyanate according
to Method C1f to afford N-(5-(trifluoromethyl)-2-methoxyphenyl)-N’-(3-carboxyphenyl)urea, which was coupled with 4-fluorourilnine according to Method D1c.

[0188] Entry 37: 4-(3-Carboxyphenoxo)aniline was synthesized according to Method A11. 5-(Trifluoromethyl)-2-methoxyaniline was converted into 5-(trifluoromethyl)-2-methoxyphenyl isocyanate according to Method B1. 4-(3-Carboxyphenoxo)aniline was reacted with 5-(trifluoromethyl)-2-methoxyphenyl isocyanate according to Method C1f to afford N-(5-(trifluoromethyl)-2-methoxyphenyl)-N’-(3-carboxyphenyl)urea, which was coupled with 4-dimethylamino)aniline according to Method D1c.

[0189] Entry 38: 4-(3-Carboxyphenoxo)aniline was synthesized according to Method A11. 5-(Trifluoromethyl)-2-methoxyaniline was converted into 5-(trifluoromethyl)-2-methoxyphenyl isocyanate according to Method B1. 4-(3-Carboxyphenoxo)aniline was reacted with 5-(trifluoromethyl)-2-methoxyphenyl isocyanate according to Method C1f to afford N-(5-(trifluoromethyl)-2-methoxyphenyl)-N’-(3-carboxyphenyl)urea, which was coupled with 5-amino-2-methoxypyridine according to Method D1c.

[0190] Entry 39: 4-(3-Carboxyphenoxo)aniline was synthesized according to Method A11. 5-(Trifluoromethyl)-2-methoxyaniline was converted into 5-(trifluoromethyl)-2-methoxyphenyl isocyanate according to Method B1. 4-(3-Carboxyphenoxo)aniline was reacted with 5-(trifluoromethyl)-2-methoxyphenyl isocyanate according to Method C1f to afford N-(5-(trifluoromethyl)-2-methoxyphenyl)-N’-(3-carboxyphenyl)urea, which was coupled with 4-morpholinoniline according to Method D1c.

[0191] Entry 40: 4-(3-Carboxyphenoxo)aniline was synthesized according to Method A11. 5-(Trifluoromethyl)-2-methoxyaniline was converted into 5-(trifluoromethyl)-2-methoxyphenyl isocyanate according to Method B1. 4-(3-Carboxyphenoxo)aniline was reacted with 5-(trifluoromethyl)-2-methoxyphenyl isocyanate according to Method C1f to afford N-(5-(trifluoromethyl)-2-methoxyphenyl)-N’-(3-carboxyphenyl)urea, which was coupled with 4-dimethylamino)aniline according to Method D1c.

[0192] Entry 41: 4-(3-(N-Methylcarbamoyl)phenoxo)aniline was synthesized according to Method A13. According to Method C3, 4-chloro-3-(trifluoromethyl)aniline was converted to the isocyanate, then reacted with 4-(3-(N-Methylcarbamoyl)phenoxo)aniline to afford the urea.

[0193] Entry 42: 4-(2-N-Methylcarbamoyl)-4-pyridoxy)aniline was synthesized according to Method A2. 4-Chloro-3-(trifluoromethyl)phenyl isocyanate was reacted with 4-(2-N-methylcarbamoyl-4-pyridoxy)aniline according to Method C1a to afford the urea.

[0194] Entry 43: 4-Chloropyridine-2-carbonyl chloride HCl salt was reacted with ammonia according to Method A2. Step 3b to form 4-chloro-2-pyridinecarboxamide. 4-Chloro-2-pyridinecarboxamide was reacted with 4-aminophenol according to Method A2. Step 4 to form 4-(2-carbamoyl-4-pyridoxy)aniline. According to Method C1a, 4-chloro-3-(trifluoromethyl)phenyl isocyanate was reacted with 4-(2-carbamoyl-4-pyridoxy)aniline to afford the urea.

[0195] Entry 44: 4-Chloropyridine-2-carbonyl chloride HCl salt was reacted with ammonia according to Method A2. Step 3b to form 4-chloro-2-pyridinecarboxamide. 4-Chloro-2-pyridinecarboxamide was reacted with 3-aminophenol according to Method A2. Step 4 to form 3-(2-carbamoyl-4-pyridoxy)aniline. According to Method C1a, 4-chloro-3-(trifluoromethyl)phenyl isocyanate was reacted with 3-(2-carbamoyl-4-pyridoxy)aniline to afford the urea.

[0196] Entry 45: 4-Chloro-N-methyl-2-pyridinecarboxamide, which was synthesized according to Method A2, Step 3a, was reacted with 3-timophenol according to Method A2. Step 4 to form 3-(2-N-methylcarbamoyl)-4-pyridoxy)aniline. According to Method C1a, 4-chloro-3-(trifluoromethyl)phenyl isocyanate was reacted with 3-(2-N-methylcarbamoyl)-4-pyridoxy)aniline to afford the urea.

[0197] Entry 46: 5-(4-Aminophenoxo)isoindoline-1,3-dione was synthesized according to Method A3. According to Method C1a, 4-chloro-3-(trifluoromethyl)phenyl isocyanate was reacted with 5-(4-aminophenoxo)isoindoline-1,3-dione to afford the urea.

[0198] Entry 47: 4-(2-N-Methylcarbamoyl)-4-pyridoxy)-2-methylamine was synthesized according to Method A5. According to Method C1a, 4-chloro-3-(trifluoromethyl)phenyl isocyanate was reacted with 5-(4-aminophenoxo)isoindoline-1,3-dione to afford the urea.

[0199] Entry 48: 4-(3-N-Methylsulfonylphenoxo)aniline was synthesized according to Method A15. According to Method C1a, 4-chloro-3-(trifluoromethyl)phenyl isocyanate was reacted with 4-(3-N-methylsulfonyl)phenoxo)aniline to afford the urea.

[0200] Entry 49: 4-(2-N-Methylcarbamoyl)-4-pyridoxy)-2-chloroaniline was synthesized according to Method A6. According to Method C1a, 4-chloro-3-(trifluoromethyl)phenyl isocyanate was reacted with 4-(2-N-methylcarbamoyl)-4-pyridoxy)-2-chloroaniline to afford the urea.

[0201] Entry 50: According to Method A2, Step 4, 4-amino-2-methylphenol was reacted with 4-chloro-N-methyl-2-pyridinecarboxamide, which had been synthesized according to Method A2, Step 3b, to give 4-(2-N-methylcarbamoyl)-4-pyridoxy)-4-methylaniline. According to Method C1a, 4-chloro-3-(trifluoromethyl)phenyl isocyanate was reacted with 3-(2-N-methylcarbamoyl)-4-pyridoxy)-4-methylaniline to afford the urea.

[0202] Entry 51: 4-Chloropyridine-2-carbonyl chloride was reacted with ethylamine according to Method A2, Step 3b. The resulting 4-chloro-N-ethyl-2-pyridinecarboxamide was reacted with 4-aminophenol according to Method A2. Step 4 to give 4-(2-N-ethylcarbamoyl)-4-pyridoxy)aniline. According to Method C1a, 4-chloro-3-(trifluoromethyl)phenyl isocyanate was reacted with 4-(2-N-ethylcarbamoyl)-4-pyridoxy)aniline to afford the urea.

[0203] Entry 52: According to Method A2, Step 4, 4-amino-2-chlorophenol was reacted with 4-chloro-N-methyl-2-pyridinecarboxamide, which had been synthesized according to Method A2, Step 3b, to give 4-(2-N-methylcarbamoyl)-4-pyridoxy)-3-chloroaniline. According to Method C1a, 4-chloro-3-(trifluoromethyl)phenyl isocyanate was reacted with 4-(2-N-methylcarbamoyl)-4-pyridoxy)-3-chloroaniline to afford the urea.

[0204] Entry 53: 4-(4-Methylthiophenoxo)-1-nitrobenzene was oxidized according to Method A19, Step 1 to give 4-(4-methylsulfonyl)phenoxo)-1-nitrobenzene. The nitrobenzene was reduced according to Method A19, Step 2 to give 4-(4-methylsulfonyl)aniline. According to Method C1a, 4-chloro-3-(trifluoromethyl)phenyl isocyanate was reacted with 4-(4-methylsulfonyl)phenoxo)-1-aniline to afford the urea.

[0205] Entry 54: 4-Bromobenzensulfonflumine chloride was reacted with methylamine according to Method A15, Step 1 to afford N-methyl-4-bromobenzensulfonflumine. N-Methyl-4-bromobenzensulfonflumine was coupled with phenol according to Method A4. Step 2 to afford 4-(4-N-methylsulfonyl-phenoxo)benzene. 4-(4-(4-N-Methylsulfonyl) phenoxo)benzene was converted into 4-(4-(4-N-methylsulfonyl)phenoxo)-1-nitrobenzene according to Method A15, Step 3. 4-(4-(4-N-Methylsulfonyl)phenoxo)-1-nitrobenzene was reduced to 4-(4-N-methylsulfonyl)phenoxo)aniline.
according to Method A15, Step 4. According to Method A1, 4-chloro-3-(trifluoromethyl)phenyl isocyanate was reacted with 4-(3-N-methylsulfamoyl)phenyl oxime anilide to afford the urea.

[0206] Entry 55: 5-Hydroxy-2-methylpyridine was coupled to 1-fluoro-4-nitrobenzene according to Method A18, Step 1 to give 4-(5-(2-Methyl)pyridyloxy)-1-nitrobenzene. The methylpyridine was oxidized according to the carboxylic acid, then esterified according to Method A18, Step 2 to give 4-(5-(2-methoxy carbonyl)pyridyloxy)-1-nitrobenzene. The nitrobenzene was reduced according the Method A18, Step 3 to give 4-(5-(2-methoxy carbonyl)pyridyloxy) anilide. The anilide was reacted with 4-chloro-3-(trifluoromethyl)phenyl isocyanate according to Method C1a to afford the urea.

[0207] Entry 56: 5-Hydroxy-2-methylpyridine was coupled to 1-fluoro-4-nitrobenzene according to Method A18, Step 1 to give 4-(5-(2-Methyl)pyridyloxy)-1-nitrobenzene. The methylpyridine was oxidized according to the carboxylic acid, then esterified according to Method A18, Step 2 to give 4-(5-(2-methoxy carbonyl)pyridyloxy)-1-nitrobenzene. The nitrobenzene was reduced according the Method A18, Step 3 to give 4-(5-(2-methoxy carbonyl)pyridyloxy) anilide. The anilide was reacted with 4-chloro-3-(trifluoromethyl)phenyl isocyanate according to Method C1a to give N-(4-chloro-3-(trifluoromethyl)phenyl)N’-(4-(2-methoxy carbonyl)-5-pyridyloxy)phenylurea. The methyl ester was reacted with methylamine according to Method D2 to afford N-(4-chloro-3-trifluoromethyl)phenyl-N’-(4-(2-methylcarbamoyl)-5-pyridyloxy)phenylurea.

