(19) DANMARK

(10) DK/EP 2639226 T3

(12) Oversættelse af europæisk patentskrift

Patent- og Varemærkestyrelsen

(51) Int.Cl.: *C 07 D 239/22 (2006.01)* *A 61 K 31/513 (2006.01)* *A 61 P 31/12 (2006.01)*
C 07 D 239/54 (2006.01) *C 07 D 401/10 (2006.01)* *C 07 D 403/10 (2006.01)*
C 07 D 405/10 (2006.01) *C 07 D 409/10 (2006.01)* *C 07 D 413/10 (2006.01)*
C 07 D 417/10 (2006.01)

(45) Oversættelsen bekendtgjort den: **2016-12-19**

(80) Dato for Den Europæiske Patentmyndigheds bekendtgørelse om meddelelse af patentet: **2016-08-31**

(86) Europæisk ansøgning nr.: **12182277.9**

(86) Europæisk indleveringsdag: **2008-09-17**

(87) Den europæiske ansøgnings publiceringsdag: **2013-09-18**

(30) Prioritet: **2007-09-17 US 972881 P** **2008-09-13 US 96792 P**

(62) Stamansøgningsnr: **11171399.6**

(84) Designerede stater: **AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI LT LU LV MC MT NL NO PL PT RO SE SI SK TR**

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(54) Benævnelse: **Antiinfektiøse pyrimidiner og anvendelser heraf**

(56) Fremdragne publikationer:
DE FRANCESCO R ET AL: "Challenges and successes in developing new therapies for hepatitis C", NATURE, NATURE PUBLISHING GROUP, LONDON, UK, vol. 436, no. 7053, 18 August 2005 (2005-08-18), pages 953-960, XP002504755, ISSN: 0028-0836
RAFFAELE DE FRANCESCO ET AL: "Approaching a new era for hepatitis C virus therapy: inhibitors of the NS3-4A serine protease and the NS5B RNA-dependent RNA polymerase", ANTIVIRAL RESEARCH, ELSEVIER SCIENCE BV., AMSTERDAM, NL, vol. 58, 1 January 2003 (2003-01-01), pages 1-16, XP002414639, ISSN: 0166-3542

DESCRIPTION

CROSS-REFERENCE TO RELATED PATENT APPLICATIONS

[0001] This patent application claims priority to U.S. Provisional Patent Application No. 60/972,881 (filed September 17, 2007) and U.S. Provisional Patent Application No. 61/096,792 (filed September 13, 2008).

FIELD OF THE INVENTION

[0002] This invention is directed to: (a) a single formulation comprising one or more compounds and salts thereof that, *inter alia,* are useful as hepatitis C virus (HCV) inhibitors and one or more additional therapeutic agents selected from the group consisting of interferon agents, ribavirin, HCV inhibitors, and anti-HIV agents; and (b) a product comprising such compounds and salts and one or more additional therapeutic agents selected from the group consisting of interferon agents, ribavirin, HCV inhibitors, and anti-HIV agents for use in inhibiting replication of an RNA virus or treating hepatitis C in a mammal in need of such treatment.

BACKGROUND OF THE INVENTION

[0003] Hepatitis C is a blood-borne, infectious, viral disease that is caused by a hepatotropic virus called HCV. At least six different HCV genotypes (with several subtypes within each genotype) are known to date. In North America, HCV genotype 1a predominates, followed by HCV genotypes 1b, 2a, 2b, and 3a. In the United States, HCV genotypes 1, 2, and 3 are the most common, with about 80% of the hepatitis C patients having HCV genotype 1. In Europe, HCV genotype 1b is predominant, followed by HCV genotypes 2a, 2b, 2c, and 3a. HCV genotypes 4 and 5 are found almost exclusively in Africa. As discussed below, the patient's HCV genotype is clinically important in determining the patient's potential response to therapy and the required duration of such therapy.

[0004] An HCV infection can cause liver inflammation (hepatitis) that is often asymptomatic, but ensuing chronic hepatitis can result in cirrhosis of the liver (fibrotic scarring of the liver), liver cancer, and/or liver failure. The World Health Organization estimates that about 170 million persons worldwide are chronically infected with HCV, and from about three to about four million persons are newly infected globally each year. According to the Centers for Disease Control and Prevention, about four million people in the United States are infected with HCV. Co-infection with the human immunodeficiency virus (HIV) is common, and rates of HCV infection among HIV positive populations are higher.

[0005] There is a small chance of clearing the virus spontaneously, but the majority of patients with chronic hepatitis C will not clear it without treatment. Indications for treatment typically include proven HCV infection and persistent abnormal liver function tests. There are two treatment regimens that are primarily used to treat hepatitis C: monotherapy (using an interferon agent - either a "conventional" or longer-acting pegylated interferon) and combination therapy (using an interferon agent and ribavirin). Interferon, which is injected into the bloodstream, works by bolstering the immune response to HCV; and ribavirin, which is taken orally, is believed to work by preventing HCV replication. Taken alone, ribavirin does not effectively suppress HCV levels, but an interferon/ribavirin combination is more effective than interferon alone. Typically, hepatitis C is treated with a combination of pegylated interferon alpha and ribavirin for a period of 24 or 48 weeks, depending on the HCV genotype.

[0006] The goal of treatment is sustained viral response -- meaning that HCV is not measurable in the blood after therapy is completed. Following treatment with a combination of pegylated interferon alpha and ribavirin, sustained cure rates (sustained viral response) of about 75% or better occur in people with HCV genotypes 2 and 3 in 24 weeks of treatment, about 50% in those with HCV genotype 1 with 48 weeks of treatment, and about 65% in those with HCV genotype 4 in 48 weeks of treatment.

[0007] Treatment may be physically demanding, particularly for those with prior history of drug or alcohol abuse, because both interferon and ribavirin have numerous side effects. Common interferon-associated side effects include flu-like symptoms, extreme fatigue, nausea, loss of appetite, thyroid problems, high blood sugar, hair loss, and skin reactions at the injection site. Possible serious interferon-associated side effects include psychoses (e.g., suicidal behavior), heart problems (e.g., heart attack, low blood pressure), other internal organ damage, blood problems (e.g., blood counts falling dangerously low), and new or worsening autoimmune disease (e.g., rheumatoid arthritis). Ribavirin-associated side effects include anemia, fatigue, irritability, skin rash, nasal stuffiness, sinusitis, and cough. Ribavirin can also cause birth defects, so pregnancy in female patients and

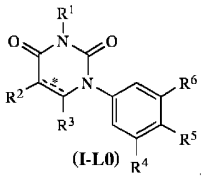
female partners of male patients must be avoided during treatment and for six months afterward.

[0008] Some patients do not complete treatment because of the serious side effects discussed above; other patients (non-responders) continue to have measurable HCV levels despite treatment; and yet other patients (relapsers) "clear" the virus during therapy, but the virus returns sometime after completion of the treatment regimen. Thus, there continues to be a need for alternative compounds, compositions, and methods of treatment (used either in combination with or in lieu of an interferon agent and/or ribavirin) to alleviate the symptoms of hepatitis C, thereby providing partial or complete relief. This invention provides compounds (including salts thereof), compositions, and compounds for use in methods of treatment that generally address such a need.

[0009] De Francesco et al, Antiviral Research, 58 (2003), 1-16, reviews inhibitors of the NS3-4A serine protease and the NS5B RNA-dependent RNA Polymerase.
De Francesco et al, Nature Vol. 436 953-960, reviews small molecule inhibitors of HCV.
Koch et al, J. Med. Chem. (2006) 49 1693-1705 discusses 2-(2-thienyl)-5,6-dihydroxy-4-carboxypyrimidines as inhibitors of the HCV NS5B polymerase.

SUMMARY OF THE INVENTION

[0010] This invention is directed to single formulation comprising one or more compounds that correspond in structure to formula **I-L0** and one or more additional therapeutic agents selected from the group consisting of interferon agents, ribavirin, HCV inhibitors, and anti-HIV agents:



(I-L0)

[0011] In formula **I-L0:**

is selected from the group consisting of single carbon-carbon bond and double carbon-carbon bond;

R^1 is selected from the group consisting of hydrogen and methyl;

R^2 is selected from the group consisting of hydrogen, halo, hydroxy, methyl, cyclopropyl, and cyclobutyl;

R^3 is selected from the group consisting of hydrogen, halo, oxo, and methyl;

R^4 is selected from the group consisting of halo, alkyl, alkenyl, alkynyl, nitro, cyano, azido, alkyloxy, alkenyloxy, alkynyloxy, amino, aminocarbonyl, aminosulfonyl, alkylsulfonyl, carbocyclyl, and heterocyclyl, wherein:

1. **(a)** the amino, aminocarbonyl, and aminosulfonyl optionally are substituted with:
    1. **(1)** one or two substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, and alkylsulfonyl, or
    2. **(2)** two substituents that, together with the amino nitrogen, form a single-ring heterocyclyl, and
2. **(b)** the alkyl, alkenyl, alkynyl, alkyloxy, alkenyloxy, alkynyloxy, and alkylsulfonyl, optionally are substituted with one or more substituents independently selected from the group consisting of halo, oxo, nitro, cyano, azido, hydroxy, amino, alkyloxy, trimethylsilyl, carbocyclyl, and heterocyclyl, wherein:

    the amino optionally is substituted with:

    1. **(1)** one or two substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, alkylcarbonyl, alkylsulfonyl, alkyloxycarbonyl, carbocyclyl, heterocyclyl, carbocyclylalkyl, and heterocyclylalkyl, or
    2. **(2)** two substituents that, together with the amino nitrogen, form a single-ring heterocyclyl, and
3. **(c)** the carbocyclyl and heterocyclyl optionally are substituted with up to three substituents independently selected from the

group consisting of alkyl, alkenyl, alkynyl, halo, oxo, nitro, cyano, azido, hydroxy, amino, alkyloxy, trimethylsilyl, carbocyclyl, and heterocyclyl, wherein:

the amino optionally is substituted with:

1. **(1)** one or two substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, alkylcarbonyl, alkylsulfonyl, alkyloxycarbonyl, carbocyclyl, heterocyclyl, carbocyclylalkyl, and heterocyclylalkyl, or
2. **(2)** two substituents that, together with the amino nitrogen, form a single-ring heterocyclyl;

R^5 is selected from the group consisting of hydrogen, hydroxy, alkyl, alkenyl, alkynyl, alkyloxy, alkenyloxy, alkynyloxy, alkylsulfonyloxy, carbocyclylsulfonyloxy, haloalkylsulfonyloxy, and halo;

R^6 is selected from the group consisting of fused 2-ring carbocyclyl and fused 2-ring heterocyclyl, wherein each such substituent optionally is substituted with one or more substituents independently selected from the group consisting of R^E, R^F, R^G, R^H, R^I, R^J, and R^K;

each R^E is independently selected from the group consisting of halo, nitro, hydroxy, oxo, carboxy, cyano, amino, imino, azido, and aldehydo, wherein:

the amino optionally is substituted with one or two substituents independently selected from the group consisting of alkyl, alkenyl, and alkynyl;

each R^F is independently selected from the group consisting of alkyl, alkenyl, and alkynyl, wherein:

each such substituent optionally is substituted with one or more substituents independently selected from the group consisting of carboxy, hydroxy, halo, amino, imino, nitro, azido, oxo, aminosulfonyl, alkylsulfonyl, alkyloxycarbonyl, alkenyloxycarbonyl, alkynyloxycarbonyl, alkylcarbonyloxy, alkenylcarbonyloxy, alkynylcarbonyloxy, alkyloxy, alkenyloxy, alkynyloxy, carbocyclyl, heterocyclyl, cyano, and aminocarbonyl, wherein:

the amino, imino, aminosulfonyl, aminocarbonyl, carbocyclyl, and heterocyclyl optionally are substituted with one or two substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, alkylsulfonyl, alkenylsulfonyl, alkynylsulfonyl, alkylsulfonylamino, hydroxy, and alkyloxy,
wherein:

amino portion of the alkylsulfonylamino optionally is substituted with a substituent selected from the group consisting of alkyl, alkenyl, and alkynyl;

each R^G is independently selected from the group consisting of carbocyclyl and heterocyclyl, wherein:

each such substituent optionally is substituted with one or more substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, carboxy, hydroxy, halo, amino, nitro, azido, oxo, aminosulfonyl, alkyloxycarbonyl, alkenyloxycarbonyl, alkynyloxycarbonyl, alkylcarbonyloxy, alkenylcarbonyloxy, alkynylcarbonyloxy, alkyloxy, alkenyloxy, alkynyloxy, carbocyclyl, heterocyclyl, cyano, and aminocarbonyl, wherein:

the amino, aminosulfonyl, and aminocarbonyl optionally are substituted with one or two substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, alkylsulfonyl, alkenylsulfonyl, and alkynylsulfonyl;

each R^H is independently selected from the group consisting of alkyloxy, alkenyloxy, alkynyloxy, alkylsulfonyloxy, alkenylsulfonyloxy, and alkynylsulfonyloxy, wherein:

each such substituent optionally is substituted with one or more substituents independently selected from the group consisting of carboxy, hydroxy, halo, amino, nitro, azido, oxo, aminosulfonyl, alkyloxycarbonyl, alkenyloxycarbonyl, alkynyloxycarbonyl, alkylcarbonyloxy, alkenylcarbonyloxy, alkynylcarbonyloxy, alkyloxy, alkenyloxy, alkynyloxy, carbocyclyl, heterocyclyl, cyano, and aminocarbonyl, wherein:

the amino, aminosulfonyl, and aminocarbonyl optionally are substituted with one or two substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, alkylsulfonyl, alkenylsulfonyl, and alkynylsulfonyl;

each R^I is independently selected from the group consisting of alkylcarbonyl, alkenylcarbonyl, alkynylcarbonyl, aminocarbonyl, alkyloxycarbonyl, carbocyclylcarbonyl, and heterocyclylcarbonyl, wherein:

1. **(a)** the alkylcarbonyl, alkenylcarbonyl, and alkynylcarbonyl optionally are substituted with one or more substituents independently selected from the group consisting of carboxy, hydroxy, halo, amino, nitro, azido, oxo, aminosulfonyl, alkyloxycarbonyl, alkenyloxycarbonyl, alkynyloxycarbonyl, alkylcarbonyloxy, alkenylcarbonyloxy, alkynylcarbonyloxy, alkyloxy, alkenyloxy, alkynyloxy, carbocyclyl, heterocyclyl, cyano, and aminocarbonyl, and
2. **(b)** the aminocarbonyl optionally is substituted with one or two substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, alkyloxyalkyl, carbocyclyl, heterocyclyl, alkylsulfonyl, and alkylsulfonylamino, wherein:

   the carbocyclyl and heterocyclyl optionally are substituted with one or two substituents independently selected from the group consisting of halo, alkyl, and oxo;

each R^J is independently selected from the group consisting of carbocyclylsulfonylamino, heterocyclylsulfonylamino, alkylcarbonylamino, alkenylcarbonylamino, alkynylcarbonylamino, alkyloxycarbonylamino, alkenyloxycarbonylamino, alkynyloxycarbonylamino, alkylsulfonylamino, alkenylsulfonylamino, alkynylsulfonylamino, aminocarbonylamino, alkyloxycarbonylaminoimino, alkylsulfonylaminoimino, alkenylsulfonylaminoimino, and alkynylsulfonylaminoimino, wherein:

1. **(a)** the amino portion of such substituents optionally is substituted with a substituent independently selected from the group consisting of carbocyclylalkyl, heterocyclylalkyl, alkylcarbonyloxy, aminocarbonylalkyl, alkyl, alkenyl, alkynyl, alkylcarbonyl, alkenylcarbonyl, alkynylcarbonyl, alkyloxycarbonyl, alkyloxyalkyloxycarbonyl, alkylcarbonyloxyalkyl, and alkylsulfonyl, wherein:
   1. **(1)** the carbocyclyl portion of the carbocyclylalkyl and the heterocyclyl portion of the heterocyclylalkyl optionally are substituted with one or more substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, carboxy, hydroxy, alkyloxy, alkenyloxy, alkynyloxy, halo, nitro, cyano, azido, oxo, and amino, and
   2. **(2)** the amino portion of the aminocarbonylalkyl optionally is substituted with one or two substituents independently selected from the group consisting of alkyl, alkenyl, and alkynyl,
2. **(b)** the alkyl, alkenyl, and alkynyl portion of such substituents optionally is substituted with one or more substituents independently selected from the group consisting of carboxy, halo, oxo, amino, alkyloxycarbonyl, alkylcarbonyloxy, hydroxy, alkyloxy, carbocyclyl, heterocyclyl, and cyano, wherein:

   the amino optionally is substituted with one or two substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, alkyloxy, alkenyloxy, and alkynyloxy, wherein:

   the alkyl optionally is substituted with one or more hydroxy;

3. **(c)** the carbocyclyl and heterocyclyl portions of such substituents optionally are substituted with one or more substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, carboxy, hydroxy, alkyloxy, alkenyloxy, alkynyloxy, halo, nitro, cyano, azido, and amino, wherein:

   the amino optionally is substituted with one or two substituents independently selected from the group consisting of alkyl, alkenyl, and alkynyl; and

each R^K is independently selected from the group consisting of aminosulfonyl, alkylsulfonyl, alkenylsulfonyl, and alkynylsulfonyl, wherein:

1. **(a)** the alkylsulfonyl, alkenylsulfonyl, and alkynylsulfonyl optionally are substituted with one or more substituents independently selected from the group consisting of carboxy, hydroxy, halo, amino, nitro, azido, oxo, aminosulfonyl, alkyloxycarbonyl, alkenyloxycarbonyl, alkynyloxycarbonyl, alkylcarbonyloxy, alkenylcarbonyloxy, alkynylcarbonyloxy, alkyloxy, alkenyloxy, alkynyloxy, carbocyclyl, heterocyclyl, cyano, and aminocarbonyl, wherein:

   the amino, aminosulfonyl, and aminocarbonyl optionally are substituted with one or two substituents independently selected from the group consisting of alkyl, alkenyl, and alkynyl; and

2. **(b)** the aminosulfonyl optionally is substituted with one or two substituents independently selected from the group consisting of alkyl, alkenyl, and alkynyl.

[0012] This invention also is directed to a product comprising one or more compounds and/or salts of the invention, and one or more additional therapeutic agents selected from the group consisting of interferon agents, ribavirin, HCV inhibitors, and anti-HIV agents as a combined preparation for simultaneous, sequential or both simultaneous and sequential use in inhibiting replication of an RNA virus (including HCV), treat a disease treatable by inhibiting HCV ribonucleic acid (RNA) polymerase (including hepatitis C).

[0013] Further benefits of Applicants' invention will be apparent to one skilled in the art from reading this patent application.

BRIEF DESCRIPTION OF THE DRAWINGS

[0014]

Figure **1** shows an illustrative PXRD pattern for the ethanol solvate of compound **IB-L0-2.3.**

Figure **2** shows an illustrative TGA profile of the ethanol solvate of compound **IB-L0-2.3.**

Figure **3** shows an illustrative PXRD pattern for the acetonitrile solvate of compound **IB-L0-2.3.**

Figure **4** shows an illustrative PXRD pattern for the ethyl acetate solvate of compound **IB-L0-2.3.**

Figure **5** shows an illustrative PXRD pattern for the 2-propanol solvate of compound **IB-L0-2.3.**

Figure **6** shows an illustrative PXRD pattern for the methanol solvate of compound **IB-L0-2.3.**

Figure **7** shows an illustrative PXRD pattern for the 1-propanol solvate of compound **IB-L0-2.3.**

Figure **8** shows an illustrative PXRD pattern for the solvent free crystalline compound **IB-L0-2.3.**

Figure **9** shows an illustrative PXRD pattern for the hydrate of compound **IB-L0-2.3.**

Figure **10** shows an illustrative PXRD pattern for the pattern A monosodium salt of compound **IB-L0-2.3.**

Figure **11** shows an illustrative TGA profile of the pattern A monosodium salt of compound **IB-L0-2.3.**

Figure **12** shows an illustrative PXRD pattern for the pattern B monosodium salt of compound **IB-L0-2.3.**

Figure **13** shows an illustrative TGA profile of the pattern B monosodium salt of compound **IB-L0-2.3.**

Figure **14** shows an illustrative PXRD pattern for the pattern C monosodium salt of compound **IB-L0-2.3.**

Figure **15** shows an illustrative PXRD pattern for the disodium salt of compound **IB-L0-2.3.**

Figure **16** shows an illustrative TGA profile of the disodium salt of compound **IB-L0-2.3.**

Figure **17** shows an illustrative PXRD pattern for the monopotassium salt of compound **IB-L0-**

Figure **18** shows an illustrative TGA profile of the monopotassium salt of compound **IB-L0-2.3.**

Figure **19** shows an illustrative PXRD pattern for the pattern A monocholine salt of compound **IB-L0-2.3.**

Figure **20** shows an illustrative TGA profile of the pattern A monocholine salt of compound **IB-L0-2.3.**

Figure **21** shows an illustrative PXRD pattern for the pattern B monocholine salt of compound **IB-L0-2.3.**

Figure **22** shows an illustrative TGA profile of the pattern B monocholine salt of compound **IB-L0-2.3.**

Figure **23** shows an illustrative PXRD pattern for the dicholine salt of compound **IB-L0-2.3.**

DETAILED DESCRIPTION OF THE INVENTION

[0015] This detailed description is intended only to acquaint others skilled in the art with Applicants' invention, its principles, and its practical application so that others skilled in the art may adapt and apply the invention in its numerous forms, as they may be best suited to the requirements of a particular use. This description and its specific examples are intended for purposes of illustration only.

A. Definitions.

[0016] The term "alkyl" (alone or in combination with another term(s)) means a straight-or branched-chain saturated hydrocarbyl substituent typically containing from 1 to about 20 carbon atoms, more typically from 1 to about 8 carbon atoms, and even more typically from 1 to about 6 carbon atoms. Examples of such substituents include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, iso-amyl, and hexyl. As in this definition, throughout this detailed description Applicants have provided illustrative examples. The provision of such illustrative examples should not be interpreted as if the provided illustrative examples are the only options available to one skilled in the art.

[0017] The term "alkenyl" (alone or in combination with another term(s)) means a straight- or branched-chain hydrocarbyl substituent containing one or more double bonds and typically from 2 to about 20 carbon atoms, more typically from about 2 to about 8 carbon atoms, and even more typically from about 2 to about 6 carbon atoms. Examples of such substituents include ethenyl (vinyl), 2-propenyl, 3-propenyl, 1,4-pentadienyl, 1,4-butadienyl, 1-butenyl, 2-butenyl, and 3-butenyl.

[0018] The term "alkynyl" (alone or in combination with another term(s)) means a straight- or branched-chain hydrocarbyl substituent containing one or more triple bonds and typically from 2 to about 20 carbon atoms, more typically from about 2 to about 8 carbon atoms, and even more typically from about 2 to about 6 carbon atoms. Examples of such substituents include ethynyl, 2-propynyl, 3-propynyl, 2-butynyl, and 3-butynyl.

[0019] The term "carbocyclyl" (alone or in combination with another term(s)) means a saturated cyclic (*i.e.,* "cycloalkyl"), partially saturated cyclic *(i.e.,* "cycloalkenyl"), or completely unsaturated (*i.e.,* "aryl") hydrocarbyl substituent containing from 3 to 14 carbon ring atoms ("ring atoms" are the atoms bound together to form the ring or rings of a cyclic substituent). A carbocyclyl may be a single ring, which typically contains from 3 to 6 ring atoms. Examples of such single-ring carbocyclyls include cyclopropyl (cyclopropanyl), cyclobutyl (cyclobutanyl), cyclopentyl (cyclopentanyl), cyclopentenyl, cyclopentadienyl, cyclohexyl (cyclohexanyl), cyclohexenyl, cyclohexadienyl, and phenyl. A carbocyclyl alternatively may be 2 or 3 rings fused together, such as naphthalenyl, tetrahydronaphthalenyl (tetralinyl), indenyl, indanyl (dihydroindenyl), anthracenyl, phenanthrenyl, and decalinyl.

[0020] The term "cycloalkyl" (alone or in combination with another term(s)) means a saturated cyclic hydrocarbyl substituent containing from 3 to 14 carbon ring atoms. A cycloalkyl may be a single carbon ring, which typically contains from 3 to 6 carbon ring atoms. Examples of single-ring cycloalkyls include cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl. A cycloalkyl alternatively may be 2 or 3 carbon rings fused together, such as, decalinyl.

[0021] The term "aryl" (alone or in combination with another term(s)) means an aromatic carbocyclyl containing from 6 to 14 carbon ring atoms. Examples of aryls include phenyl, naphthalenyl, and indenyl.

[0022] In some instances, the number of carbon atoms in a hydrocarbyl substituent (e.g., alkyl, alkenyl, alkynyl, or cycloalkyl) is indicated by the prefix "C_x-Cy-", wherein x is the minimum and y is the maximum number of carbon atoms in the substituent. Thus, for example, "C_1-C_6-alkyl" refers to an alkyl substituent containing from 1 to 6 carbon atoms. Illustrating further, C_3-C_6-cycloalkyl means a saturated hydrocarbyl ring containing from 3 to 6 carbon ring atoms.

[0023] The term "hydrogen" (alone or in combination with another term(s)) means a hydrogen radical, and may be depicted as -H.

[0024] The term "hydroxy" (alone or in combination with another term(s)) means -OH.

[0025] The term "nitro" (alone or in combination with another term(s)) means -NO_2.