[0208] Entry 57: N-(4-Chloro-3-(trifluoromethyl)phenyl)-N’(4-amino phenyl)urea was prepared according to Method C1a. N-(4-Chloro-3-(trifluoromethyl)phenyl)N’-(4-amino phenyl)urea was coupled with mono-methyl isophthalic acid according to Method D1a to afford the urea.

[0209] Entry 58: N-(4-Chloro-3-(trifluoromethyl)phenyl)-N’-(4-amino phenyl)urea was prepared according to Method C1a. N-(4-Chloro-3-(trifluoromethyl)phenyl)N’-(4-amino phenyl)urea was coupled with mono-methyl isophthalic acid according to Method D1a to afford the urea.

[0210] Entry 59: 4-Chloropyridine-2-carboxyl chloride was reacted with dimethylamine according to Method A2, Step 3b. The resulting 4-chloro-N,N-dimethyl-2-pyridinecarboxamide was reacted with 4-amino phenol according to Method A2, Step 4 to give 4-(2-[N,N-dimethylcarbamoyl]-4-pyridyloxy)aniline. According to Method C1a, 4-chloro-3-(trifluoromethyl)phenyl isocyanate was reacted with 4-(2-[N,N-dimethylcarbamoyl]-4-pyridyloxy)aniline to afford the urea.

[0211] Entry 60: 4-Hydroxyacetophenone was reacted with 4-fluorobenzene according to Method A13, Step 1 to give 4-(4-acetylphenoxo)nitrone benzene. The nitrone benzene was reduced according to Method 13, Step 4 to afford 4-(4-acetylphenoxo)aniline, which was converted to the 4-(4-[1-(N-methylaminomethyl)phenoxo]anilide HCl salt according to Method 16. According to Method C1a, 4-chloro-3-(trifluoromethyl)phenyl isocyanate was reacted with 4-(4-acetylphenoxo)aniline to afford the urea.

[0212] Entry 61: 4-(3-Carboxyphenyl)-1-nitrobenzene was synthesized according to Method A13, Step 2. 4-(3-Carboxyphenyl)-1-nitrobenzene was coupled with 4-(2-aminoethyl)morpholine according to Method A13, Step 3 to give 4-(3-(N-(2-morpholinylethyl)carbamoylphenoxo)-1-nitrobenzene. According to Method A13 Step 4, 4-(3-(N-(2-morpholinylethyl)carbamoylphenoxo)-1-nitrobenzene was reduced to 4-(3-(N-(2-morpholinylethyl)carbamoylphenoxo)-1-nitrobenzene anilide. According to Method C1a, 4-chloro-3-(trifluoromethyl)phenyl isocyanate was reacted with 4-(3-(N-(2-morpholinylethyl)carbamoylphenoxo)-1-nitrobenzene anilide. The anilide was reacted with 4-chloro-3-(trifluoromethyl)phenyl isocyanate according to Method C1a to afford the urea.

[0213] Entry 62: 4-(3-Carboxyphenyl)-1-nitrobenzene was synthesized according to Method A13, Step 2. 4-(3-Carboxyphenyl)-1-nitrobenzene was coupled with 1-[2-aminoethyl]peridine according to Method A13, Step 3 to give 4-(3-(N-(2-piperidinylethyl)carbamoylphenoxo)-1-nitrobenzene. According to Method A13 Step 4, 4-(3-(N-(2-piperidinylethyl)carbamoylphenoxo)-1 nitrobenzene was reduced to 4-(3-(N-(2-piperidinylethyl)carbamoylphenoxo)-1 nitrobenzene anilide. According to Method C1a, 4-chloro-3-(trifluoromethyl)phenyl isocyanate was reacted with 4-(3-(N-(2-piperidinylethyl)carbamoylphenoxo)-1 nitrobenzene anilide. According to Method C1a, 4-chloro-3-(trifluoromethyl)phenyl isocyanate was reacted with 4-(3-(N-(2-piperidinylethyl)carbamoylphenoxo)-1-nitrobenzene anilide. According to Method C1a, 4-chloro-3-(trifluoromethyl)phenyl isocyanate was reacted with 4-(3-(N-(2-piperidinylethyl)carbamoylphenoxo)-1 nitrobenzene anilide. According to Method C1a, 4-chloro-3-(trifluoromethyl)phenyl isocyanate was reacted with 4-(3-(N-(2-piperidinylethyl)carbamoylphenoxo)-1 nitrobenzene anilide. According to Method C1a, 4-chloro-3-(trifluoromethyl)phenyl isocyanate was reacted with 4-(3-(N-(2-piperidinylethyl)carbamoylphenoxo)-1 nitrobenzene anilide. According to Method C1a, 4-chloro-3-(trifluoromethyl)phenyl isocyanate was reacted with 4-(3-(N-(2-piperidinylethyl)carbamoylphenoxo)-1 nitrobenzene anilide. According to Method C1a, 4-chloro-3-(trifluoromethyl)phenyl isocyanate was reacted with 4-(3-(N-(2-piperidinylethyl)carbamoylphenoxo)-1 nitrobenzene anilide. According to Method C1a, 4-chloro-3-(trifluoromethyl)phenyl isocyanate was reacted with 4-(3-(N-(2-piperidinylethyl)carbamoylphenoxo)-1 nitrobenzene anilide. According to Method C1a, 4-chloro-3-(trifluoromethyl)phenyl isocyanate was reacted with 4-(3-(N-(2-piperidinylethyl)carbamoylphenoxo)-1 nitrobenzene anilide. According to Method C1a, 4-chloro-3-(trifluoromethyl)phenyl isocyanate was reacted with 4-(3-(N-(2-piperidinylethyl)carbamoylphenoxo)-1 nitrobenzene anilide. According to Method C1a, 4-chloro-3-(trifluoromethyl)phenyl isocyanate was reacted with 4-(3-(N-(2-piperidinylethyl)carbamoylphenoxo)-1 nitrobenzene anilide. According to Method C1a, 4-chloro-3-(trifluoromethyl)phenyl isocyanate was reacted with 4-(3-(N-(2-piperidinylethyl)carbamoylphenoxo)-1 nitrobenzene anilide. According to Method C1a, 4-chloro-3-(trifluoromethyl)phenyl isocyanate was reacted with 4-(3-(N-(2-piperidinylethyl)carbamoylphenoxo)-1 nitrobenzene anilide. According to Method C1a, 4-chloro-3-(trifluoromethyl)phenyl isocyanate was reacted with 4-(3-(N-(2-piperidinylethyl)carbamoylphenoxo)-1 nitrobenzene anilide. According to Method C1a, 4-chloro-3-(trifluoromethyl)phenyl isocyanate was reacted with 4-(3-(N-(2-piperidinylethyl)carbamoylphenoxo)-1 nitrobenzene anilide. According to Method C1a, 4-chloro-3-(trifluoromethyl)phenyl isocyanate was reacted with 4-(3-(N-(2-piperidinylethyl)carbamoylphenoxo)-1 nitrobenzene anilide. According to Method C1a, 4-chloro-3-(trifluoromethyl)phenyl isocyanate was reacted with 4-(3-(N-(2-piperidinylethyl)carbamoylphenoxo)-1 nitrobenzene anilide. According to Method C1a, 4-chloro-3-(trifluoromethyl)phenyl isocyanate was reacted with 4-(3-(N-(2-piperidinylethyl)carbamoylphenoxo-
ylcarbamoylaniline according to Method D1b to give N-(4-chloro-3-(trifluoromethyl)phenyl)-N′-(4-(3-methylcarbamoylphenyl)carbamoyl)urea.

[0219] Entry 68: 5-(4-Aminophenoxo)-2-methylsindoline-1,3-dione was synthesized according to Method A9. According to Method C1a, 4-chloro-3-(trifluoromethyl)phenyl isocyanate was reacted with 5-(4-aminophenoxo)-2-methylsindoline-1,3-dione to afford the urea.

[0220] Entry 69: 4-Chloro-N-methylpyridinecarboxamide was synthesized as described in Method A2, Step 3b. The chloropyridine was reacted with 3-aminothiophenol according to Method A2, Step 4 to give 3-(4-(2-N-methylcarbamoyl)phenylthio)aniline. According to Method C1a, 4-chloro-3-(trifluoromethyl)phenyl isocyanate was reacted with 3-(4-(2-N-methylcarbamoyl)phenylthio)aniline to afford the urea.

[0221] Entry 70: 4-(2-(N-(2-Morpholin-4-yl)carbamoyl)pyridyl)oxo)aniline was synthesized according to Method A10. According to Method C1a, 4-chloro-3-(trifluoromethyl)phenyl isocyanate was reacted with 4-(2-(N-(2-morpholin-4-yl)carbamoyl)pyridyl)oxo)aniline to afford the urea.

[0222] Entry 71: 4-(3-(5-Methoxy carbonyl)pyridyl)oxo)aniline was synthesized according to Method A14. 4-Chloro-3-(trifluoromethyl)phenyl isocyanate was reacted with 4-(3-(5-methoxy carbonyl)pyridyl)oxo)aniline according to Method C1a to afford the urea. N-(4-Chloro-3-(trifluoromethyl)phenyl)-N′-(4-(3-(5-methoxy carbonyl)pyridyl)oxo)phenylurea was saponified according to Method D4, Step 1, and the corresponding acid was coupled with 4-(2-aminoethyl)morpholine to afford the amide.

[0223] Entry 72: 4-(3-(5-Methoxy carbonyl)pyridyl)oxo)aniline was synthesized according to Method A14. 4-Chloro-3-(trifluoromethyl)phenyl isocyanate was reacted with 4-(3-(5-methoxy carbonyl)pyridyl)oxo)aniline according to Method C1a to afford the urea. N-(5-(Trifluoromethyl)-2-methoxyphenyl)-N′-(4-(3-(5-methoxy carbonyl)pyridyl)oxo)phenylurea was saponified according to Method D4, Step 1, and the corresponding acid was coupled with methyleamine according to Method D4, Step 2 to afford the amide.

[0224] Entry 73: 4-(3-(5-Methoxy carbonyl)pyridyl)oxo)aniline was synthesized according to Method A14. 4-Chloro-3-(trifluoromethyl)phenyl isocyanate was reacted with 4-(3-(5-methoxy carbonyl)pyridyl)oxo)aniline according to Method C1a to afford the urea. N-(5-(Trifluoromethyl)-2-methoxyphenyl)-N′-(4-(3-(5-methoxy carbonyl)pyridyl)oxo)phenylurea was saponified according to Method D4, Step 1, and the corresponding acid was coupled with N,N-dimethylmethylenediamine according to Method D4, Step 2 to afford the amide.

[0225] Entry 74: 4-Chloropyridine-2-carbonyl chloride HCl salt was reacted with 2-hydroxyethylamine according to Method A2, Step 3b to form 4-chloro-N-(2-trisopropylisilyloxethyl)pyridine-2-carboxamide. 4-Chloro-N-(2-trisopropylisilyloxethyl)pyrididine-2-carboxamide was reacted with trisopropylisilyl chloride, followed by 4-aminophenol according to Method A17 to form 4-(4-(2-N-(2-trisopropylisilyloxethyl)carbamoyl)pyridyl)oxo)aniline. According to Method C1a, 4-chloro-3-(trifluoromethyl)phenyl isocyanate was reacted with 4-(4-(2-N-(2-trisopropylisilyloxethyl)carbamoyl)pyridyl)oxo)aniline to afford N-(4-chloro-3-(trifluoromethyl)phenyl)-N′-(4-(4-(2-N-(2-trisopropylisilyloxethyl)carbamoyl)pyridyl)oxo)phenylurea.

[0226] Entry 75: 4-(3-Carboxyphenoxy)aniline was synthesized according to Method A11. 4-Chloro-3-(trifluoromethyl)phenyl isocyanate was reacted with 4-(3-(5-methylcarbonyl)pyridyl)oxy)aniline according to Method C1f to afford the urea, which was coupled with 3-aminopyridine according to Method D1c.

[0227] Entry 76: 4-(3-Carboxyphenoxy)aniline was synthesized according to Method A11. 4-Chloro-3-(trifluoromethyl)phenyl isocyanate was reacted with 4-(3-carboxyphenoxy)aniline according to Method C1f to afford the urea, which was coupled with 4-fluoroaniline according to Method D1c.

[0228] Entry 77: 4-(3-Carboxyphenoxy)aniline was synthesized according to Method A11. 4-Chloro-3-(trifluoromethyl)phenyl isocyanate was reacted with 4-(3-carboxyphenoxy)aniline according to Method C1f to afford the urea, which was coupled with 4-fluoroaniline according to Method D1c.

[0229] Entry 78: 4-(3-Carboxyphenoxy)aniline was synthesized according to Method A11. 4-Chloro-3-(trifluoromethyl)phenyl isocyanate was reacted with 4-(3-carboxyphenoxy)aniline according to Method C1f to afford the urea, which was coupled with 4-(dimethylamino)aniline according to Method D1c.

[0230] Entry 79: 4-(3-Carboxyphenoxy)aniline was synthesized according to Method A11. 4-Chloro-3-(trifluoromethyl)phenyl isocyanate was reacted with 4-(3-carboxyphenoxy)aniline according to Method C1f to afford the urea, which was coupled with N-phenylethylenediamine according to Method D1c.

[0231] Entry 80: 4-(3-Carboxyphenoxy)aniline was synthesized according to Method A11. 4-Chloro-3-(trifluoromethyl)phenyl isocyanate was reacted with 4-(3-carboxyphenoxy)aniline according to Method C1f to afford the urea, which was coupled with 2-methoxyethylenediamine according to Method D1c.

[0232] Entry 81: 4-(3-Carboxyphenoxy)aniline was synthesized according to Method A11. 4-Chloro-3-(trifluoromethyl)phenyl isocyanate was reacted with 4-(3-carboxyphenoxy)aniline according to Method C1f to afford the urea, which was coupled with 5-amino-2-methoxy pyridine according to Method D1c.

[0233] Entry 82: 4-(3-Carboxyphenoxy)aniline was synthesized according to Method A11. 4-Chloro-3-(trifluoromethyl)phenyl isocyanate was reacted with 4-(3-carboxyphenoxy)aniline according to Method C1f to afford the urea, which was coupled with 4-morpholinonaniline according to Method D1c.

[0234] Entry 83: 4-(3-Carboxyphenoxy)aniline was synthesized according to Method A11. 4-Chloro-3-(trifluoromethyl)phenyl isocyanate was reacted with 4-(3-carboxyphenoxy)aniline according to Method C1f to afford the urea, which was coupled with N-(2-pyridyl)pyrrolidine according to Method D1c.

[0235] Entry 84: 4-Chloropyridine-2-carbonyl chloride HCl salt was reacted with 2-hydroxyethylamine according to Method A2, Step 3b to form 4-chloro-N-(2-trisopropylisilyloxethyl)pyridine-2-carboxamide. 4-Chloro-N-(2-trisopropylisilyloxethyl)pyridine-2-carboxamide was reacted with trisopropylisilyl chloride, followed by 4-aminophenol according to Method A17 to form 4-(4-(2-N-(2-trisopropylisilyloxethyl)carbamoyl)pyridyl)oxo)aniline. According to Method C1a, 4-chloro-3-(trifluoromethyl)phenyl isocyanate was reacted with 4-(4-(2-N-(2-trisopropylisilyloxethyl)carbamoyl)pyridyl)oxo)aniline to afford N-(4-chloro-3-(trifluoromethyl)phenyl)-N′-(4-(4-(2-N-(2-trisopropylisilyloxethyl)carbamoyl)pyridyl)oxo)phenylurea.
[0236] Entry 85: 4-(2-(N-Methylcarbamoyl)-4-pyridyl)-aniline was synthesized according to Method A2. 4-Bromo-3-(trifluoroethyl)aniline was converted to 4-bromo-3-(trifluoroethyl)phenyl isocyanate according to Method B1. According to Method C1a, 4-bromo-3-(trifluoroethyl)phenyl isocyanate was reacted with 4-(2-(N-methylcarbamoyl)-4-pyridyl)-aniline to afford the are.  

[0237] Entry 86: 4-(2-(N-Methylcarbamoyl)-4-pyridyl)-aniline was synthesized according to Method A6. 4-Bromo-3-(trifluoromethyl)aniline was converted into 4-bromo-3-(trifluoromethyl)phenyl isocyanate according to Method B1. According to Method C1a, 4-bromo-3-(trifluoromethyl)phenyl isocyanate was reacted with 4-(2-(N-methylcarbamoyl)-4-pyridyl)-aniline to afford the are.  

[0238] Entry 87: According to Method A2, Step 4, 4-amino-2-chlorophenol was reacted with 4-chloro-N-methyl-2-pyridinecarboxamide, which had been synthesized according to Method A2. Step 3b, to give 4-(2-(N-methylcarbamoyl)-4-pyridyl)-3-chloroaniline. 4-Bromo-3-(trifluoromethyl)phenyl isocyanate was converted into 4-bromo-3-(trifluoromethyl)phenyl isocyanate according to Method B1. According to Method C1a, 4-bromo-3-(trifluoromethyl)phenyl isocyanate was reacted with 4-(2-(N-methylcarbamoyl)-4-pyridyl)-3-chloroaniline to afford the are.  

[0239] Entry 88: 4-Chloropyridine-2-carbonyl chloride was reacted with ethylamine according to Method A2. Step 3b. The resulting 4-chloro-N-ethyl-2-pyridinecarboxamide was reacted with 4-aminophenol according to Method A2. Step 4 to give 4-(2-(N-ethylcarbamoyl)-4-pyridyl)-aniline. 4-Bromo-3-(trifluoromethyl)aniline was converted into 4-bromo-3-(trifluoromethyl)phenyl isocyanate according to Method B1. According to Method C1a, 4-bromo-3-(trifluoromethyl)phenyl isocyanate was reacted with 4-(2-(N-ethylcarbamoyl)-4-pyridyl)-aniline to afford the are.  

[0240] Entry 89: 4-Chloro-N-methyl-2-pyridinecarboxamide, which was synthesized according to Method A2, Step 3a, was reacted with 3-aminophenol according to Method A2, Step 4 to form 3-(2-(N-methylcarbamoyl)-4-pyridyl)aniline. 4-Bromo-3-(trifluoromethyl)aniline was converted into 4-bromo-3-(trifluoromethyl)phenyl isocyanate according to Method B1. According to Method C1a, 4-bromo-3-(trifluoromethyl)phenyl isocyanate was reacted with 3-(2-(N-methylcarbamoyl)-4-pyridyl)aniline to afford the are.  

[0241] Entry 90: According to Method A2, Step 2, 4-amino-2-methylphenol was reacted with 4-chloro-N-methyl-2-pyridinecarboxamide, which had been synthesized according to Method A2. Step 3b, to give 3-(2-(N-methylcarbamoyl)-4-pyridyl)-4-methylaniline. 4-Bromo-3-(trifluoromethyl)aniline was converted into 4-bromo-3-(trifluoromethyl)phenyl isocyanate according to Method B1. According to Method C1a, 4-bromo-3-(trifluoromethyl)phenyl isocyanate was reacted with 3-(2-(N-methylcarbamoyl)-4-pyridyl)-4-methylaniline to afford the are.  

[0242] Entry 91: 4-Chloropyridine-2-carbonyl chloride was reacted with dimethylamine according to Method A2. Step 3b. The resulting 4-chloro-N,N-dimethyl-2-pyridinecarboxamide was reacted with 4-aminophenol according to Method A2, Step 4 to give 4-(2-(N,N-dimethylcarbamoyl)-4-pyridyl)-aniline. 4-Bromo-3-(trifluoromethyl)aniline was converted into 4-bromo-3-(trifluoromethyl)phenyl isocyanate according to Method B1. According to Method C1a, 4-bromo-3-(trifluoromethyl)phenyl isocyanate was reacted with 4-(2-(N,N-dimethylcarbamoyl)-4-pyridyl)-aniline to afford the are.  

[0243] Entry 92: 4-Chloro-N-methylpyridinecarboxamide was synthesized as described in Method A2, Step 3b. The chloropyridine was reacted with 4-aminophenol according to Method A2. Step 4 to give 4-(2-(N-methylcarbamoyl)-phenylthio)-aniline. 4-Bromo-3-(trifluoromethyl)aniline was converted into 4-bromo-3-(trifluoromethyl)phenyl isocyanate according to Method B1. According to Method C1a, 4-bromo-3-(trifluoromethyl)phenyl isocyanate was reacted with 4-(2-(N-methylcarbamoyl)-phenylthio)-aniline to afford the are.  

[0244] Entry 93: 4-Chloro-N-methylpyridinecarboxamide was synthesized as described in Method A2, Step 3b. The chloropyridine was reacted with 3-aminophenol according to Method A2, Step 4 to give 3-(2-(N-methylcarbamoyl)-phenylthio)-aniline. 4-Bromo-3-(trifluoromethyl)aniline was converted into 4-bromo-3-(trifluoromethyl)phenyl isocyanate according to Method B1. According to Method C1a, 4-bromo-3-(trifluoromethyl)phenyl isocyanate was reacted with 3-(2-(N-methylcarbamoyl)-phenylthio)-aniline to afford the are.  