[0026] The term "cyano" (alone or in combination with another term(s)) means -CN, which also may be depicted as -C≡N.

[0027] The term "keto" (alone or in combination with another term(s)) means an oxo radical, and may be depicted as =O.

[0028] The term "carboxy" (alone or in combination with another term(s)) means -C(O)-OH.

[0029] The term "amino" (alone or in combination with another term(s)) means -NH_2.

[0030] The term "imino" (alone or in combination with another term(s)) means =NH.

[0031] The term "aminoimino" (alone or in combination with another term(s)) means =NNH_2.

[0032] The term "halogen" or "halo" (alone or in combination with another term(s)) means a fluorine radical (which may be depicted as -F), chlorine radical (which may be depicted as -Cl), bromine radical (which may be depicted as -Br), or iodine radical (which may be depicted as -I).

[0033] A substituent is "substitutable" if it comprises at least one carbon or nitrogen atom that is bonded to one or more hydrogen atoms. Thus, for example, hydrogen, halogen, and cyano do not fall within this definition. In addition, a sulfur atom in a heterocyclyl containing such atom is substitutable with one or two oxo substituents.

[0034] If a substituent is described as being "substituted", a non-hydrogen radical is in the place of hydrogen radical on a carbon or nitrogen of the substituent. Thus, for example, a substituted alkyl substituent is an alkyl substituent in which at least one non-hydrogen radical is in the place of a hydrogen radical on the alkyl substituent. To illustrate, monofluoroalkyl is alkyl substituted with a fluoro radical, and difluoroalkyl is alkyl substituted with two fluoro radicals. It should be recognized that if there are more than one substitution on a substituent, each non-hydrogen radical may be identical or different (unless otherwise stated).

[0035] If a substituent is described as being "optionally substituted", the substituent may be either (1) not substituted or (2) substituted. If a substituent is described as being optionally substituted with up to a particular number of non-hydrogen radicals, that substituent may be either (1) not substituted; or (2) substituted by up to that particular number of non-hydrogen radicals or by up to the maximum number of substitutable positions on the substituent, whichever is less. Thus, for example, if a substituent is described as a heteroaryl optionally substituted with up to 3 non-hydrogen radicals, then any heteroaryl with less than 3 substitutable positions would be optionally substituted by up to only as many non-hydrogen radicals as the heteroaryl has substitutable positions. To illustrate, tetrazolyl (which has only one substitutable position) would be optionally substituted with up to one non-hydrogen radical. To illustrate further, if an amino nitrogen is described as being optionally substituted with up to 2 non-hydrogen radicals, then a primary amino nitrogen will be optionally substituted with up to 2 non-hydrogen radicals, whereas a secondary amino nitrogen will be optionally substituted with up to only 1 non-hydrogen radical.

[0036] This patent application uses the terms "substituent" and "radical" interchangeably.

[0037] The prefix "halo" indicates that the substituent to which the prefix is attached is substituted with one or more independently selected halogen radicals. For example, haloalkyl means an alkyl substituent in which at least one hydrogen radical is replaced with a halogen radical. Examples of haloalkyls include chloromethyl, 1-bromoethyl, fluoromethyl, difluoromethyl, trifluoromethyl, and 1,1,1-trifluoroethyl. It should be recognized that if a substituent is substituted by more than one halogen radical, those halogen radicals may be identical or different (unless otherwise stated).

[0038] The prefix "perhalo" indicates that every hydrogen radical on the substituent to which the prefix is attached is replaced with independently selected halogen radicals, *i.e.,* each hydrogen radical on the substituent is replaced with a halogen radical. If all the halogen radicals are identical, the prefix typically will identify the halogen radical. Thus, for example, the term "perfluoro" means that every hydrogen radical on the substituent to which the prefix is attached is substituted with a fluorine radical. To illustrate, the term "perfluoroalkyl" means an alkyl substituent wherein a fluorine radical is in the place of each hydrogen radical.

[0039] The term "carbonyl" (alone or in combination with another term(s)) means -C(O)-.

[0040] The term "aminocarbonyl" (alone or in combination with another term(s)) means -C(O)-NH_2.

[0041] The term "oxy" (alone or in combination with another term(s)) means an ether substituent, and may be depicted as -O-.

[0042] The term "alkoxy" (alone or in combination with another term(s)) means an alkylether substituent, i.e., -O-alkyl. Examples of such a substituent include methoxy (-O-CH_3), ethoxy, n-propoxy, isopropoxy, n-butoxy, iso-butoxy, sec-butoxy, and tert-butoxy.

[0043] The term "alkylcarbonyl" (alone or in combination with another term(s)) means -C(O)-alkyl.

[0044] The term "aminoalkylcarbonyl" (alone or in combination with another term(s)) means -C(O)-alkyl-NH_2.

[0045] The term "alkoxycarbonyl" (alone or in combination with another term(s)) means -C(O)-O-alkyl.

[0046] The term "carbocyclylcarbonyl" (alone or in combination with another term(s)) means -C(O)-carbocyclyl.

[0047] Similarly, the term "heterocyclylcarbonyl" (alone or in combination with another term(s)) means -C(O)-heterocyclyl.

[0048] The term "carbocyclylalkylcarbonyl" (alone or in combination with another term(s)) means -C(O)-alkyl-carbocyclyl.

[0049] Similarly, the term "heterocyclylalkylcarbonyl" (alone or in combination with another term(s)) means -C(O)-alkyl-heterocyclyl.

[0050] The term "carbocyclyloxycarbonyl" (alone or in combination with another term(s)) means -C(O)-O-carbocyclyl.

[0051] The term "carbocyclylalkoxycarbonyl" (alone or in combination with another term(s)) means -C(O)-O-alkyl-carbocyclyl.

[0052] The term "thio" or "thia" (alone or in combination with another term(s)) means a thiaether substituent, *i.e.*, an ether substituent wherein a divalent sulfur atom is in the place of the ether oxygen atom. Such a substituent may be depicted as -S-. This, for example, "alkyl-thio-alkyl" means alkyl-S-alkyl (alkyl-sulfanyl-alkyl).

[0053] The term "thiol" or "sulfhydryl" (alone or in combination with another term(s)) means a sulfhydryl substituent, and may be depicted as -SH.

[0054] The term "(thiocarbonyl)" (alone or in combination with another term(s)) means a carbonyl wherein the oxygen atom has been replaced with a sulfur. Such a substituent may be depicted as -C(S)-.

[0055] The term "sulfonyl" (alone or in combination with another term(s)) means $-S(O)_2-$.

[0056] The term "aminosulfonyl" (alone or in combination with another term(s)) means $-S(O)_2-NH_2$.

[0057] The term "sulfinyl" or "sulfoxido" (alone or in combination with another term(s)) means -S(O)-.

[0058] The term "heterocyclyl" (alone or in combination with another term(s)) means a saturated (*i.e.*, "heterocycloalkyl"), partially saturated (*i.e.*, "heterocycloalkenyl"), or completely unsaturated (*i.e.*, "heteroaryl") ring structure containing a total of 3 to 14 ring atoms. At least one of the ring atoms is a heteroatom (*i.e.*, oxygen, nitrogen, or sulfur), with the remaining ring atoms being independently selected from the group consisting of carbon, oxygen, nitrogen, and sulfur.

[0059] A heterocyclyl may be a single ring, which typically contains from 3 to 7 ring atoms, more typically from 3 to 6 ring atoms, and even more typically 5 to 6 ring atoms. Examples of single-ring heterocyclyls include furanyl, dihydrofuranyl, tetrahydrofuranyl, thiophenyl (thiofuranyl), dihydrothiophenyl, tetrahydrothiophenyl, pyrrolyl, pyrrolinyl, pyrrolidinyl, imidazolyl, imidazolinyl, imidazolidinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, triazolyl, tetrazolyl, oxazolyl, oxazolidinyl, isoxazolidinyl, isoxazolyl, thiazolyl, isothiazolyl, thiazolinyl, isothiazolinyl, thiazolidinyl, isothiazolidinyl, thiodiazolyl, oxadiazolyl (including 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl (furazanyl), or 1,3,4-oxadiazolyl), oxatriazolyl (including 1,2,3,4-oxatriazolyl or 1,2,3,5-oxatriazolyl), dioxazolyl (including 1,2,3-dioxazolyl, 1,2,4-dioxazolyl, 1,3,2-dioxazolyl, or 1,3,4-dioxazolyl), oxathiazolyl, oxathiolyl, oxathiolanyl, pyranyl, dihydropyranyl, thiopyranyl, tetrahydrothiopyranyl, pyridinyl (azinyl), piperidinyl, diazinyl (including pyridazinyl (1,2-diazinyl), pyrimidinyl (1,3-diazinyl), or pyrazinyl (1,4-diazinyl)), piperazinyl, triazinyl (including 1,3,5-triazinyl, 1,2,4-triazinyl, and 1,2,3-triazinyl)), oxazinyl (including 1,2-oxazinyl, 1,3-oxazinyl, or 1,4-oxazinyl)), oxathiazinyl (including 1,2,3-oxathiazinyl, 1,2,4-oxathiazinyl, 1,2,5-oxathiazinyl, or 1,2,6-oxathiazinyl)), oxadiazinyl (including 1,2,3-oxadiazinyl, 1,2,4-oxadiazinyl, 1,4,2-oxadiazinyl, or 1,3,5-oxadiazinyl)), morpholinyl, azepinyl, oxepinyl, thiepinyl, and diazepinyl.

[0060] A heterocyclyl alternatively may be 2 or 3 rings fused together, such as, for example, indolizinyl, pyranopyrrolyl, 4H-quinolizinyl, purinyl, naphthyridinyl, pyridopyridinyl (including pyrido[3,4-b]-pyridinyl, pyrido[3,2-b]-pyridinyl, or pyrido[4,3-b]-pyridinyl), and pteridinyl. Other examples of fused-ring heterocyclyls include benzo-fused heterocyclyls, such as indolyl, isoindolyl (isobenzazolyl, pseudoisoindolyl), indoleninyl (pseudoindolyl), isoindazolyl (benzpyrazolyl), benzazinyl (including quinolinyl (1-benzazinyl) or isoquinolinyl (2-benzazinyl)), phthalazinyl, quinoxalinyl, quinazolinyl, benzodiazinyl (including cinnolinyl (1,2-benzodiazinyl) or quinazolinyl (1,3-benzodiazinyl)), benzopyranyl (including chromanyl or isochromanyl), benzoxazinyl (including 1,3,2-benzoxazinyl, 1,4,2-benzoxazinyl, 2,3,1-benzoxazinyl, or 3,1,4-benzoxazinyl), and benzisoxazinyl (including 1,2-benzisoxazinyl or 1,4-benzisoxazinyl).

[0061] The term "2-fused ring" heterocyclyl (alone or in combination with another term(s)) means a saturated, partially saturated, or aryl heterocyclyl containing 2 fused rings. Examples of 2-fused-ring heterocyclyls include indolizinyl, quinolizinyl, purinyl,

naphthyridinyl, pteridinyl, indolyl, isoindolyl, indoleninyl, isoindazolyl, phthalazinyl, quinoxalinyl, quinazolinyl, benzodiazinyl, benzopyranyl, benzothiopyranyl, benzoxazolyl, anthranilyl, benzodioxolyl, benzodioxanyl, benzoxadiazolyl, benzofuranyl, isobenzofuranyl, benzothiazolyl, benzothiadiazolyl, benzimidazolyl, benzotriazolyl, benzoxazinyl, and tetrahydroisoquinolinyl.

[0062] The term "heteroaryl" (alone or in combination with another term(s)) means an aromatic heterocyclyl containing from 5 to 14 ring atoms. A heteroaryl may be a single ring or 2 or 3 fused rings. Examples of heteroaryl substituents include 6-membered ring substituents such as pyridyl, pyrazyl, pyrimidinyl, pyridazinyl, and 1,3,5-, 1,2,4- or 1,2,3-triazinyl; 5-membered ring substituents such as imidazyl, furanyl, thiophenyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, 1,2,3-, 1,2,4-, 1,2,5-, or 1,3,4-oxadiazolyl and isothiazolyl; 6/5-membered fused ring substituents such as benzothiofuranyl, benzisoxazolyl, benzoxazolyl, purinyl, and anthranilyl; and 6/6-membered fused rings such as benzopyranyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, and benzoxazinyl.

[0063] A prefix attached to a multi-component substituent only applies to the first component. To illustrate, the term "alkylcycloalkyl" contains two components: alkyl and cycloalkyl. Thus, the C_1-C_6-prefix on C_1-C_6-alkylcycloalkyl means that the alkyl component of the alkylcycloalkyl contains from 1 to 6 carbon atoms; the C_1-C_6-prefix does not describe the cycloalkyl component. To illustrate further, the prefix "halo" on haloalkoxyalkyl indicates that only the alkoxy component of the alkoxyalkyl substituent is substituted with one or more halogen radicals. If halogen substitution may alternatively or additionally occur on the alkyl component, the substituent would instead be described as "halogen-substituted alkoxyalkyl" rather than "haloalkoxyalkyl." And finally, if the halogen substitution may only occur on the alkyl component, the substituent would instead be described as "alkoxyhaloalkyl."