[0245] Entry 94: 4-(2-(N-2-Morpholin-4-yl)ethylcarbamoyl)pyridylxoy aniline was synthesized according to Method A10. 4-Bromo-3-(trifluoromethyl)aniline was converted into 4-bromo-3-(trifluoromethyl)phenyl isocyanate according to Method B1. According to Method C1a, 4-bromo-3-(trifluoromethyl)phenyl isocyanate was reacted with 4-(2-(N-2-Morpholin-4-yl)ethylcarbamoyl)pyridylxoy aniline to afford the are.  

[0246] Entry 95: 4-(2-(N-Methylcarbamoyl)-4-pyridyl)-aniline was synthesized according to Method A2. 4-Chloro-2-methoxy-5-(trifluoromethyl)-aniline was synthesized according to Method A7. 4-Chloro-2-methoxy-5-(trifluoromethyl)-aniline was converted into 4-chloro-2-methoxy-5-(trifluoromethyl)phenyl isocyanate according to Method A1. According to Method C1a, 4-chloro-2-methoxy-5-(trifluoromethyl)phenyl isocyanate was reacted with 4-(2-(N-methylcarbamoyl)-4-pyridyl)-aniline to afford the are.  

[0247] Entry 96: 4-(2-(N-Methylcarbamoyl)-4-pyridyl)-2-chloroaniline was synthesized according to Method A6. 4-Chloro-2-methoxy-5-(trifluoromethyl)aniline was synthesized according to Method A7. 4-Chloro-2-methoxy-5-(trifluoromethyl)aniline was converted into 4-chloro-2-methoxy-5-(trifluoromethyl)phenyl isocyanate according to Method A1. According to Method C1a, 4-chloro-2-methoxy-5-(trifluoromethyl)phenyl isocyanate was reacted with 4-(2-(N-methylcarbamoyl)-4-pyridyl)-2-chloroaniline to afford the are.  

[0248] Entry 97: According to Method A2, Step 4, 4-amino-2-chlorophenol was reacted with 4-chloro-N-methyl-2-pyridinecarboxamide, which had been synthesized according to Method A2. Step 3b, to give 4-(2-(N-methylcarbamoyl)-4-pyridyl)-3-chloroaniline. 4-Chloro-2-methoxy-5-(trifluoromethyl)aniline was synthesized according to Method A7. 4-Chloro-2-methoxy-5-(trifluoromethyl)aniline was converted into 4-chloro-2-methoxy-5-(trifluoromethyl)phenyl isocyanate according to Method B1. According to Method C1a, 4-chloro-2-methoxy-5-(trifluoromethyl)phenyl isocyanate was reacted with 4-(2-(N-methylcarbamoyl)-4-pyridyl)-3-chloroaniline to afford the are.  

[0249] Entry 98: 4-Chloro-N-methyl-2-pyridinecarboxamide, which was synthesized according to Method A2, Step 3a, was reacted with 3-aminophenol according to Method A2, Step 4 to form 3-(2-(N-methylcarbamoyl)-4-pyridyl)aniline. 4-Chloro-2-methoxy-5-(trifluoromethyl)aniline was synthesized according to Method A7. 4-Chloro-2-methoxy-5-(trifluoromethyl)aniline was converted into 4-chloro-2-methoxy-5-(trifluoromethyl)phenyl isocyanate according to Method A1. According to Method C1a, 4-chloro-2-methoxy-5-(trifluoromethyl)phenyl isocyanate was reacted with 4-(2-(N-methylcarbamoyl)-4-pyridyl)-3-chloroaniline to afford the are.
Method B1. According to Method C1a, 4-chloro-2-methoxy-5-(trifluoromethyl)phenyl isocyanate was reacted with 3-(2-N-methylcarbamoyl)-4-pyridyloxy)aniline to afford the urea.

[0251] Entry 99: 4-Chloropyridine-2-carbonyl chloride was reacted with ethylamine according to Method A2, Step 3b. The resulting 4-chloro-N-ethyl-2-pyridinecarboxamide was reacted with 4-aminophenol according to Method A2, Step 4 to give 4-(2-(N-ethylcarbamoyl)-4-pyridyloxy)aniline. 4-Chloro-2-methoxy-5-(trifluoromethyl)aniline was synthesized according to Method A7. 4-Chloro-2-methoxy-5-(trifluoromethyl)aniline was converted into 4-chloro-2-methoxy-5-(trifluoromethyl)phenyl isocyanate according to Method B1. According to Method C1a, 4-chloro-2-methoxy-5-(trifluoromethyl)phenyl isocyanate was reacted with 4-(2-(N-ethylcarbamoyl)-4-pyridyloxy)aniline to afford the urea.

[0252] Entry 100: 4-Chloropyridine-2-carbonyl chloride was reacted with dimethylamine according to Method A2, Step 3b. The resulting 4-chloro-N,N-dimethyl-2-pyridinecarboxamide was reacted with 4-aminophenol according to Method A2, Step 4 to give 4-(2-(N,N-dimethylcarbamoyl)-4-pyridyloxy)aniline. 4-Chloro-2-methoxy-5-(trifluoromethyl)aniline was synthesized according to Method A7. 4-Chloro-2-methoxy-5-(trifluoromethyl)aniline was converted into 4-chloro-2-methoxy-5-(trifluoromethyl)phenyl isocyanate according to Method B1. According to Method C1a, 4-chloro-2-methoxy-5-(trifluoromethyl)phenyl isocyanate was reacted with 4-(2-(N,N-dimethylcarbamoyl)-4-pyridyloxy)aniline to afford the urea.

[0253] Entry 101: 4-Chloro-N-methyl-2-pyridinecarboxamide, which was synthesized according to Method A2, Step 3a, was reacted with 3-aminophenol according to Method A2, Step 4 to form 3-(2-(N-methylcarbamoyl)-4-pyridyloxy)aniline. 2-Amino-3-methoxynaphthalene was synthesized as described Method A1. According to Method C3, 2-amino-3-methoxynaphthalene was reacted with bis(trichloromethyl) carbonate followed by 3-(2-(N-methylcarbamoyl)-4-pyridyloxy)aniline to form the urea.

[0254] Entry 102: 4-(2-(N-Methylcarbamoyl)-4-pyridyloxy)aniline was synthesized according to Method A2, 5-tert-Butyl-2-(2,5-dimethylpyrrolyl)aniline was synthesized according to Method A4. 5-tert-Butyl-2-(2,5-dimethylpyrrolyl)aniline was reacted with CDF followed by 4-(2-(N-methylcarbamoyl)-4-pyridyloxy)aniline according to Method C2d to afford the urea.

[0255] Entry 103: 4-Chloro-N-methyl-2-pyridinecarboxamide was synthesized according to Method A2, Step 3b. 4-Chloro-N-methyl-2-pyridinecarboxamide was reacted with 4-aminophenol according to Method A2, Step 4 using DMAC in place of DMF to give 4-(2-(N-methylcarbamoyl)-4-pyridyloxy)aniline. According to Method C2b, reaction of 3-aminomethoxyquinoline with CDF followed by 4-(2-(N-methylcarbamoyl)-4-pyridyloxy)aniline afforded bis(4-(2-(N-methylcarbamoyl)-4-pyridyloxy)phenyl)urea.

Tables

[0256] The compounds listed in Tables 1-6 below were synthesized according to the general methods shown above, and the more detailed exemplary procedures are in the entry listings above and characterizations are indicated in the tables.

TABLE 1

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>mp (°C)</th>
<th>HPLC (min.)</th>
<th>TLC Solvent System</th>
<th>Mass Spec.</th>
<th>Synth. Method</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Source</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

3-tert-Butylphenyl Ureas

![Chemical Structure](image)
### TABLE 1-continued

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>mp (°C)</th>
<th>HPLC (min.)</th>
<th>TLC R&lt;sub&gt;y&lt;/sub&gt;</th>
<th>TLC Solvent System</th>
<th>Mass Spec. [Source]</th>
<th>Synth. Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>OMe</td>
<td>133-135</td>
<td>0.68</td>
<td>100% EtOAc</td>
<td>448 (M + H)&lt;sup&gt;+&lt;/sup&gt; (FAB)</td>
<td>A8 C2d</td>
<td></td>
</tr>
</tbody>
</table>

### TABLE 2

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>mp (°C)</th>
<th>HPLC (min.)</th>
<th>TLC R&lt;sub&gt;y&lt;/sub&gt;</th>
<th>TLC Solvent System</th>
<th>Mass Spec. [Source]</th>
<th>Synth. Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>Me</td>
<td>5.93</td>
<td>448</td>
<td>(M + H)&lt;sup&gt;+&lt;/sup&gt; (HPLC ES-MS)</td>
<td>A13 C1a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>OMe</td>
<td>120-122</td>
<td>0.67</td>
<td>100% EtOAc</td>
<td>478 (M + H)&lt;sup&gt;+&lt;/sup&gt; (FAB)</td>
<td>A8 C2d</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>OMe</td>
<td>0.40</td>
<td>460</td>
<td>80% EtOAc/50% hexane (HPLC ES-MS)</td>
<td>460 A2 C2d</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### TABLE 2-continued

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>mp (°C)</th>
<th>HPLC (min.)</th>
<th>TLC R_f</th>
<th>Mass Spec. [Source]</th>
<th>Synth. Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td></td>
<td>0.79</td>
<td>50% EtOAc/50% hexane</td>
<td>446 (M + H)⁺ (HPLC ES-MS)</td>
<td>A12 C2d</td>
<td></td>
</tr>
</tbody>
</table>

### TABLE 3

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>mp (°C)</th>
<th>HPLC (min.)</th>
<th>TLC R_f</th>
<th>Mass Spec. [Source]</th>
<th>Synth. Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td></td>
<td>250 (dec)</td>
<td>460 (M + H)⁺ (FAH)</td>
<td>A13 C2a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td></td>
<td>206-208</td>
<td>446 (M + H)⁺ (HPLC ES-MS)</td>
<td>A3 step 2, A8 step 4, H1, C1a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td></td>
<td>0.54</td>
<td>445 (M + H)⁺ (HPLC ES-MS)</td>
<td>A13 C3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td></td>
<td>0.20</td>
<td>461 (M + H)⁺ (HPLC ES-MS)</td>
<td>A2 C4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### TABLE 3-continued

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>mp (°C.)</th>
<th>HPLC (min.)</th>
<th>TLC System</th>
<th>Mass Spec. [Sourced]</th>
<th>Synth. Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td><img src="image" alt="Structure" /></td>
<td>0.27</td>
<td>1% EtOH/99% EtOAc</td>
<td>A2 447 (M + H)+ (HPLC ES-MS)</td>
<td>C4</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td><img src="image" alt="Structure" /></td>
<td>0.62</td>
<td>100% EtOAc</td>
<td>A2 461 (M + H)+ (FAB)</td>
<td>C2a</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td><img src="image" alt="Structure" /></td>
<td>114-117</td>
<td>1% EtOH/99% EtOAc</td>
<td>A2 447 (M + H)+ (FAB)</td>
<td>C4</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td><img src="image" alt="Structure" /></td>
<td>0.54</td>
<td>100% EtOAc</td>
<td>A8 490 (M + H)+ (FAH)</td>
<td>C2a</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td><img src="image" alt="Structure" /></td>
<td>0.29</td>
<td>5% MeOH/45% EtOAc/50% pet ether</td>
<td>A5 475 (M + H)+ (HPLC ES-MS)</td>
<td>C1c</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td><img src="image" alt="Structure" /></td>
<td>0.17</td>
<td>50% EtOAc/50% pet ether</td>
<td>A6 495 (M + H)+ (HPLC ES-MS)</td>
<td>B1 C1a</td>
<td></td>
</tr>
<tr>
<td>Entry</td>
<td>R</td>
<td>mp (°C)</td>
<td>HPLC Rf</td>
<td>TLC Solvent System</td>
<td>Mass Spec</td>
<td>Synth. Method</td>
</tr>
<tr>
<td>-------</td>
<td>------------------------</td>
<td>---------</td>
<td>---------</td>
<td>--------------------</td>
<td>-----------</td>
<td>---------------</td>
</tr>
<tr>
<td>18</td>
<td></td>
<td></td>
<td>0.48</td>
<td>100% ES0Ac</td>
<td>475 (M + H)+ (HPLC ES-MS)</td>
<td>A2 step 4,  ill, C1a</td>
</tr>
<tr>
<td>19</td>
<td></td>
<td>194-196</td>
<td>0.31</td>
<td>5% MeOH/45% EtOAc/50% pet ether</td>
<td>475 (M + H)+ (HPLC ES-MS)</td>
<td>A2 ill, C1a</td>
</tr>
<tr>
<td>20</td>
<td></td>
<td>214-216</td>
<td>0.25</td>
<td>5% MeOH/45% EtOAc/50% pet ether</td>
<td>495 (M + H)+ (HPLC ES-MS)</td>
<td>A2 C1a</td>
</tr>
<tr>
<td>21</td>
<td></td>
<td>208-210</td>
<td>0.30</td>
<td>50% EtOAc/50% hexane</td>
<td>481 (M + H)+ (HPLC ES-MS)</td>
<td>A19 C2a</td>
</tr>
<tr>
<td>22</td>
<td></td>
<td>188-190</td>
<td>0.30</td>
<td>70% EtOAc/30% hexane</td>
<td>447 (M + H)+ (HPLC ES-MS)</td>
<td>A15, step 4, C1a</td>
</tr>
<tr>
<td>23</td>
<td></td>
<td></td>
<td>0.50</td>
<td>70% EtOAc/30% hexane</td>
<td>472 (M + H)+ (FAB)</td>
<td>A3 ill, C1a</td>
</tr>
<tr>
<td>24</td>
<td></td>
<td>203-205</td>
<td>0.13</td>
<td>100% EtOAc</td>
<td>479 (M + H)+ (HPLC ES-MS)</td>
<td>A2 ill, C1a</td>
</tr>
</tbody>
</table>
### TABLE 3-continued

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>mp (°C)</th>
<th>HPLC (min.)</th>
<th>TLC Rf</th>
<th>Solvent System</th>
<th>Mass Spec. [Source]</th>
<th>Synth. Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>0.09</td>
<td>75% EioAc/25% hexane</td>
<td>458 (M + H)+ (HPLC ES-MS)</td>
<td>A12, C2d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>26</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>169-171</td>
<td>0.67</td>
<td>50% EioAc/50% pet ether</td>
<td>474 (M + H)+ (HPLC ES-MS)</td>
<td>A13 step 1, A13 step 4, A16, B1, C1a</td>
<td></td>
</tr>
<tr>
<td>27</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>218-219</td>
<td>0.40</td>
<td>50% EioAc/50% pet ether</td>
<td>477 (M + H)+ (HPLC ES-MS)</td>
<td>A2 step 3b, A2 step 4, B1, C1a</td>
<td></td>
</tr>
<tr>
<td>28</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>212-214</td>
<td>0.30</td>
<td>40% EioAc/60% hexane</td>
<td></td>
<td>A9, B1, C1a</td>
<td></td>
</tr>
<tr>
<td>29</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>0.33</td>
<td>50% EioAc/50% pet ether</td>
<td>474 (M + H)+ (HPLC ES-MS)</td>
<td>A5 step 3b, A2 step 4, B1, C1a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>210-211</td>
<td></td>
<td></td>
<td>A2, B1, C1a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Entry</td>
<td>R</td>
<td>mp °C</td>
<td>HPLC (min.)</td>
<td>TLC Rf</td>
<td>Solvent System</td>
<td>Mass Spec. [Source]</td>
<td>Synth. Method</td>
</tr>
<tr>
<td>-------</td>
<td>--------------------</td>
<td>------</td>
<td>-------------</td>
<td>--------</td>
<td>----------------</td>
<td>--------------------</td>
<td>---------------</td>
</tr>
<tr>
<td>31</td>
<td></td>
<td>210-204</td>
<td>0.43</td>
<td>10% MeOH/CH2Cl2</td>
<td>A14</td>
<td>B1</td>
<td>C1a</td>
</tr>
<tr>
<td>32</td>
<td></td>
<td>247-249</td>
<td>0.57</td>
<td>10% MeOH/CH2Cl2</td>
<td>A14</td>
<td>B1</td>
<td>C1b</td>
</tr>
<tr>
<td>33</td>
<td></td>
<td>217-219</td>
<td>0.07</td>
<td>10% MeOH/CH2Cl2</td>
<td>A14</td>
<td>B1</td>
<td>C1c</td>
</tr>
<tr>
<td>34</td>
<td></td>
<td></td>
<td>0.11</td>
<td>70% EtOAc/30% hexane</td>
<td>A11</td>
<td>B1</td>
<td>C1d</td>
</tr>
<tr>
<td>35</td>
<td></td>
<td></td>
<td>0.38</td>
<td>70% EtOAc/30% hexane</td>
<td>A11</td>
<td>B1</td>
<td>C1e</td>
</tr>
<tr>
<td>-------</td>
<td>---</td>
<td>----------</td>
<td>------</td>
<td>-----</td>
<td>---------</td>
<td>------------------</td>
<td>--------------</td>
</tr>
<tr>
<td>36</td>
<td></td>
<td></td>
<td>0.77</td>
<td>70%</td>
<td>A11</td>
<td>B1</td>
<td>D1c</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>EIOAc/</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>30%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>hexane</td>
<td></td>
<td></td>
</tr>
<tr>
<td>37</td>
<td>Me</td>
<td></td>
<td>0.58</td>
<td>70%</td>
<td>A11</td>
<td>B1</td>
<td>D1c</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>EIOAc/</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>30%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>hexane</td>
<td></td>
<td></td>
</tr>
<tr>
<td>38</td>
<td></td>
<td></td>
<td>0.58</td>
<td>70%</td>
<td>A11</td>
<td>B1</td>
<td>D1c</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>EIOAc/</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>30%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>hexane</td>
<td></td>
<td></td>
</tr>
<tr>
<td>39</td>
<td></td>
<td></td>
<td>0.17</td>
<td>70%</td>
<td>A11</td>
<td>B1</td>
<td>D1c</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>EIOAc/</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>30%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>hexane</td>
<td></td>
<td></td>
</tr>
<tr>
<td>40</td>
<td></td>
<td></td>
<td>0.21</td>
<td>70%</td>
<td>A11</td>
<td>B1</td>
<td>D1c</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>EIOAc/</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>30%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>hexane</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**5-(Trifluoromethyl)-2-methoxyphenyl Ureas**
<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>mp (°C)</th>
<th>HPLC (min.)</th>
<th>TLC Rf</th>
<th>Solvent System</th>
<th>Mass Spec. [Source]</th>
<th>Synth. Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>41</td>
<td><img src="image1" alt="Structure" /></td>
<td>163-165</td>
<td>0.08</td>
<td>464</td>
<td>EtOAc/ether (HPLC ES-MS)</td>
<td>464 (M + H)+ C3</td>
<td>A13 C3</td>
</tr>
<tr>
<td>42</td>
<td><img src="image2" alt="Structure" /></td>
<td>215</td>
<td>0.06</td>
<td>465</td>
<td>EtOAc/ether (HPLC ES-MS)</td>
<td>465 (M + H)+ C1a</td>
<td>A2 C1a</td>
</tr>
<tr>
<td>43</td>
<td><img src="image3" alt="Structure" /></td>
<td></td>
<td>0.10</td>
<td>451</td>
<td>EtOAc/ether (HPLC ES-MS)</td>
<td>451 (M + H)+ C1a</td>
<td>A2 C1a</td>
</tr>
<tr>
<td>44</td>
<td><img src="image4" alt="Structure" /></td>
<td></td>
<td>0.25</td>
<td>451</td>
<td>EtOAc/ether (HPLC ES-MS)</td>
<td>451 (M + H)+ C1a</td>
<td>A2 C1a</td>
</tr>
<tr>
<td>45</td>
<td><img src="image5" alt="Structure" /></td>
<td></td>
<td>0.31</td>
<td>465</td>
<td>EtOAc/ether (HPLC ES-MS)</td>
<td>465 (M + H)+ C1a</td>
<td>A2 C1a</td>
</tr>
<tr>
<td>46</td>
<td><img src="image6" alt="Structure" /></td>
<td>176-179</td>
<td>0.23</td>
<td>476 (M + H)+ hexane (FAB)</td>
<td>476 (M + H)+ C1a</td>
<td>A3 C1a</td>
<td></td>
</tr>
</tbody>
</table>
TABLE 4-continued

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>mp (°C)</th>
<th>HPLC (min.)</th>
<th>TLC R&lt;sub&gt;p&lt;/sub&gt;</th>
<th>TLC Solvent System</th>
<th>Mass Spec. [Source]</th>
<th>Synth. Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>47</td>
<td></td>
<td>0.29</td>
<td>478</td>
<td>5% MeOH/45% EIOAc/50% pet ether</td>
<td>A5</td>
<td>Clc</td>
<td></td>
</tr>
<tr>
<td>48</td>
<td></td>
<td>206-209</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>A15 Clc</td>
</tr>
<tr>
<td>49</td>
<td></td>
<td>0.22</td>
<td>499</td>
<td>50% EIOAc/50% pet ether</td>
<td>A6</td>
<td>Clc</td>
<td></td>
</tr>
<tr>
<td>50</td>
<td></td>
<td>0.54</td>
<td>479</td>
<td>100% EIOAc</td>
<td></td>
<td></td>
<td>Clc A2</td>
</tr>
<tr>
<td>51</td>
<td></td>
<td>0.33</td>
<td>479</td>
<td>5% MeOH/45% EIOAc/50% pet ether</td>
<td>A2</td>
<td>Clc</td>
<td></td>
</tr>
<tr>
<td>52</td>
<td></td>
<td>0.18</td>
<td>499</td>
<td>5% MeOH/45% EIOAc/50% pet ether</td>
<td>A2</td>
<td>Clc</td>
<td></td>
</tr>
<tr>
<td>53</td>
<td></td>
<td>0.30</td>
<td>485</td>
<td>50% EIOAc/50% hexane</td>
<td></td>
<td></td>
<td>Clc A19</td>
</tr>
</tbody>
</table>