[0064] If substituents are described as being "independently selected" from a group, each substituent is selected independent of the other. Each substituent therefore may be identical to or different from the other substituent(s).

[0065] When words are used to describe a substituent, the rightmost-described component of the substituent is the component that has the free valence.

[0066] When a chemical formula is used to describe a substituent, the dash on the left side of the formula indicates the portion of the substituent that has the free valence.

[0067] When a chemical formula is used to describe a linking element between two other elements of a depicted chemical structure, the leftmost dash of the substituent indicates the portion of the substituent that is bound to the left element in the depicted structure. The rightmost dash, on the other hand, indicates the portion of the substituent that is bound to the right element in the depicted structure. To illustrate, if the depicted chemical structure is X-L-Y and L is described as -C(O)-N(H)-, then the chemical would be X-C(O)-N(H)-Y.

[0068] With reference to the use of the words "comprise" or "comprises" or "comprising" in this patent application (including the claims), Applicants note that unless the context requires otherwise, those words are used on the basis and clear understanding that they are to be interpreted inclusively, rather than exclusively, and that Applicants intend each of those words to be so interpreted in construing this patent application, including the claims below.

[0069] ChemDraw software has been used to generate the compound names in this patent application.

[0070] The term "amorphous" as applied to a compound refers to a solid-state in which the compound molecules are present in a disordered arrangement and do not form a distinguishable crystal lattice or unit cell. When subjected to X-ray powder diffraction, an amorphous compound does not produce any characteristic crystalline peaks.

[0071] The term "crystalline form" as applied to a compound refers to a solid-state in which the compound molecules are arranged to form a distinguishable crystal lattice (i) comprising distinguishable unit cells, and (ii) yielding diffraction pattern peaks when subjected to X-ray radiation.

[0072] The term "purity", unless otherwise qualified, means the chemical purity of a compound according to conventional HPLC assay.

[0073] The term "phase purity" means the solid-state purity of a compound with regard to a particular crystalline or amorphous form of the compound as determined by X-ray powder diffraction analytical methods.

[0074] The term "phase pure" refers to purity with respect to other solid-state forms of the compound, and does not necessarily imply a high degree of chemical purity with respect to other compounds.

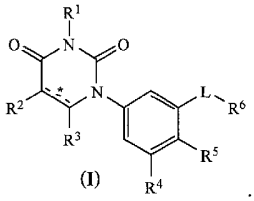
[0075] The term "PXRD" means X-ray powder diffraction.

[0076] The term "TGA" means thermogravimetric analysis.

[0077] The term "DSC" means differential scanning calorimetry.

B. Compounds.

[0078] This invention is directed, in part, to compounds that are phenyl-uracil derivatives that correspond in structure to formula **I:**



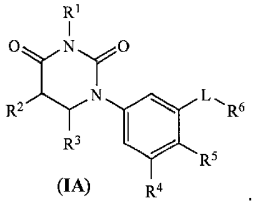
(I)

[0079] In these compounds,

is selected from the group consisting of single carbon-carbon bond and double carbon-carbon bond.

[0080] In some embodiments,

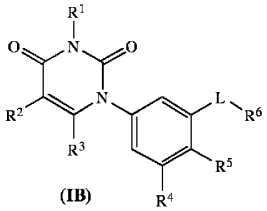
is a single carbon-carbon bond. In these embodiments, the compounds of formula **I** correspond in structure to the following formula *(i.e.,* formula **IA):**



(IA)

[0081] In other embodiments,

is a double carbon-carbon bond. In these embodiments, the compounds of formula **I** correspond in structure to the following formula (*i.e.,* formula **IB):**



(IB)

B1. Substituent R^1.

[0082] R^1 is selected from the group consisting of hydrogen and methyl

[0083] In some embodiments, R^1 is hydrogen.

[0084] In some embodiments, R^1 is methyl.

[0085] In some embodiments, R^1 is selected from the group consisting of hydrogen and methyl.

B2. Substituent R^2.

[0086] R^2 is selected from the group consisting of hydrogen, halo, hydroxy, methyl, cyclopropyl, and cyclobutyl.

[0087] In some embodiments, R^2 is hydrogen.

[0088] In some embodiments, R^2 is halo. In some such embodiments, R^2 is selected from the group consisting of fluoro and chloro. In other such embodiments, R^2 is fluoro. In yet other such embodiments, R^2 is chloro. In yet other such embodiments, R^2 is bromo. In further such embodiments, R^2 is iodo.

[0089] In some embodiments, R^2 is hydroxy.

[0090] In some embodiments, R^2 is methyl.

[0091] In some embodiments, R^2 is cyclopropyl.

[0092] In some embodiments, R^2 is cyclobutyl.

[0093] In some embodiments, R^2 is selected from the group consisting of hydrogen, methyl, hydroxy, and halo. In some such embodiments, R^2 is selected from the group consisting of hydrogen, methyl, hydroxy, fluoro, and chloro. In other such embodiments, R^2 is selected from the group consisting of hydrogen, methyl, hydroxy, and fluoro. In yet other such embodiments, R^2 is selected from the group consisting of hydrogen, methyl, hydroxy, and chloro. In yet other such embodiments, R^2 is selected from the group consisting of hydrogen, methyl, hydroxy, and bromo. In further such embodiments, R^2 is selected from the group consisting of hydrogen, methyl, hydroxy, and iodo.

[0094] In some embodiments, R^2 is selected from the group consisting of hydrogen, methyl, and halo. In some such embodiments, R^2 is selected from the group consisting of hydrogen, methyl, fluoro, and chloro. In other such embodiments, R^2 is selected from the group consisting of hydrogen, methyl, and fluoro. In yet other such embodiments, R^2 is selected from the group consisting of hydrogen, methyl, and chloro. In yet other such embodiments, R^2 is selected from the group consisting of hydrogen, methyl, and bromo. In further such embodiments, R^2 is selected from the group consisting of hydrogen, methyl, and iodo.

[0095] In some embodiments, R^2 is selected from the group consisting of hydrogen and halo. In some such embodiments, R^2 is selected from the group consisting of hydrogen, fluoro, and chloro. In other such embodiments, R^2 is selected from the group consisting of hydrogen and fluoro. In yet other such embodiments, R^2 is selected from the group consisting of hydrogen and chloro. In yet other such embodiments, R^2 is selected from the group consisting of hydrogen and bromo. In further such embodiments, R^2 is selected from the group consisting of hydrogen and iodo.

B3. Substituent R^3.

[0096] R^3 is selected from the group consisting of hydrogen, halo, oxo, and methyl. In some such embodiments, R^3 is selected from the group consisting of hydrogen, fluoro, oxo, and methyl. In other such embodiments, R^3 is selected from the group consisting of hydrogen, chloro, oxo, and methyl. In yet other such embodiments, R^3 is selected from the group consisting of

hydrogen, bromo, oxo, and methyl. In yet other such embodiments, R^3 is selected from the group consisting of hydrogen, iodo, oxo, and methyl.

[0097] In some embodiments, R^3 is selected from the group consisting of hydrogen, halo, and oxo. In some such embodiments, R^3 is selected from the group consisting of hydrogen, fluoro, and oxo. In other such embodiments, R^3 is selected from the group consisting of hydrogen, chloro, and oxo. In yet other such embodiments, R^3 is selected from the group consisting of hydrogen, bromo, and oxo. In yet other such embodiments, R^3 is selected from the group consisting of hydrogen, iodo, and oxo.

[0098] In some embodiments, R^3 is selected from the group consisting of hydrogen and methyl.

[0099] In some embodiments, R^3 is hydrogen.

[0100] In some embodiments, R^3 is methyl.

[0101] In some embodiments, R^3 is oxo.

[0102] In some embodiments, R^3 is halo. In some such embodiments, R^3 is fluoro. In other such embodiments, R^3 is chloro. In yet other such embodiments, R^3 is bromo. In further such embodiments, R^3 is iodo.

B4. Substituent R^4.

[0103] R^4 is selected from the group consisting of halo, alkyl, alkenyl, alkynyl, nitro, cyano, azido, alkyloxy, alkenyloxy, alkynyloxy, amino, aminocarbonyl, aminosulfonyl, alkylsulfonyl, carbocyclyl, and heterocyclyl, wherein:

1. **(a)** the amino, aminocarbonyl, and aminosulfonyl optionally are substituted with:
    1. **(1)** one or two substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, and alkylsulfonyl, or
    2. **(2)** two substituents that, together with the amino nitrogen, form a single-ring heterocyclyl,
2. **(b)** the alkyl, alkenyl, alkynyl, alkyloxy, alkenyloxy, alkynyloxy, and alkylsulfonyl, optionally are substituted with one or more substituents independently selected from the group consisting of halo, oxo, nitro, cyano, azido, hydroxy, amino, alkyloxy, trimethylsilyl, carbocyclyl, and heterocyclyl, wherein:

    the amino optionally is substituted with:

    1. **(1)** one or two substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, alkylcarbonyl, alkylsulfonyl, alkyloxycarbonyl, carbocyclyl, heterocyclyl, carbocyclylalkyl, and heterocyclylalkyl, or
    2. **(2)** two substituents that, together with the amino nitrogen, form a single-ring heterocyclyl, and

3. (c) the carbocyclyl and heterocyclyl optionally are substituted with up to three substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, halo, oxo, nitro, cyano, azido, hydroxy, amino, alkyloxy, trimethylsilyl, carbocyclyl, and heterocyclyl, wherein:

    the amino optionally is substituted with:

    1. **(1)** one or two substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, alkylcarbonyl, alkylsulfonyl, alkyloxycarbonyl, carbocyclyl, heterocyclyl, carbocyclylalkyl, and heterocyclylalkyl, or
    2. **(2)** two substituents that, together with the amino nitrogen, form a single-ring heterocyclyl.

[0104] In some embodiments, R^4 is selected from the group consisting of halo, alkyl, alkenyl, alkynyl, nitro, cyano, azido, alkyloxy, alkenyloxy, alkynyloxy, amino, aminocarbonyl, aminosulfonyl, alkylsulfonyl, carbocyclyl, and heterocyclyl, wherein:

the amino, aminocarbonyl, and aminosulfonyl optionally are substituted with:

1. **(1)** one or two substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, and alkylsulfonyl, or

2. **(2)** two substituents that, together with the amino nitrogen, form a single-ring heterocyclyl.

[0105] In some embodiments, R^4 is selected from the group consisting of halo, alkyl, alkenyl, alkynyl, nitro, cyano, azido, alkyloxy, alkenyloxy, alkynyloxy, amino, aminocarbonyl, aminosulfonyl, alkylsulfonyl, carbocyclyl, and heterocyclyl, wherein:

the alkyl, alkenyl, alkynyl, alkyloxy, alkenyloxy, alkynyloxy, and alkylsulfonyl, optionally are substituted with one or more substituents independently selected from the group consisting of halo, oxo, nitro, cyano, azido, hydroxy, amino, alkyloxy, trimethylsilyl, carbocyclyl, and heterocyclyl, wherein:

the amino optionally is substituted with:

1. **(1)** one or two substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, alkylcarbonyl, alkylsulfonyl, alkyloxycarbonyl, carbocyclyl, heterocyclyl, carbocyclylalkyl, and heterocyclylalkyl, or
2. **(2)** two substituents that, together with the amino nitrogen, form a single-ring heterocyclyl.

[0106] In some embodiments, R^4 is selected from the group consisting of halo, alkyl, alkenyl, alkynyl, nitro, cyano, azido, alkyloxy, alkenyloxy, alkynyloxy, amino, aminocarbonyl, aminosulfonyl, alkylsulfonyl, carbocyclyl, and heterocyclyl, wherein:

the carbocyclyl and heterocyclyl optionally are substituted with up to three substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, halo, oxo, nitro, cyano, azido, hydroxy, amino, alkyloxy, trimethylsilyl, carbocyclyl, and heterocyclyl, wherein:

the amino optionally is substituted with:

1. **(1)** one or two substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, alkylcarbonyl, alkylsulfonyl, alkyloxycarbonyl, carbocyclyl, heterocyclyl, carbocyclylalkyl, and heterocyclylalkyl, or
2. **(2)** two substituents that, together with the amino nitrogen, form a single-ring heterocyclyl.