3-(Trifluoromethyl)-4-chlorophenyl Ureas
### TABLE 4-continued

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>mp (°C)</th>
<th>HPLC (min.)</th>
<th>TLC Rf</th>
<th>TLC Solvent System</th>
<th>Mass Spec. [Source]</th>
<th>Synth. Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>54</td>
<td></td>
<td>196-200</td>
<td>0.30</td>
<td>0.30</td>
<td>70% EtOAc/30% hexane</td>
<td>502</td>
<td>A15 Cl1</td>
</tr>
<tr>
<td>55</td>
<td></td>
<td>228-230</td>
<td>0.30</td>
<td>0.30</td>
<td>30% EtOAc/70% C6H12Cl2</td>
<td>466</td>
<td>Cl10</td>
</tr>
<tr>
<td>56</td>
<td></td>
<td>238-245</td>
<td></td>
<td>0.30</td>
<td>60% EtOAc/20% hexane</td>
<td>492</td>
<td>C1d D1a</td>
</tr>
<tr>
<td>57</td>
<td></td>
<td>221-222</td>
<td>0.75</td>
<td>0.75</td>
<td>80% EtOAc/20% TFA</td>
<td>479</td>
<td>C1d D2</td>
</tr>
<tr>
<td>58</td>
<td></td>
<td>247</td>
<td>0.35</td>
<td>0.35</td>
<td>100% EtOAc</td>
<td>500</td>
<td>C1a D1a</td>
</tr>
<tr>
<td>59</td>
<td></td>
<td>198-200</td>
<td>0.09</td>
<td>0.09</td>
<td>100% EtOAc</td>
<td>479</td>
<td>A2 Cl1</td>
</tr>
<tr>
<td>60</td>
<td></td>
<td>158-160</td>
<td>0.64</td>
<td>0.64</td>
<td>50% EtOAc/50% pet ether</td>
<td>479</td>
<td>Cl1a</td>
</tr>
<tr>
<td>Entry</td>
<td>R</td>
<td>m.p. (°C)</td>
<td>HPLC (min.)</td>
<td>TLC R&lt;sub&gt;f&lt;/sub&gt;</td>
<td>TLC Solvent System</td>
<td>Mass Spec [Source]</td>
<td>Synth. Method</td>
</tr>
<tr>
<td>-------</td>
<td>------------</td>
<td>-----------</td>
<td>-------------</td>
<td>------------------</td>
<td>-------------------</td>
<td>-------------------</td>
<td>---------------</td>
</tr>
<tr>
<td>61</td>
<td></td>
<td>195-197</td>
<td>0.39</td>
<td>10%</td>
<td>MeOH/CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>A13</td>
<td>C1a</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>62</td>
<td></td>
<td>170-172</td>
<td>0.52</td>
<td>10%</td>
<td>MeOH/CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>A13</td>
<td>C1a</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>63</td>
<td></td>
<td>168-171</td>
<td>0.39</td>
<td>10%</td>
<td>MeOH/CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>A13</td>
<td>C1a</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>64</td>
<td></td>
<td>176-177</td>
<td>0.35</td>
<td>10%</td>
<td>MeOH/CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>A13</td>
<td>C1a</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>65</td>
<td></td>
<td>130-133</td>
<td></td>
<td></td>
<td></td>
<td>487 (M + H)&lt;sup&gt;+&lt;/sup&gt;</td>
<td>A2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HPLC ES-MS</td>
<td>B1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>C1a</td>
</tr>
<tr>
<td>66</td>
<td></td>
<td>155</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>A2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>C1a</td>
</tr>
</tbody>
</table>
### TABLE 4-continued

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>mp (°C)</th>
<th>HPLC (min.)</th>
<th>TLC R&lt;sub&gt;f&lt;/sub&gt;</th>
<th>Mass Spec. [Source]</th>
<th>Synth. Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>67</td>
<td></td>
<td>225-229</td>
<td>6.23</td>
<td>100% EtOAc</td>
<td>C1c D3 D1b</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>68</td>
<td></td>
<td>234-236</td>
<td>6.29</td>
<td>40% EtOAc/60% hexane</td>
<td>A9 C1a</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>69</td>
<td></td>
<td>6.48</td>
<td></td>
<td>50% EtOAc/50% pet ether</td>
<td>481 ES-MS</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>70</td>
<td></td>
<td>6.46</td>
<td></td>
<td>5% MeOH/95% iHPLC</td>
<td>564 A10 C1a</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>71</td>
<td></td>
<td>199-201</td>
<td>6.50</td>
<td>10% MeOH</td>
<td>A14 C1a D4</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>72</td>
<td></td>
<td>235-237</td>
<td>6.55</td>
<td>10% MeOH</td>
<td>A14 C1a D4</td>
<td></td>
</tr>
</tbody>
</table>
TABLE 4-continued

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>mp (°C)</th>
<th>HPLC (min.)</th>
<th>TLC R&lt;sub&gt;4&lt;/sub&gt;</th>
<th>TLC Solvent System</th>
<th>Mass Spec. [Source]</th>
<th>Synth. Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>73</td>
<td></td>
<td>200-201</td>
<td>0.21</td>
<td>50% MeOH/C&lt;sub&gt;2&lt;/sub&gt;D&lt;sub&gt;2&lt;/sub&gt;O</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>O</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>A14</td>
<td>C1a</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>D4</td>
</tr>
<tr>
<td>74</td>
<td></td>
<td>145-148</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>O</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>75</td>
<td></td>
<td>0.12</td>
<td></td>
<td>70% EIOAc/ES-MS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>527 (M + H); (HPLC)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>A11 C1f</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>D1c</td>
</tr>
<tr>
<td>76</td>
<td></td>
<td>0.18</td>
<td></td>
<td>70% EIOAc/ES-MS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>A11 C1f</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>D1c</td>
</tr>
<tr>
<td>77</td>
<td></td>
<td>0.74</td>
<td></td>
<td>70% EIOAc/ES-MS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>A11 C1f</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>D1c</td>
</tr>
</tbody>
</table>
### TABLE 4-continued

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>TBP</th>
<th>HPLC</th>
<th>TLC</th>
<th>Mass</th>
<th>Synth. Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>78</td>
<td><img src="image1" alt="Structure" /></td>
<td>0.58</td>
<td>70%</td>
<td>EIOAc/30% hexane</td>
<td>A121</td>
<td></td>
</tr>
<tr>
<td>79</td>
<td><img src="image2" alt="Structure" /></td>
<td>0.47</td>
<td>70%</td>
<td>EIOAc/30% hexane</td>
<td>A11</td>
<td></td>
</tr>
<tr>
<td>80</td>
<td><img src="image3" alt="Structure" /></td>
<td>0.18</td>
<td>70%</td>
<td>EIOAc/30% hexane</td>
<td>A11</td>
<td></td>
</tr>
<tr>
<td>81</td>
<td><img src="image4" alt="Structure" /></td>
<td>0.58</td>
<td>70%</td>
<td>EIOAc/30% hexane</td>
<td>A11</td>
<td></td>
</tr>
<tr>
<td>82</td>
<td><img src="image5" alt="Structure" /></td>
<td>0.37</td>
<td>70%</td>
<td>EIOAc/30% hexane</td>
<td>A11</td>
<td></td>
</tr>
</tbody>
</table>
TABLE 4-continued

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>mp (°C.)</th>
<th>HPLC (min.)</th>
<th>TLC Rf</th>
<th>Mass Spec. [Source]</th>
<th>Synth. Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>83</td>
<td><img src="image1" alt="Chemical Structure" /></td>
<td>6.19</td>
<td>70%</td>
<td>EIOAc/ EIOAc/ hexane</td>
<td>A11</td>
<td>CIF</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>D1c</td>
</tr>
<tr>
<td>84</td>
<td><img src="image2" alt="Chemical Structure" /></td>
<td>179-183</td>
<td></td>
<td></td>
<td>A2</td>
<td>A17</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>C1a</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>D5</td>
</tr>
</tbody>
</table>

TABLE 5

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>mp (°C.)</th>
<th>HPLC (min.)</th>
<th>TLC Rf</th>
<th>Mass Spec. [Source]</th>
<th>Synth. Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>85</td>
<td><img src="image3" alt="Chemical Structure" /></td>
<td>186-187</td>
<td>6.13</td>
<td>50%</td>
<td>S99 (M + H)+</td>
<td>A2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>B1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>C1a</td>
</tr>
</tbody>
</table>
### TABLE 5-continued

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>mp (°C)</th>
<th>HPLC (min.)</th>
<th>TLC Rf</th>
<th>TLC Solvent System</th>
<th>Mass Spec. (Source)</th>
<th>Synth. Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>86</td>
<td></td>
<td>150-152</td>
<td>0.31</td>
<td>50% EtoAc/ 50% pet ether</td>
<td>545 (M + H)+</td>
<td>A6 B1 C1a</td>
<td></td>
</tr>
<tr>
<td>87</td>
<td></td>
<td>217-219</td>
<td>0.16</td>
<td>50% EtoAc/ 50% pet ether</td>
<td>545 (M + H)+</td>
<td>A2 B1 C1a</td>
<td></td>
</tr>
<tr>
<td>88</td>
<td></td>
<td>183-184</td>
<td>0.31</td>
<td>50% EtoAc/ 50% pet ether</td>
<td>525 (M + H)+</td>
<td>A2 B1 C1a</td>
<td></td>
</tr>
<tr>
<td>89</td>
<td></td>
<td></td>
<td>0.21</td>
<td>50% EtoAc/ 50% pet ether</td>
<td>511 (M + H)+</td>
<td>A2 B1 C1a</td>
<td></td>
</tr>
<tr>
<td>90</td>
<td></td>
<td></td>
<td>0.28</td>
<td>50% EtoAc/ 50% pet ether</td>
<td>525 (M + H)+</td>
<td>A2 B1 C1a</td>
<td></td>
</tr>
<tr>
<td>91</td>
<td></td>
<td>214-216</td>
<td>0.28</td>
<td>50% EtoAc/ 50% pet ether</td>
<td>522 (M + H)+</td>
<td>A2 B1 C1a</td>
<td></td>
</tr>
</tbody>
</table>
### TABLE 5-continued

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>mp (°C)</th>
<th>HPLC (min.)</th>
<th>TLC</th>
<th>Solvent System</th>
<th>Mass Spec.</th>
<th>[Source]</th>
<th>Synth. Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>92</td>
<td></td>
<td>6.47</td>
<td>50% EtOAc/50% pet ether</td>
<td>527 (M + H)+</td>
<td>HPLC ES-MS</td>
<td>A2 step 3b, A2 step 4</td>
<td>B1, C1a</td>
<td></td>
</tr>
<tr>
<td>93</td>
<td></td>
<td>6.46</td>
<td>50% EtOAc/50% pet ether</td>
<td>527 (M + H)+</td>
<td>HPLC ES-MS</td>
<td>A2 step 3b, A2 step 4</td>
<td>I1, C1a</td>
<td></td>
</tr>
<tr>
<td>94</td>
<td></td>
<td>145-150</td>
<td>5% MeOH/95% CH2Cl2</td>
<td>0.41</td>
<td>HPLC ES-MS</td>
<td>A10</td>
<td>H1, C1a</td>
<td></td>
</tr>
</tbody>
</table>

### TABLE 6

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>mp (°C)</th>
<th>HPLC (min.)</th>
<th>TLC</th>
<th>Solvent System</th>
<th>Mass Spec.</th>
<th>[Source]</th>
<th>Synth. Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>95</td>
<td></td>
<td>140-144</td>
<td>0.29</td>
<td>5% MeOH/45% EtOAc/50% pet ether</td>
<td>495 (M + H)+</td>
<td>HPLC ES-MS</td>
<td>A2</td>
<td>A7, B1, C1a</td>
</tr>
</tbody>
</table>
TABLE 6-continued

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>mp (°C)</th>
<th>HPLC (min.)</th>
<th>TLC R&lt;sub&gt;y&lt;/sub&gt;</th>
<th>Solvent System</th>
<th>Mass Spec. [Source]</th>
<th>Synth. Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>96</td>
<td></td>
<td>244-245</td>
<td>0.39</td>
<td>529</td>
<td>3% MeOH (M + H)+</td>
<td>A6</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>45% (HPLC B1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>EtOAc/2% pet ether</td>
<td>ES-MS C1a</td>
<td></td>
</tr>
<tr>
<td>97</td>
<td></td>
<td>220-221</td>
<td>0.25</td>
<td>529</td>
<td>3% MeOH (M + H)+</td>
<td>A2</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>45% (HPLC B1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>EtOAc/2% pet ether</td>
<td>ES-MS C1a</td>
<td></td>
</tr>
<tr>
<td>98</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0% MeOH (M + H)+</td>
<td>A2</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>45% (HPLC B1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>EtOAc/2% pet ether</td>
<td>ES-MS C1a</td>
<td></td>
</tr>
<tr>
<td>99</td>
<td></td>
<td>180-181</td>
<td>0.52</td>
<td>509</td>
<td>3% MeOH (M + H)+</td>
<td>A2</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>45% (HPLC B1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>EtOAc/2% pet ether</td>
<td>ES-MS C1a</td>
<td></td>
</tr>
<tr>
<td>100</td>
<td></td>
<td>162-165</td>
<td>A2</td>
<td>A2</td>
<td>A7</td>
<td>B1</td>
<td>C1a</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Entry</td>
<td>R</td>
<td>mp (°C)</td>
<td>HPLC (min.)</td>
<td>TLC Solvent System</td>
<td>Mass Spec (Source)</td>
<td>Synth. Method</td>
<td></td>
</tr>
<tr>
<td>-------</td>
<td>----------------</td>
<td>---------</td>
<td>-------------</td>
<td>--------------------</td>
<td>--------------------</td>
<td>---------------</td>
<td></td>
</tr>
<tr>
<td>101</td>
<td><img src="image1" alt="Chemical Structure" /></td>
<td>162-165</td>
<td>A1</td>
<td>C3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>102</td>
<td><img src="image2" alt="Chemical Structure" /></td>
<td>0.10</td>
<td>50% EtOAc/ 50% hexane</td>
<td>A2 (M + H)+</td>
<td>A4 (HPLC ES-MS)</td>
<td>C2a</td>
<td></td>
</tr>
<tr>
<td>103</td>
<td><img src="image3" alt="Chemical Structure" /></td>
<td>125-130</td>
<td>40% EtOAc/ 60% hexane</td>
<td>512 (M + H)+</td>
<td>(ESI+)</td>
<td>C2b</td>
<td></td>
</tr>
</tbody>
</table>

### Biological Examples

#### P38 Kinase Assay

**[0257]** The in vitro inhibitory properties of compounds were determined using a p38 kinase inhibition assay. P38 activity was detected using an in vitro kinase assay run in 96-well microtiter plates. Recombinant human p38 (0.5 μg/mL) was mixed with substrate (myelin basic protein, 5 μg/mL) in kinase buffer (25 mM Hepes, 20 mM MgCl₂ and 150 mM NaCl) and compound. One μCi/well of ³²P-labeled ATP (10 μM) was added to a final volume of 100 μL. The reaction was run at 32°C for 30 min. and stopped with a 1M HCl solution. The amount of radioactivity incorporated into the substrate was determined by trapping the labeled substrate onto negatively charged glass fiber filter paper using a 1% phosphoric acid solution and read with a scintillation counter. Negative controls include substrate plus ATP alone. **[0258]** All compounds exemplified displayed p38 IC₅₀ of between 1 nM and 10 μM.

#### LPS Induced TNFα Production in Mice:

**[0259]** The in vivo inhibitory properties of selected compounds were determined using mice. LPS-induced TNFα production in vivo model. BALB/c mice (Charles River Breeding Laboratories; Kingston, N.Y.) in groups of ten were treated with either vehicle or compound by the route noted. After one hour, endotoxin (E. coli lipopolysaccharide (LPS) 100 μg) was administered intraperitoneally (i.p.). After 90 min, animals were euthanized by carbon dioxide asphyxiation and plasma was obtained from individual animals by cardiac puncture into heparinized tubes. The samples were clarified by centrifugation at 12,500xg for 5 min at 4°C. The supernatants were decanted to new tubes, which were stored as needed at −20°C. TNFα levels in sera were measured using a commercial murine TNF ELISA kit (Genzyme).** [0260]** The preceding examples can be repeated with similar success by substituting the generically or specifically described reagents and/or operating conditions of this invention for those used in the preceding examples.
From the foregoing discussion, one skilled in the art can easily ascertain the essential characteristics of this invention and, without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.

What is claimed is:

1-38. (canceled)

39. A method of treating a condition mediated by p38 within a host, said method comprising administering to said host a compound of Formula I:

A-D-B

or a pharmaceutically acceptable salt thereof, wherein D is —NH—C(O)—NH—,

A is a substituted moiety of up to 40 carbon atoms of the formula: —L-(M-L')ₜ, where L is a 5 or 6 membered cyclic structure bound directly to D, L' comprises a substituted cyclic moiety having at least 5 members, M is a bridging group having at least one atom, q is an integer of from 1-3; and each cyclic structure of L and L' contains 0-4 members of the group consisting of nitrogen, oxygen and sulfur, and

B is a substituted or unsubstituted, up to tricyclic aryl or hetarencyclic moiety of up to 30 carbon atoms with at least one 6-member cyclic structure bound directly to D containing 0-4 members of the group consisting of nitrogen, oxygen and sulfur other than phenyl, wherein L' is substituted by at least one substituent selected from the group consisting of —SO₃Rₙ, —C(O)Rₚ, and —(NRₚ)₂Rₚₚ; wherein Rₚ is hydrogen or a carbon based moiety of up to 24 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally halogen substituted, up to per halo; wherein Rₚₚ is hydrogen or a carbon based moiety of up to 30 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen, hydroxyl and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen, or

Rₚₚₚ=RSₙ where Rₚ and Rₚₚ are

a) independently hydrogen,

b) a carbon based moiety of up to 30 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen, hydroxyl and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen, or

c) one of Rₚ or Rₚₚ is —C(O)—, a C₃-C₆ divalent alkyne group or a substituted C₃-C₆ divalent alkyne group bound to the moiety L to form a cyclic structure with at least 5 members, wherein the substituents of the substituted C₃-C₆ divalent alkyne group are selected from the group consisting of halogen, hydroxyl, and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen; where B is substituted, L is substituted or L' is additionally substituted, the substituents are selected from the group consisting of halogen, up to per-halo, and Wn, wherein n is 0-3; wherein each W is independently selected from the group consisting of —CN, —CO₂Rₚ, —C(O)NRₚRₚₚ, —C(O)─Rₚ, —NO₂, —ORₚ, —SRₚ, —NRₚRₚₚ, —NRₚC(O)ORₚ, —NRₚC(O)Rₚ, —Q-Ar, and carbon based moieties of up to 24 carbon atoms, optionally containing heteroatoms selected from N, S and O and optionally substituted by one or more substituents independently selected from the group consisting of —CN, —CO₂Rₚ, —C(O)NRₚRₚₚ, —C(O)─Rₚ, —NO₂, —ORₚ, —SRₚ, —NRₚRₚₚ, —NRₚC(O)ORₚ, —NRₚC(O)Rₚ and halogen up to per-halo; with each Rₚ independently selected from H or a carbon based moiety of up to 24 carbon atoms, optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen, wherein Q is —O—, —S—, —N(Rₚ)₂—, —(CH₂)ₚ—, —C(O)—, —CH(OH)—, —(CH₂)ₚO—, —(CH₂)ₚS—, —(CH₂)ₚNRₚ—, —O(CH₂)ₚ—CHXₚ—, —CXₚ—, —S—(CH₂)ₚ— and —N(Rₚ)(CH₂)ₚ—, where n=1-3, and Xₚ=halogen; and

Ar is a 5- or 6-member aromatic structure containing 0-2 members selected from the group consisting of nitrogen, oxygen and sulfur, which is optionally substituted by halogen, up to per-halo, and optionally substituted by Zₚ, wherein n₁ is 0 to 3 and each Z is independently selected from the group consisting of —CN, —CO₂Rₚ, —C(O)NRₚRₚₚ, —C(O)─Rₚ, —NO₂, —ORₚ, —SRₚ, —NRₚRₚₚ, —NRₚC(O)ORₚ, —NRₚC(O)Rₚ and a carbon based moiety of up to 24 carbon atoms, optionally containing heteroatoms selected from N, S and O and optionally substituted by one or more substituents selected from the group consisting of —CN, —CO₂Rₚ, —C(O)NRₚRₚₚ, —C(O)─Rₚ, —NO₂, —ORₚ, —SRₚ, —NRₚRₚₚ, —NRₚC(O)ORₚ, —NRₚC(O)Rₚ and —NRₚC(O)ORₚ with Rₚ as defined above.