[0107] In some embodiments, R^4 is selected from the group consisting of halo, alkyl, alkenyl, alkynyl, nitro, cyano, azido, alkyloxy, alkenyloxy, alkynyloxy, amino, aminocarbonyl, aminosulfonyl, alkylsulfonyl, carbocyclyl, and heterocyclyl, wherein:

1. **(a)** the amino, aminocarbonyl, and aminosulfonyl optionally are substituted with:
    1. **(1)** one or two substituents independently selected from the group consisting of alkyl, alkenyl, and alkynyl, or,
    2. **(2)** two substituents that, together with the amino nitrogen, form a single-ring heterocyclyl; and
2. **(b)** the alkyl, alkenyl, alkynyl, alkyloxy, alkenyloxy, alkynyloxy, alkylsulfonyl, carbocyclyl, and heterocyclyl optionally are substituted with up to three substituents independently selected from the group consisting of halo, oxo, nitro, cyano, azido, hydroxy, amino, alkyloxy, carbocyclyl, and heterocyclyl, wherein the amino optionally is substituted with:
    1. **(1)** one or two substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, alkylcarbonyl, alkylsulfonyl, alkyloxycarbonyl, carbocyclyl, heterocyclyl, carbocyclylalkyl, and heterocyclylalkyl, or,
    2. **(2)** two substituents that, together with the amino nitrogen, form a single-ring heterocyclyl.

[0108] In some embodiments, R^4 is selected from the group consisting of halo, alkyl, alkenyl, alkynyl, nitro, cyano, azido, alkyloxy, alkenyloxy, alkynyloxy, amino, aminocarbonyl, aminosulfonyl, alkylsulfonyl, carbocyclyl, and heterocyclyl, wherein:

the amino, aminocarbonyl, and aminosulfonyl optionally are substituted with:

1. **(1)** one or two substituents independently selected from the group consisting of alkyl, alkenyl, and alkynyl, or,
2. **(2)** two substituents that, together with the amino nitrogen, form a single-ring heterocyclyl.

[0109] In some embodiments, R^4 is selected from the group consisting of halo, alkyl, alkenyl, alkynyl, nitro, cyano, azido, alkyloxy, alkenyloxy, alkynyloxy, amino, aminocarbonyl, aminosulfonyl, alkylsulfonyl, carbocyclyl, and heterocyclyl, wherein:

the alkyl, alkenyl, alkynyl, alkyloxy, alkenyloxy, alkynyloxy, alkylsulfonyl, carbocyclyl, and heterocyclyl optionally are substituted with up to three substituents independently selected from the group consisting of halo, oxo, nitro, cyano, azido, hydroxy, amino, alkyloxy, carbocyclyl, and heterocyclyl, wherein the amino optionally is substituted with:

1. **(1)** one or two substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, alkylcarbonyl, alkylsulfonyl, alkyloxycarbonyl, carbocyclyl, heterocyclyl, carbocyclylalkyl, and heterocyclylalkyl, or,
2. **(2)** two substituents that, together with the amino nitrogen, form a single-ring

heterocyclyl.

[0110] In some embodiments, R^4 is selected from the group consisting of halo, C_1-C_4-alkyl, C_2-C_4-alkenyl, C_2-C_4-alkynyl, amino, C_1-C_4-alkylsulfonyl, C_3-C_6-carbocyclyl, and 5-6-membered heterocyclyl, wherein:

1. **(a)** the amino optionally is substituted with one or two substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, and alkylsulfonyl,
2. **(b)** the C_1-C_4-alkyl, C_2-C_4-alkenyl, and C_2-C_4-alkynyl optionally are substituted with one or more substituents independently selected from the group consisting of halo, oxo, hydroxy, alkyloxy, and trimethylsilyl, and
3. **(c)** the C_3-C_6-carbocyclyl and 5-6-membered heterocyclyl optionally are substituted with up to three substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, halo, and amino, wherein:

   the amino optionally is substituted with one or two substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, and alkylsulfonyl.

[0111] In some embodiments, R^4 is selected from the group consisting of C_1-C_4-alkyl, C_2-C_4-alkenyl, C_2-C_4-alkynyl, amino, C_1-C_4-alkylsulfonyl, C_3-C_6-carbocyclyl, and 5-6-membered heterocyclyl, wherein:

1. **(a)** the amino optionally is substituted with one or two substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, and alkylsulfonyl,
2. **(b)** the C_1-C_4-alkyl, C_2-C_4-alkenyl, and C_2-C_4-alkynyl optionally are substituted with one or more substituents independently selected from the group consisting of halo, oxo, hydroxy, alkyloxy, and trimethylsilyl, and
3. **(c)** the C_3-C_6-carbocyclyl and 5-6-membered heterocyclyl optionally are substituted with up to three substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, halo, and amino, wherein:

   the amino optionally is substituted with one or two substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, and alkylsulfonyl.

[0112] In some embodiments, R^4 is selected from the group consisting of halo, C_1-C_4-alkyl, C_3-C_6-carbocyclyl, and 5-6-membered heterocyclyl, wherein:

1. **(a)** the C_1-C_4-alkyl optionally is substituted with up to three substituents independently selected from the group consisting of halo, oxo, hydroxy, alkyloxy, and trimethylsilyl, and
2. **(b)** the C_3-C_6-carbocyclyl and 5-6-membered heterocyclyl optionally are substituted with one or two substituents independently selected from the group consisting of alkyl, halo, and alkylsulfonylamino.

[0113] In some embodiments, R^4 is selected from the group consisting of halo, C_1-C_4-alkyl, C_3-C_6-carbocyclyl, and 5-6-membered heterocyclyl, wherein:

1. **(a)** the C_1-C_4-alkyl optionally is substituted with one or two substituents independently selected from the group consisting of halo, oxo, hydroxy, alkyloxy, and trimethylsilyl, and
2. **(b)** the C_3-C_6-carbocyclyl and 5-6-membered heterocyclyl optionally are substituted with a substituent selected from the group consisting of alkyl, halo, and alkylsulfonylamino.

[0114] In some embodiments, R^4 is selected from the group consisting of C_1-C_4-alkyl, C_3-C_6-carbocyclyl, and 5-6-membered heterocyclyl, wherein:

1. **(a)** the C_1-C_4-alkyl optionally is substituted with up to three substituents independently selected from the group consisting of halo, oxo, hydroxy, alkyloxy, and trimethylsilyl, and
2. **(b)** the C_3-C_6-carbocyclyl and 5-6-membered heterocyclyl optionally are substituted with one or two substituents independently selected from the group consisting of alkyl, halo, and alkylsulfonylamino.

[0115] In some embodiments, R^4 is selected from the group consisting of halo, tert-butyl, C_3-C_6-carbocyclyl, and 5-6-membered heterocyclyl, wherein:

the C_3-C_6-carbocyclyl and 5-6-membered heterocyclyl optionally are substituted with a substituent selected from the group consisting of alkyl, halo, and alkylsulfonylamino.

[0116] In some embodiments, R^4 is selected from the group consisting of tert-butyl, C_3-C_6-carbocyclyl, and 5-6-membered heterocyclyl, wherein:

the C_3-C_6-carbocyclyl and 5-6-membered heterocyclyl optionally are substituted with a substituent selected from the group consisting of alkyl, halo, and alkylsulfonylamino.

[0117] In some embodiments, R^4 is selected from the group consisting of halo, alkyl, haloalkyl, carboxyalkyl, hydroxyalkyl, alkyloxyalkyl, trimethylsilylalkynyl, alkylcarbocyclyl, carbocyclyl, alkylheterocyclyl, heterocyclyl, halocarbocyclyl, alkylsulfonylamino, and alkylsulfonyl.

[0118] In some embodiments, R^4 is selected from the group consisting of halo, alkyl, alkenyl, alkynyl, nitro, cyano, azido, alkyloxy, alkenyloxy, alkynyloxy, amino, aminocarbonyl, aminosulfonyl, alkylsulfonyl, carbocyclyl, and heterocyclyl.

[0119] In some embodiments, R^4 is selected from the group consisting of halo, C_1-C_4-alkyl, C_2-C_4-alkenyl, C_2-C_4-alkynyl, amino, C_1-C_4-alkylsulfonyl, C_3-C_6-carbocyclyl, and 5-6-membered heterocyclyl. In some such embodiment, R^4 is selected from the group consisting of halo, C_1-C_4-alkyl, C_2-C_4-alkenyl, C_2-C_4-alkynyl, amino, C_1-C_4-alkylsulfonyl, C_6-carbocyclyl, and 5-6-membered heterocyclyl. In other such embodiment, R^4 is selected from the group consisting of halo, C_1-C_4-alkyl, C_2-C_4-alkenyl, C_2-C_4-alkynyl, amino, C_1-C_4-alkylsulfonyl, phenyl, and 5-6-membered heteroaryl.

[0120] In some embodiments, R^4 is selected from the group consisting of C_1-C_4-alkyl, C_2-C_4-alkenyl, C_2-C_4-alkynyl, amino, C_1-C_4-alkylsulfonyl, C_3-C_6-carbocyclyl, and 5-6-membered heterocyclyl. In some such embodiment, R^4 is selected from the group consisting of C_1-C_4-alkyl, C_2-C_4-alkenyl, C_2-C_4-alkynyl, amino, C_1-C_4-alkylsulfonyl, C_6-carbocyclyl, and 5-6-membered heterocyclyl. In other such embodiment, R^4 is selected from the group consisting of C_1-C_4-alkyl, C_2-C_4-alkenyl, C_2-C_4-alkynyl, amino, C_1-C_4-alkylsulfonyl, phenyl, and 5-6-membered heteroaryl.

[0121] In some embodiments, R^4 is selected from the group consisting of halo, C_1-C_4-alkyl, C_3-C_6-carbocyclyl, and 5-6-membered heterocyclyl. In some such embodiments, R^4 is selected from the group consisting of halo, C_1-C_4-alkyl, C_6-carbocyclyl, and 5-6-membered heterocyclyl. In other such embodiments, R^4 is selected from the group consisting of halo, C_1-C_4-alkyl, phenyl, and 5-6-membered heteroaryl.

[0122] In some embodiments, R^4 is selected from the group consisting of C_1-C_4-alkyl, C_3-C_6-carbocyclyl, and 5-6-membered heterocyclyl. In some such embodiments, R^4 is selected from the group consisting of C_1-C_4-alkyl, C_6-carbocyclyl, and 5-6-membered heterocyclyl. In other such embodiments, R^4 is selected from the group consisting of C_1-C_4-alkyl, phenyl, and 5-6-membered heteroaryl.

[0123] In some embodiments, R^4 is selected from the group consisting of halo, tert-butyl, C_3-C_6-carbocyclyl, and 5-6-membered heterocyclyl. In some such embodiments, R^4 is selected from the group consisting of halo, tert-butyl, C_6-carbocyclyl, and 5-6-membered heterocyclyl. In other such embodiments, R^4 is selected from the group consisting of halo, tert-butyl, phenyl, and 5-6-membered heteroaryl.

[0124] In some embodiments, R^4 is selected from the group consisting of tert-butyl, C_3-C_6-carbocyclyl, and 5-6-membered heterocyclyl. In some such embodiments, R^4 is selected from the group consisting of tert-butyl, C_6-carbocyclyl, and 5-6-membered heterocyclyl. In other such embodiments, R^4 is selected from the group consisting of tert-butyl, phenyl, and 5-6-membered heteroaryl.

[0125] In some embodiments, R^4 is selected from the group consisting of C_3-C_6-carbocyclyl and 5-6-membered heterocyclyl. In some such embodiments, R^4 is selected from the group consisting of C_6-carbocyclyl, and 5-6-membered heterocyclyl. In other such embodiments, R^4 is selected from the group consisting of phenyl and 5-6-membered heteroaryl.

[0126] Suitable carbocyclyls for the above embodiments include, for example, cyclopropyl and phenyl.

[0127] Suitable heterocyclyls for the above embodiments include, for example, furanyl, thienyl, and pyridinyl.

[0128] In some embodiments, R^4 is selected from the group consisting of halo, alkyl, and alkyloxy.

[0129] In some embodiments, R^4 is alkyl.

[0130] In some embodiments, R^4 is tert-butyl.

B5. Substituent R^5.

[0131] R^5 is selected from the group consisting of hydrogen, hydroxy, alkyl, alkenyl, alkynyl, alkyloxy, alkenyloxy, alkynyloxy, alkylsulfonyloxy, carbocyclylsulfonyloxy, haloalkylsulfonyloxy, and halo.

[0132] In some embodiments, R^5 is selected from the group consisting of hydrogen, hydroxy, alkyloxy, and halo. In some such embodiments, R^5 is selected from the group consisting of hydrogen, hydroxy, alkyloxy, and fluoro. In other such embodiments, R^5 is selected from the group consisting of hydrogen, hydroxy, alkyloxy, and fluoro. In yet other such embodiments, R^5 is selected from the group consisting of hydrogen, hydroxy, alkyloxy, and chloro. In yet other such embodiments, R^5 is selected from the group consisting of hydrogen, hydroxy, alkyloxy, and bromo. In further such embodiments, R^5 is selected from the group consisting of hydrogen, hydroxy, alkyloxy, and iodo.