40. A method as in claim 39 for the treatment of a disease other than cancer.

41. A method as in claim 39 wherein the condition within a host treated by administering a compound of formula I is rheumatoid arthritis, osteoarthritis, septic arthritis, tumor metastasis, periodontal disease, carmel ulceration, proteinuria, coronary thrombosis from atherosclerotic plaque, aneurysmal aortic, birth control, dystrophic epidermolysis bullosa, degenerative cartilage loss following traumatic joint injury, osteoecenas mediated by MMP activity, temporomandibular joint disease or demyelinating disease of the nervous system.

42. A method as in claim 39 wherein M is a bridging group which is one or more groups selected from the group consisting of —O—, —S—, —N(Rₚ)₂—, —(CH₂)ₚ—, —C(O)—, —CH(OH)—, —(CH₂)ₚO—, —(CH₂)ₚS—, —(CH₂)ₚN—, —(CH₂)ₚNRₚ— and —O(CH₂)ₚ—CHXₚ—, where n=1-3, and Xₚ=halogen; and

43. A method as in claim 39 wherein Zₚ is independently selected from the group consisting of —CN, —CO₂Rₚ, —C(O)NRₚRₚₚ, —C(O)─Rₚ, —NO₂, —ORₚ, —SRₚ, —NRₚRₚₚ, —NRₚC(O)ORₚ, —NRₚC(O)Rₚ and a carbon based moiety of up to 24 carbon atoms, optionally containing heteroatoms selected from N, S and O and optionally substituted by one or more substituents selected from the group consisting of —CN, —CO₂Rₚ, —C(O)NRₚRₚₚ, —C(O)─Rₚ, —NO₂, —ORₚ, —SRₚ, —NRₚRₚₚ, —NRₚC(O)ORₚ, —NRₚC(O)Rₚ and —NRₚC(O)ORₚ with Rₚ as defined above.
(R')_1—O(CH_2)_m—ClX (where m = 1–3), X = halogen or polyether, where R' is as defined in claim 1.

43. A method as in claim 42, wherein said substituted cyclic moiety L is phenyl, pyridyl or pyrimidinyl.

44. A method of claim 39 wherein L is substituted by —O(R)R or —SO_2R, wherein R is NR or R.

45. A method of claim 39 wherein the cyclic structures of B and L bound directly to D are substituted in the ortho position by hydrogen.

46. A method of claim 39 wherein B is substituted with 1-3 substituents which are chlorine, C_3-C_5 alkoxy or C_1-C_5 alkyl, substituted by one or more halogen substituents up to per halo substituted C_1-C_5 alkyl.

47. A method of claim 39 wherein B is substituted by trifluoromethyl or tert-butyl, and optionally halogen up to per halo.

48. A method of claim 39 wherein the pharmaceutically acceptable salt of a compound of formula I is a base salt of hydrochloric acid or p-toluenesulfonic acid (tosylate salt).

49. A method of claim 39 wherein the pharmaceutically acceptable salt of a compound of formula I is a pharmaceutically acceptable salt of N-(4-chloro-3-(trifluoromethyl)phenyl)-N-(2-N-methylcarbamoyl)-4-pyridyloxyphenylurea that is a base salt of hydrochloric acid or p-toluenesulfonic acid (tosylate salt).

50. A method as in claim 39 wherein the condition within a host treated by administering a compound of formula I is rheumatic fever, bone resorption, postmenopausal osteoporosis, sepsis, gram negative sepsis, septice shock, endotoxin shock, toxic shock syndrome, systemic inflammatory response syndrome, inflammatory bowel disease (Crohn’s disease and ulcerative colitis), Jarisch-Herxheimer reaction, asthma, adult respiratory distress syndrome, acute pulmonary fibrotic disease, pulmonary sarcoidosis, allergic respiratory disease, silicosis, coal worker’s pneumoconiosis, alveolar injury, hepatic failure, liver disease during acute inflammation, severe alcoholic hepatitis, malaria (Plasmodium falci-parum malaria and cerebral malaria), non-insulin-dependent diabetes mellitus (NIDDM), congestive heart failure, damage following heart disease, atherosclerosis, Alzheimer’s disease, acute encephalitis, brain injury, multiple sclerosis (demyelination and oligodendrocyte loss in multiple sclerosis), advanced cancer, lymphoid malignancy, pancreatitis, impaired wound healing in infection, inflammation and cancer, myelodysplastic syndromes, systemic lupus erythematosus, biliary cirrhosis, bowel necrosis, psoriasis, radiation injury/toxicity following administration of monoclonal antibodies, host-versus-graft reaction (ischemia reperfusion injury and allograft rejections of kidney, liver, heart, and skin), lung allograft reaction (obliterative bronchiitis) or complications due to total hip replacement.

51. A method as in claim 39 wherein the condition within a host treated by administering a compound of formula I is an infectious disease selected from the group consisting of tuberculosis, Helicobacter pylori infection during peptic ulcer disease, Chagas’s disease resulting from Trypanosoma cruzi infection, effects of Shiga-like toxin resulting from E. coli infection, effects of enterotoxin A resulting from Staphylococcus infection, meningococcal infection, and infections from Borrelia burgdorferi, Treponema pallidum, cytomegalovirus, influenza virus, Théler’s encephalomyelitis virus, and the human immunodeficiency virus (HIV).
53. A method as in claim 52 wherein the host has one of the following conditions: rheumatoid arthritis, osteoarthritis, septic arthritis, tumor metastasis, periodontal disease, corneal ulceration, proteinuria, coronary thrombosis from atherosclerotic plaque, aneurysmal aortic, birth control, dystrophic epidermolysis bullosa, degenerative cartilage loss following traumatic joint injury, osteopenias mediated by MMP activity, tempo mandibular joint disease or demyelinating disease of the nervous system.

54. A method as in claim 52 where the compound administered is a tosylate salt.

55. A method as in claim 52 wherein the host has one of the following conditions: rheumatic fever, bone resorption, postmenopausal osteoporosis, sepsis, gram negative sepsis, septic shock, endotoxic shock, toxic shock syndrome, systemic inflammatory response syndrome, inflammatory bowel disease (Crohn’s disease and ulcerative colitis), Jarisch-Herxheimer reaction, asthma, adult respiratory distress syndrome, acute pulmonary fibrotic disease, pulmonary sarcoidosis, allergic respiratory disease, silicosis, coal worker’s pneumoconiosis, alveolar injury, hepatic failure, liver disease during acute inflammation, severe alcoholic hepatitis, malaria (Plasmodium falciparum malaria and cerebral malaria), non-insulin-dependent diabetes mellitus (NIDDM), congestive heart failure, damage following heart disease, atherosclerosis, Alzheimer’s disease, acute encephalitis, brain injury, multiple sclerosis (demyelination and oligodendrocyte loss in multiple sclerosis), advanced cancer, lymphoid malignancy, pancreatitis, impaired wound healing in infection, inflammation and cancer, myelodysplastic syndromes, systemic lupus erythematosus, biliary cirrhosis, bowel necrosis, psoriasis, radiation injury/toxicity following administration of monoclonal antibodies, host-versus-graft reaction (ischemia reperfusion injury and allograft rejections of kidney, liver, heart, and skin), lung allograft rejection (obstructive bronchitis) or complications due to total hip replacement.

56. A method for a treatment of the disease within a host selected from the group consisting of rheumatoid arthritis, osteoarthritis, septic arthritis, tumor metastasis, periodontal disease, corneal ulceration, proteinuria, coronary thrombosis from atherosclerotic plaque, aneurysmal aortic, birth control, dystrophic epidermolysis bullosa, degenerative cartilage loss following traumatic joint injury, osteopenias mediated by MMP activity, tempo mandibular joint disease or demyelinating disease of the nervous system said method comprising administering to a host a compound selected from the group consisting of:

N-(4-chloro-3-(trifluoromethyl)phenyl)-N-(4-(2-(N-methylcarbamoyl)-4-pyridyloxy)phenyl)urea;
N-(2-methoxy-4-chloro-5-(trifluoromethyl)phenyl)-N'-(3-{2-(N-methylcarbamoyl)-4-pyridyloxy}phenyl)urea and their pharmaceutically acceptable salts.

A method for a treatment of the condition within a host selected from the group consisting of rheumatic fever, bone resorption, postmenopausal osteoporosis, sepsis, gram negative sepsis, septic shock, endotoxic shock, toxic shock syndrome, systemic inflammatory response syndrome, inflammatory bowel disease (Crohn's disease and ulcerative colitis), Jarisch-Herzheimer reaction, asthma, adult respiratory distress syndrome, acute pulmonary fibrotic disease, pulmonary sarcoidosis, allergic respiratory disease, silicosis, coal worker's pneumoconiosis, alveolar injury, hepatic failure, liver disease during acute inflammation, severe alcoholic hepatitis, malaria (Plasmodium falciparum malaria and cerebral malaria), non-insulin-dependent diabetes mellitus (NIDDM), congestive heart failure, damage following heart disease, atherosclerosis, Alzheimer's disease, acute encephalitis, brain injury, multiple sclerosis (demyelination and oligodendrocyte loss in multiple sclerosis), lymphoid malignancy, pancreatitis, impaired wound healing in infection, myelodysplastic syndromes, systemic lupus erythematosus, biliary cirrhosis, bowel necrosis, psoriasis, radiation injury/toxicity following administration of monoclonal antibodies, host-versus-graft reaction (ischemia reperfusion injury and allograft rejections of kidney, liver, heart, and skin), lung allograft rejection (obliterative bronchitis) or complications due to total hip replacement said method comprising administering to a host a compound selected from the group consisting of:

N-(4-chloro-3-(trifluoromethyl)phenyl)-N'-(4-{2-(N-methylcarbamoyl)-4-pyridyloxy}phenyl)urea;
N-(2-methoxy-4-chloro-5-(trifluoromethyl)phenyl)-N'-(3-{2-(N-methylcarbamoyl)-4-pyridyloxy}phenyl)urea and their pharmaceutically acceptable salts.

A method for treating an infectious disease within a host selected from the group consisting of tuberculosis, Helicobacter pylori infection during peptic ulcer disease, Chagas's disease resulting from Trypanosoma cruzi infection, effects of Shiga-like toxin resulting from E. coli infection, effects of enterotoxin A resulting from Staphylococcus infection, meningococcal infection, and infections from Borrelia burgdorferi, Treponema pallidum, cytomegalovirus, influenza virus, Thiel's encephalomyelitis virus, and the human immunodeficiency virus (HIV) said method comprising administering to a host a compound selected from the group consisting of:

N-(4-chloro-3-(trifluoromethyl)phenyl)-N'-(4-{2-(N-methylcarbamoyl)-4-pyridyloxy}phenyl)urea;
N-(2-methoxy-4-chloro-5-(trifluoromethyl)phenyl)-N'-(3-{2-(N-methylcarbamoyl)-4-pyridyloxy}phenyl)urea and their pharmaceutically acceptable salts.