[0133] In some embodiments, R^5 is selected from the group consisting of hydrogen, hydroxy, methoxy, and halo. In some such embodiments, R^5 is selected from the group consisting of hydrogen, hydroxy, methoxy, and fluoro. In other such embodiments, R^5 is selected from the group consisting of hydrogen, hydroxy, methoxy, and chloro. In yet other such embodiments, R^5 is selected from the group consisting of hydrogen, hydroxy, methoxy, and bromo. In further such embodiments, R^5 is selected from the group consisting of hydrogen, hydroxy, methoxy, and iodo.

[0134] In some embodiments, R^5 is selected from the group consisting of hydrogen, hydroxy, and alkyloxy. In some such

embodiments, R^5 is selected from the group consisting of hydrogen, hydroxy, methoxy, and ethoxy.

[0135] In some embodiments, R^5 is s hydrogen.

[0136] In some embodiments, R^5 is hydroxy.

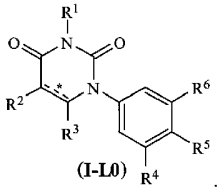
[0137] In some embodiments, R^5 is alkyloxy.

[0138] In some embodiments, R^5 is methoxy.

[0139] In some embodiments, R^5 is ethoxy.

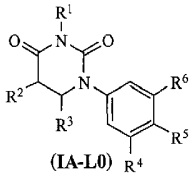
B6. Substituent L.

[0140] L is a bond, and the compounds of formula I correspond in structure to formula **I-L0:**



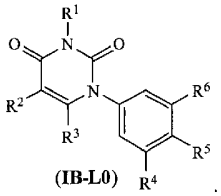
(I-L0)

[0141] In some such embodiments, the compounds correspond in structure to the following formula (*i.e.,* formula **IA-L0):**



(IA-L0)

[0142] In other such embodiments, the compounds correspond in structure to the following formula (*i.e.*, formula **IB-L0):**



(IB-L0)

B7. Substituent R^6.

[0143] In some embodiments, R^6 is selected from the group consisting of fused 2-ring carbocyclyl and fused 2-ring heterocyclyl, wherein each such substituent optionally is substituted with one or more substituents independently selected from the group consisting of R^E, R^F, R^G, R^H, R^1, R^J, and R^K.

[0144] In some such embodiments, the fused 2-ring carbocyclyl and fused 2-ring heterocyclyl are not substituted.

[0145] In other such embodiments, the fused 2-ring carbocyclyl and fused 2-ring heterocyclyl are substituted with a substituent selected from the group consisting of R^E, R^F, R^G, R^H, R^I, R^J, and R^K. In some such embodiments, the fused 2-ring carbocyclyl and fused 2-ring heterocyclyl are substituted with a substituent selected from the group consisting of R^E, R^F, R^I, R^J, and R^K. In other such embodiments, fused 2-ring carbocyclyl and fused 2-ring heterocyclyl are substituted with a substituent selected from

the group consisting of R^E, R^F, and R^J. In yet other such embodiments, the fused 2-ring carbocyclyl and fused 2-ring heterocyclyl are substituted with a substituent selected from the group consisting of R^F and R^J. In other such embodiments, the fused 2-ring carbocyclyl and fused 2-ring heterocyclyl are substituted with R^J.

[0146] In yet other such embodiments, the fused 2-ring carbocyclyl and fused 2-ring heterocyclyl are substituted with two substituents independently selected from the group consisting of R^E, R^F, R^G, R^H, R^I, R^J, and R^K. In some such embodiments, the fused 2-ring carbocyclyl and fused 2-ring heterocyclyl are substituted with two substituents independently selected from the group consisting of R^E, R^F, R^I, R^J, and R^K. In other such embodiments, the fused 2-ring carbocyclyl and fused 2-ring heterocyclyl are substituted with two substituents independently selected from the group consisting of R^E, R^F, and R^J. In other such embodiments, the fused 2-ring carbocyclyl and fused 2-ring heterocyclyl are substituted with two substituents independently selected from the group consisting of R^F and R^J.

[0147] In further such embodiments, the fused 2-ring carbocyclyl and fused 2-ring heterocyclyl are substituted with three substituents independently selected from the group consisting of R^E, R^F, R^G, R^H, R^I, R^J, and R^K. In some such embodiments, the fused 2-ring carbocyclyl and fused 2-ring heterocyclyl are substituted with three substituents independently selected from the group consisting of R^E, R^F, R^I, R^J, and R^K. In other such embodiments, the fused 2-ring carbocyclyl and fused 2-ring heterocyclyl are substituted with three substituents independently selected from the group consisting of R^E, R^F, and R^J. In further such embodiments, the fused 2-ring carbocyclyl and fused 2-ring heterocyclyl are substituted with three substituents independently selected from the group consisting of R^F and R^J.

[0148] In further such embodiments, the fused 2-ring carbocyclyl and fused 2-ring heterocyclyl are substituted with one, two, or three substituents independently selected from the group consisting of R^E, R^F, R^G, R^H, R^I, R^J, and R^K. In some such embodiments, the fused 2-ring carbocyclyl and fused 2-ring heterocyclyl are substituted with one, two, or three substituents independently selected from the group consisting of R^E, R^F, R^I, R^J, and R^K. In other such embodiments, the fused 2-ring carbocyclyl and fused 2-ring heterocyclyl are substituted with one, two, or three substituents independently selected from the group consisting of R^E, R^F, and R^J. In further such embodiments, the fused 2-ring carbocyclyl and fused 2-ring heterocyclyl are substituted with one, two, or three substituents independently selected from the group consisting of R^F and R^J.

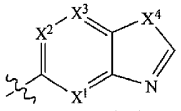
[0149] In some embodiments, R^6 is fused 2-ring carbocyclyl optionally substituted with one or more substituents independently selected from the group consisting of R^E, R^F, R^G, R^H, R^I, R^J, and R^K. In some such embodiments, the fused 2-ring carbocyclyl is not substituted. In other such embodiments, the fused 2-ring carbocyclyl is substituted with a substituent selected from the group consisting of R^E, R^F, R^G, R^H, R^I, R^J, and R^K. In yet other such embodiments, the fused 2-ring carbocyclyl is substituted with two substituents independently selected from the group consisting of R^E, R^F, R^G, R^H, R^I, R^J, and R^K. In further such embodiments, the fused 2-ring carbocyclyl is substituted with three substituents independently selected from the group consisting of R^E, R^F, R^G, R^H, R^I, R^J, and R^K. In further such embodiments, the fused 2-ring carbocyclyl is substituted with one, two, or three substituents independently selected from the group consisting of R^E, R^F, R^G, R^H, R^I, R^J, and R^K.

[0150] In some embodiments, R^6 is fused 2-ring heterocyclyl optionally substituted with one or more substituents independently selected from the group consisting of R^E, R^F, R^G, R^H, R^I, R^J, and R^K. In some such embodiments, the fused 2-ring heterocyclyl is not substituted. In other such embodiments, the fused 2-ring heterocyclyl is substituted with a substituent selected from the group consisting of R^E, R^F, R^G, R^H, R^I, R^J, and R^K. In yet other such embodiments, the fused 2-ring heterocyclyl is substituted with two substituents independently selected from the group consisting of R^E, R^F, R^G, R^H, R^I, R^J, and R^K. In further such embodiments, the fused 2-ring heterocyclyl is substituted with three substituents independently selected from the group consisting of R^E, R^F, R^G, R^H, R^I, R^J, and R^K. In further such embodiments, the fused 2-ring heterocyclyl is substituted with one, two, or three substituents independently selected from the group consisting of R^E, R^F, R^G, R^H, R^I, R^J, and R^K.

[0151] In some of the above embodiments, the optionally substituted fused 2-ring carbocyclyl is selected from the group consisting of naphthalenyl, dihydronaphthalenyl, tetrahydronaphthalenyl, hexahydronaphthalenyl, octahydronaphthalenyl, decahydronaphthalenyl, indenyl, dihydroindenyl, hexahydroindenyl, octahydroindenyl, pentalenyl, octahydropentalenyl, and hexahydropentalenyl. In some such embodiments, the optionally substituted fused 2-ring carbocyclyl is selected from the group consisting of naphthalenyl and dihydroindenyl. In some such embodiments, the optionally substituted fused 2-ring carbocyclyl is

naphthalenyl. In other such embodiments, the optionally substituted fused 2-ring carbocyclyl is dihydroindenyl. In further such embodiments, the optionally substituted fused 2-ring carbocyclyl is indenyl.

[0152] In some of the above embodiments, the optionally substituted fused 2-ring heterocyclyl is selected from the group consisting of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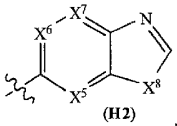
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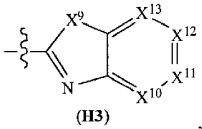
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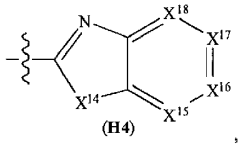
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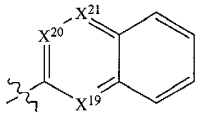
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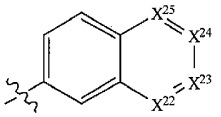
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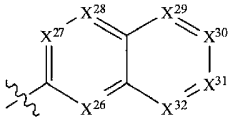
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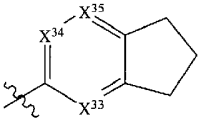
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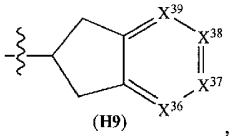
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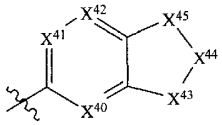
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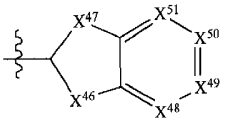
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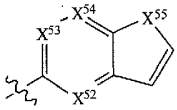
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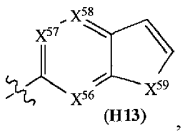
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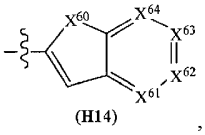
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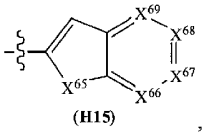
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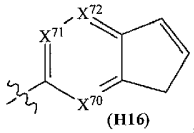
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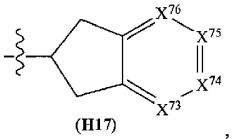
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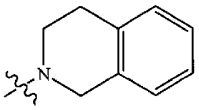
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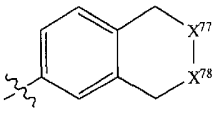
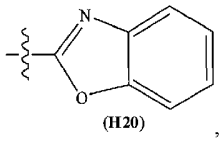
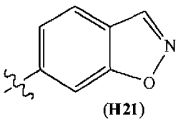
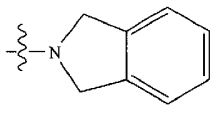

(H19) ,


(H20) ,


(H21) ,

and


(H22) ;

X^1, X^2, and X^3 are independently selected from the group consisting of N and C(H);

X^4 is selected from the group consisting of N(H), O, and S;

X^5, X^6, and X^7 are independently selected from the group consisting of N and C(H);

X^8 is selected from the group consisting of N(H), O, and S;

X^9 is selected from the group consisting of N(H), O, and S;

X^{10}, X^{11}, X^{12}, and X^{13} are independently selected from the group consisting of N and C(H);

X^{14} is selected from the group consisting of N(H), O, and S;

X^{15}, X^{16}, X^{17}, and X^{18} are independently selected from the group consisting of N and C(H);

one or more of X^{19}, X^{20}, and X^{21} is N, and the remaining one(s) is/are C(H);

one or more of X^{22}, X^{23}, X^{24}, and X^{25} is N, and the remaining one(s) is/are C(H);

one or more of X^{26}, X^{27}, and X^{28} is N, and the remaining one(s) is/are C(H);

one or more of X^{29}, X^{30}, X^{31}, and X^{32} is N, and the remaining one(s) is/are C(H);

one or more of X^{33}, X^{34}, and X^{35} is N, and the remaining one(s) is/are C(H);

one or more of X^{36}, X^{37}, X^{38}, and X^{39} is N, and the remaining one(s) is/are C(H);

X^{40}, X^{41}, and X^{42} are independently selected from the group consisting of N and C(H);

one of X^{43}, X^{44}, and X^{45} is selected from the group consisting of N(H), O, and S, and the remaining two are $C(H)_2$;

one of X^{46} and X^{47} is selected from the group consisting of N(H), O, and S, and the other one is $C(H)_2$;

X^{48}, X^{49}, X^{50}, and X^{51} are independently selected from the group consisting of N and C(H);

X^{52}, X^{53}, and X^{54} are independently selected from the group consisting of N and C(H);

X^{55} is selected from the group consisting of N(H), O, and S;

X^{56}, X^{57}, and X^{58} are independently selected from the group consisting of N and C(H);

X^{59} is selected from the group consisting of N(H), O, and S;

X^{60} is selected from the group consisting of N(H), O, and S;

X^{61}, X^{62}, X^{63}, and X^{64} are independently selected from the group consisting of N and C(H);

X^{65} is selected from the group consisting of N(H), O, and S;

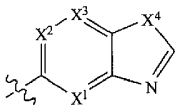
X^{66}, X^{67}, X^{68}, and X^{69} are independently selected from the group consisting of N and C(H);

one or more of X^{70} X^{71}, and X^{72} is N, and the remaining one(s) is/are C(H);

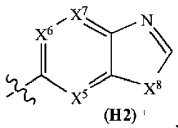
one or more of X^{73}, X^{74}, X^{75}, and X^{76} is N, and the remaining one(s) is/are C(H); and

one of X^{77} and X^{78} is N(H), and the remaining one is $C(H)_2$.

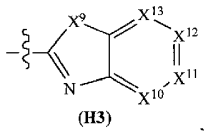
[0153] In some of the above embodiments, the optionally substituted fused 2-ring heterocyclyl is selected from the group consisting of



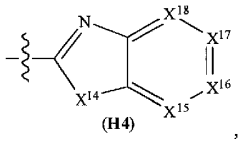
(H1) ,

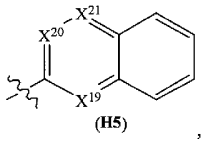


(H2) ,



(H3) ,


(H4) ,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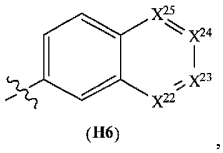
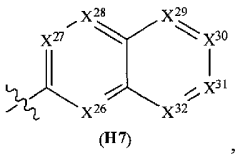

(H6) ,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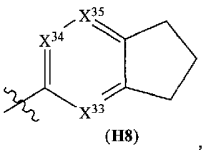
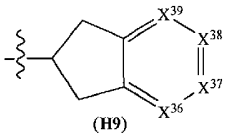
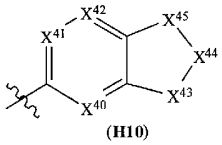
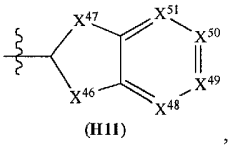
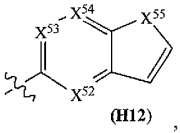
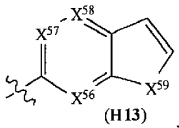

(H8) ,

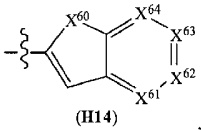

(H9) ,


(H10) ,


(H11) ,


(H12) ,


(H13) ,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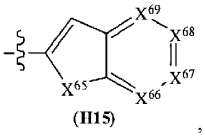
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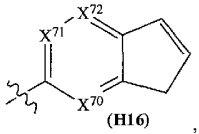
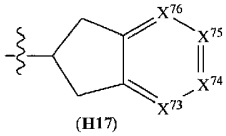
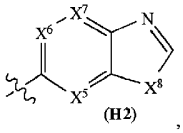
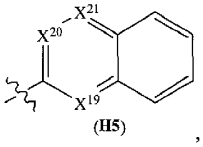
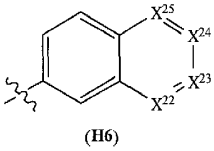

(H16) , and

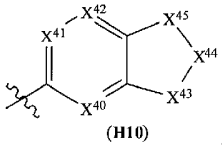

(H17)

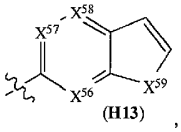
[0154] In some of the above embodiments, the optionally substituted fused 2-ring heterocyclyl is selected from the group consisting of:


(H2) ,


(H5) ,


(H6) ,


(H10) ,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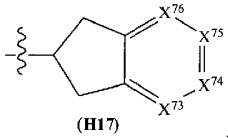
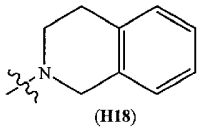
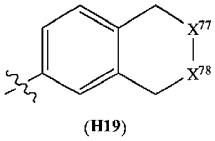
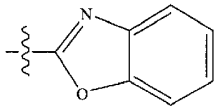
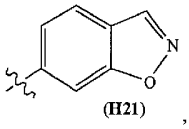
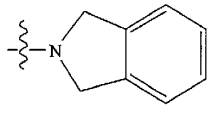

(H17) ,


(H18) ,


(H19) ,


(H20) ,


(H21) , and


(H22) .

[0155] In some of the above embodiments, X^1, X^2, and X^3 are C(H).

[0156] In some of the above embodiments, X^5, X^6, and X^7 are C(H).

[0157] In some of the above embodiments, X^{10}, X^{11}, X^{12}, and X^{13} are C(H).

[0158] In some of the above embodiments, X^{15}, X^{16}, X^{17}, and X^{18} are C(H).

[0159] In some of the above embodiments, one of X^{19}, X^{20}, and X^{21} is N.

[0160] In some of the above embodiments, one of X^{22}, X^{23}, X^{24}, and X^{25} is N.

[0161] In some of the above embodiments, one of X^{26}, X^{27}, and X^{28} is N, and one of X^{29}, X^{30}, X^{31}, and X^{32} is N.

[0162] In some of the above embodiments, X^{40}, X^{41}, and X^{42} are C(H).

[0163] In some of the above embodiments, X^{48}, X^{49}, X^{50}, and X^{51} are C(H).

[0164] In some of the above embodiments, X^{52}, X^{53}, and X^{54} are C(H).

[0165] In some of the above embodiments, X^{56}, X^{57}, and X^{58} are C(H).

[0166] In some of the above embodiments, X^{61}, X^{62}, X^{63}, and X^{64} are C(H).

[0167] In some of the above embodiments, X^{66}, X^{67}, X^{68}, and X^{69} are C(H).

[0168] In some of the above embodiments, one or more of X^{70}, X^{71}, and X^{72} is N, and the remaining one(s) is/are C(H).

[0169] In some of the above embodiments, one or more of X^{73}, X^{74}, X^{75}, and X^{76} is N, and the remaining one(s) is/are C(H).

B8. Substituent R^E.

[0170] Each R^E is independently selected from the group consisting of halo, nitro, hydroxy, oxo, carboxy, cyano, amino, imino, azido, and aldehydo, wherein the amino optionally is substituted with one or two substituents independently selected from the group consisting of alkyl, alkenyl, and alkynyl.

[0171] In some embodiment, each R^E is independently selected from the group consisting of halo, nitro, hydroxy, oxo, carboxy, amino, imino, and aldehydo, wherein the amino optionally is substituted with one or two independently selected alkyl.

[0172] In some embodiment, each R^E is independently selected from the group consisting of halo, nitro, hydroxy, oxo, carboxy, amino, imino, aldehydo, and alkylamino.

[0173] In some embodiment, each R^E is independently selected from the group consisting of chloro, fluoro, nitro, hydroxy, oxo, carboxy, amino, imino, aldehydo, and alkylamino.

[0174] In some embodiment, each R^E is independently selected from the group consisting of halo, nitro, hydroxy, oxo, carboxy, cyano, amino, imino, and azido. In some such embodiments, each R^E is halo. In other such embodiments, each R^E is nitro. In yet other such embodiments, each R^E is hydroxy. In yet other such embodiments, each R^E is oxo. In yet other such embodiments, each R^E is carboxy. In yet other such embodiments, each R^E is cyano. In yet other such embodiments, each R^E is amino. In further such embodiments, each R^E is imino. In yet further such embodiments, each R^E is and azido.

[0175] In some embodiments, each R^E is independently selected from the group consisting of halo, nitro, hydroxy, oxo, carboxy, cyano, amino, and imino.

B9. Substituent R^F.

[0176] Each R^F is independently selected from the group consisting of alkyl, alkenyl, and alkynyl, wherein:

each such substituent optionally is substituted with one or more substituents independently selected from the group consisting of carboxy, hydroxy, halo, amino, imino, nitro, azido, oxo, aminosulfonyl, alkylsulfonyl, alkyloxycarbonyl, alkenyloxycarbonyl, alkynyloxycarbonyl, alkylcarbonyloxy, alkenylcarbonyloxy, alkynylcarbonyloxy, alkyloxy, alkenyloxy, alkynyloxy, carbocyclyl, heterocyclyl, cyano, and aminocarbonyl, wherein:

the amino, imino, aminosulfonyl, aminocarbonyl, carbocyclyl, and heterocyclyl optionally are substituted with one or two substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, alkylsulfonyl, alkenylsulfonyl, alkynylsulfonyl, alkylsulfonylamino, hydroxy, and alkyloxy,
wherein:

amino portion of the alkylsulfonylamino optionally is substituted with a substituent selected from the group consisting of alkyl, alkenyl, and alkynyl.

[0177] In some embodiment, each R^F is independently selected from the group consisting of alkyl, alkenyl, and alkynyl, wherein:

each such substituent optionally is substituted with one or more substituents independently selected from the group consisting of carboxy, hydroxy, halo, amino, imino, nitro, azido, oxo, aminosulfonyl, alkylsulfonyl, alkyloxycarbonyl, alkenyloxycarbonyl, alkynyloxycarbonyl, alkylcarbonyloxy, alkenylcarbonyloxy, alkynylcarbonyloxy, alkyloxy, alkenyloxy, alkynyloxy, carbocyclyl, heterocyclyl, cyano, and aminocarbonyl, wherein:

the amino, imino, aminosulfonyl, and aminocarbonyl optionally are substituted with one or two substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, alkylsulfonyl, alkenylsulfonyl, alkynylsulfonyl, and alkylsulfonylamino,
wherein:

amino portion of the alkylsulfonylamino optionally is substituted with a substituent selected from the group consisting of alkyl, alkenyl, and alkynyl.

[0178] In some of the above embodiments, each R^F is independently selected from the group consisting of the alkyl, alkynyl, and alkynyl, wherein such substituents are not substituted.

[0179] In some embodiments, each R^F is independently selected from the group consisting of alkyl, alkenyl, and alkynyl, wherein:

each such substituent optionally is substituted with one or two substituents independently selected from the group consisting of carboxy, hydroxy, halo, amino, imino, nitro, oxo, aminosulfonyl, alkylsulfonyl, alkyloxycarbonyl, alkylcarbonyloxy, alkyloxy, carbocyclyl, heterocyclyl, cyano, and aminocarbonyl, wherein:

the amino, imino, aminosulfonyl, and aminocarbonyl optionally are substituted with one or two substituents independently selected from the group consisting of alkyl, alkylsulfonyl, and alkylsulfonylamino,
wherein:

amino portion of the alkylsulfonylamino optionally is substituted with alkyl.

[0180] In some embodiments, each R^F is an independently selected alkyl optionally substituted with a substituent selected from the group consisting of carboxy, hydroxy, halo, amino, imino, nitro, oxo, aminosulfonyl, alkylsulfonyl, alkyloxycarbonyl, alkylcarbonyloxy, alkyloxy, carbocyclyl, heterocyclyl, cyano, and aminocarbonyl, wherein:

the amino, imino, aminosulfonyl, and aminocarbonyl optionally are substituted with one or two substituents independently selected from the group consisting of alkyl, alkylsulfonyl, and alkylsulfonylamino, wherein:

amino portion of the alkylsulfonylamino optionally is substituted with alkyl.

[0181] In some embodiments, each R^F is an independently selected alkyl optionally substituted with a substituent selected from the group consisting of carboxy, halo, amino, imino, and aminosulfonyl, wherein:

the amino, imino, and aminosulfonyl optionally are substituted with one or two substituents independently selected from the group consisting of alkyl, alkylsulfonyl, and alkylsulfonylamino.

[0182] In some embodiments, each R^F is an independently selected alkyl optionally substituted with amino, wherein the amino optionally is substituted with alkylsulfonyl.

[0183] In some embodiments, each R^F is an independently selected alkyl substituted with amino, wherein the amino is substituted with alkylsulfonyl. In some such embodiments, each R^F is methylsulfonylaminomethyl.

[0184] In some embodiments, each R^F is independently selected from the group consisting of alkyl, alkenyl, and alkynyl, wherein:

each such substituent optionally is substituted with one, two, or three substituents independently selected from the group consisting of carboxy, hydroxy, halo, amino, imino, nitro, azido, oxo, aminosulfonyl, alkylsulfonyl, alkyloxycarbonyl, alkenyloxycarbonyl, alkynyloxycarbonyl, alkylcarbonyloxy, alkenylcarbonyloxy, alkynylcarbonyloxy, alkyloxy, alkenyloxy, alkynyloxy, carbocyclyl, heterocyclyl, cyano, and aminocarbonyl.

[0185] In some embodiments, each R^F is independently selected alkyl substituted with one or more substituents independently selected from the group consisting of carboxy, hydroxy, halo, amino, imino, nitro, azido, oxo, aminosulfonyl, alkylsulfonyl, alkyloxycarbonyl, alkenyloxycarbonyl, alkynyloxycarbonyl, alkylcarbonyloxy, alkenylcarbonyloxy, alkynylcarbonyloxy, alkyloxy, alkenyloxy, alkynyloxy, carbocyclyl, heterocyclyl, cyano, and aminocarbonyl.

B10. Substituent R^G.

[0186] Each R^G is independently selected from the group consisting of carbocyclyl and heterocyclyl, wherein:

each such substituent optionally is substituted with one or more substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, carboxy, hydroxy, halo, amino, nitro, azido, oxo, aminosulfonyl, alkyloxycarbonyl, alkenyloxycarbonyl, alkynyloxycarbonyl, alkylcarbonyloxy, alkenylcarbonyloxy, alkynylcarbonyloxy, alkyloxy, alkenyloxy, alkynyloxy, carbocyclyl, heterocyclyl, cyano, and aminocarbonyl, wherein:

the amino, aminosulfonyl, and aminocarbonyl optionally are substituted with one or two substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, alkylsulfonyl, alkenylsulfonyl, and alkynylsulfonyl.

[0187] In some of the above embodiments, each R^G is independently selected from the group consisting of carbocyclyl and heterocyclyl, wherein such substituents are not substituted.

[0188] In some embodiments, each R^G is independently selected from the group consisting of carbocyclyl and heterocyclyl, wherein:

each such substituent optionally is substituted with one or two substituents independently selected from the group consisting of alkyl, carboxy, hydroxy, halo, amino, nitro, oxo, aminosulfonyl, alkyloxycarbonyl, alkylcarbonyloxy, alkyloxy, carbocyclyl, heterocyclyl, cyano, and aminocarbonyl, wherein:

the amino, aminosulfonyl, and aminocarbonyl optionally are substituted with one or two substituents independently selected from

the group consisting of alkyl and alkylsulfonyl.

[0189] In some of the above embodiments, the carbocyclyl is C_3-C_6-carbocyclyl.

[0190] In some of the above embodiments, the heterocyclyl is 5-6-membered heterocyclyl.

[0191] ***B11.*** *Substituent* R^H.

[0192] Each R^H is independently selected from the group consisting of alkyloxy, alkenyloxy, alkynyloxy, alkylsulfonyloxy, alkenylsulfonyloxy, and alkynylsulfonyloxy, wherein:

each such substituent optionally is substituted with one or more substituents independently selected from the group consisting of carboxy, hydroxy, halo, amino, nitro, azido, oxo, aminosulfonyl, alkyloxycarbonyl, alkenyloxycarbonyl, alkynyloxycarbonyl, alkylcarbonyloxy, alkenylcarbonyloxy, alkynylcarbonyloxy, alkyloxy, alkenyloxy, alkynyloxy, carbocyclyl, heterocyclyl, cyano, and aminocarbonyl, wherein:

the amino, aminosulfonyl, and aminocarbonyl optionally are substituted with one or two substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, alkylsulfonyl, alkenylsulfonyl, and alkynylsulfonyl.

[0193] In some of the above embodiments, each R^H is independently selected from the group consisting of alkyloxy, alkenyloxy, alkynyloxy, alkylsulfonyloxy, alkenylsulfonyloxy, and alkynylsulfonyloxy, wherein such substituents are not substituted.

[0194] In some embodiments, each R^H is independently selected from the group consisting of alkyloxy and alkylsulfonyloxy, wherein:

each such substituent optionally is substituted with one or two substituents independently selected from the group consisting of carboxy, hydroxy, halo, amino, nitro, oxo, aminosulfonyl, alkyloxycarbonyl, alkylcarbonyloxy, alkyloxy, carbocyclyl, heterocyclyl, cyano, and aminocarbonyl, wherein:

the amino, aminosulfonyl, and aminocarbonyl optionally are substituted with one or two substituents independently selected from the group consisting of alkyl and alkylsulfonyl.

[0195] In some embodiments, each R^H is independently selected from the group consisting of alkyloxy and alkylsulfonyloxy, wherein:

each such substituent optionally is substituted with one or two substituents independently selected from the group consisting of carboxy, hydroxy, halo, amino, nitro, oxo, aminosulfonyl, alkyloxycarbonyl, alkylcarbonyloxy, alkyloxy, cyano, and aminocarbonyl, wherein:

the amino, aminosulfonyl, and aminocarbonyl optionally are substituted with one or two substituents independently selected from the group consisting of alkyl and alkylsulfonyl.

[0196] In some embodiments, each R^H is independently selected from the group consisting of alkyloxy and alkylsulfonyloxy, wherein:

each such substituent optionally is substituted with one or two substituents independently selected from the group consisting of carboxy, hydroxy, halo, amino, nitro, oxo, aminosulfonyl, alkyloxycarbonyl, alkylcarbonyloxy, alkyloxy, cyano, and aminocarbonyl.

[0197] In some embodiments, each R^H is independently selected alkyloxy.

[0198] In some embodiments, each R^H is independently selected alkylsulfonyloxy.

B12. Substituent R^I.

[0199] Each R^I is independently selected from the group consisting of alkylcarbonyl, alkenylcarbonyl, alkynylcarbonyl, aminocarbonyl, alkyloxycarbonyl, carbocyclylcarbonyl, and heterocyclylcarbonyl, wherein:

1. **(a)** the alkylcarbonyl, alkenylcarbonyl, and alkynylcarbonyl optionally are substituted with one or more substituents independently selected from the group consisting of carboxy, hydroxy, halo, amino, nitro, azido, oxo, aminosulfonyl, alkyloxycarbonyl, alkenyloxycarbonyl, alkynyloxycarbonyl, alkylcarbonyloxy, alkenylcarbonyloxy, alkynylcarbonyloxy, alkyloxy, alkenyloxy, alkynyloxy, carbocyclyl, heterocyclyl, cyano, and aminocarbonyl, and
2. **(b)** the aminocarbonyl optionally is substituted with one or two substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, alkyloxyalkyl, carbocyclyl, heterocyclyl, alkylsulfonyl, and alkylsulfonylamino, wherein:

   the carbocyclyl and heterocyclyl optionally are substituted with one or two substituents independently selected from the group consisting of halo, alkyl, and oxo.

[0200] In some embodiments, each R^I is independently selected from the group consisting of alkylcarbonyl, alkenylcarbonyl, alkynylcarbonyl, aminocarbonyl, alkyloxycarbonyl, carbocyclylcarbonyl, and heterocyclylcarbonyl, wherein such substituents are not substituted.

[0201] In some embodiments, each R^I is independently selected from the group consisting of alkylcarbonyl, aminocarbonyl, alkyloxycarbonyl, carbocyclylcarbonyl, and heterocyclylcarbonyl, wherein:

1. **(a)** the alkylcarbonyl optionally is substituted with a substituent selected from the group consisting of carboxy, hydroxy, halo, amino, nitro, oxo, aminosulfonyl, alkyloxycarbonyl, alkylcarbonyloxy, alkyloxy, and aminocarbonyl, and
2. **(b)** the aminocarbonyl optionally is substituted with a substituent selected from the group consisting of alkyl, alkyloxyalkyl, alkylsulfonyl, and alkylsulfonylamino.

[0202] In some embodiments, each R^I is independently selected from the group consisting of alkylcarbonyl and aminocarbonyl, wherein:

the aminocarbonyl optionally is substituted with a substituent selected from the group consisting of alkyl, alkyloxyalkyl, alkylsulfonyl, and alkylsulfonylamino.

[0203] In some embodiment, each R^I is independently selected from the group consisting of alkylcarbonyl, alkenylcarbonyl, alkynylcarbonyl, and aminocarbonyl, wherein:

1. **(a)** the alkylcarbonyl, alkenylcarbonyl, and alkynylcarbonyl optionally are substituted with one or more substituents independently selected from the group consisting of carboxy, hydroxy, halo, amino, nitro, azido, oxo, aminosulfonyl, alkyloxycarbonyl, alkenyloxycarbonyl, alkynyloxycarbonyl, alkylcarbonyloxy, alkenylcarbonyloxy, alkynylcarbonyloxy, alkyloxy, alkenyloxy, alkynyloxy, carbocyclyl, heterocyclyl, cyano, and aminocarbonyl, and
2. **(b)** the aminocarbonyl optionally is substituted with one or two substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, and alkylsulfonylamino.

[0204] In some of the above embodiments, each R^I is independently selected from the group consisting of alkylcarbonyl, alkenylcarbonyl, alkynylcarbonyl, and aminocarbonyl, wherein such substituents are not substituted.

[0205] In some embodiments, each R^I is independently selected from the group consisting of alkylcarbonyl and aminocarbonyl,

wherein:

1. **(a)** the alkylcarbonyl optionally is substituted with one or two substituents independently selected from the group consisting of carboxy, hydroxy, halo, amino, nitro, azido, oxo, aminosulfonyl, alkyloxycarbonyl, alkylcarbonyloxy, alkyloxy, carbocyclyl, heterocyclyl, cyano, and aminocarbonyl, and
2. **(b)** the aminocarbonyl optionally is substituted with one or two substituents independently selected from the group consisting of alkyl and alkylsulfonylamino.

[0206] In some embodiments, each R^I is independently selected from the group consisting of alkylcarbonyl and aminocarbonyl, wherein:

1. **(a)** the alkylcarbonyl optionally is substituted with one or two substituents independently selected from the group consisting of carboxy, hydroxy, halo, amino, nitro, oxo, aminosulfonyl, alkyloxycarbonyl, alkylcarbonyloxy, alkyloxy, cyano, and aminocarbonyl, and
2. **(b)** the aminocarbonyl optionally is substituted with one or two substituents independently selected from the group consisting of alkyl and alkylsulfonylamino.

[0207] In some embodiments, each R^I is independently selected from the group consisting of alkylcarbonyl and aminocarbonyl, wherein:

the alkylcarbonyl optionally is substituted with one or two substituents independently selected from the group consisting of carboxy, hydroxy, halo, amino, nitro, azido, oxo, aminosulfonyl, alkyloxycarbonyl, alkylcarbonyloxy, alkyloxy, carbocyclyl, heterocyclyl, cyano, and aminocarbonyl.

[0208] In some embodiments, each R^I is independently selected alkylcarbonyl.

[0209] In some embodiments, each R^I is independently selected aminocarbonyl.

B13. Substituent R^J.

[0210] Each R^J is independently selected from the group consisting of carbocyclylsulfonylamino, heterocyclylsulfonylamino, alkylcarbonylamino, alkenylcarbonylamino, alkynylcarbonylamino, alkyloxycarbonylamino, alkenyloxycarbonylamino, alkynyloxycarbonylamino, alkylsulfonylamino, alkenylsulfonylamino, alkynylsulfonylamino, aminocarbonylamino, alkyloxycarbonylaminoimino, alkylsulfonylaminoimino, alkenylsulfonylaminoimino, and alkynylsulfonylaminoimino, wherein:

1. **(a)** the amino portion of such substituents optionally is substituted with a substituent independently selected from the group consisting of carbocyclylalkyl, heterocyclylalkyl, alkylcarbonyloxy, aminocarbonylalkyl, alkyl, alkenyl, alkynyl, alkylcarbonyl, alkenylcarbonyl, alkynylcarbonyl, alkyloxycarbonyl, alkyloxyalkyloxycarbonyl, alkylcarbonyloxyalkyl, and alkylsulfonyl, wherein:
    1. **(1)** the carbocyclyl portion of the carbocyclylalkyl and the heterocyclyl portion of the heterocyclylalkyl optionally are substituted with one or more substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, carboxy, hydroxy, alkyloxy, alkenyloxy, alkynyloxy, halo, nitro, cyano, azido, oxo, and amino, and
    2. **(2)** the amino portion of the aminocarbonylalkyl optionally is substituted with one or two substituents independently selected from the group consisting of alkyl, alkenyl, and alkynyl,
2. **(b)** the alkyl, alkenyl, and alkynyl portion of such substituents optionally is substituted with one or more substituents independently selected from the group consisting of carboxy, halo, oxo, amino, alkyloxycarbonyl, alkylcarbonyloxy, hydroxy, alkyloxy, carbocyclyl, heterocyclyl, and cyano, wherein:

    the amino optionally is substituted with one or two substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, alkyloxy, alkenyloxy, and

    alkynyloxy, wherein:

the alkyl optionally is substituted with one or more hydroxy;

3. **(c)** the carbocyclyl and heterocyclyl portions of such substituents optionally are substituted with one or more substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, carboxy, hydroxy, alkyloxy, alkenyloxy, alkynyloxy, halo, nitro, cyano, azido, and amino, wherein:

   the amino optionally is substituted with one or two substituents independently selected from the group consisting of alkyl, alkenyl, and alkynyl.

[0211] In some embodiment, each R^J is independently selected from the group consisting of carbocyclylsulfonylamino, heterocyclylsulfonylamino, alkylcarbonylamino, alkenylcarbonylamino, alkynylcarbonylamino, alkyloxycarbonylamino, alkenyloxycarbonylamino, alkynyloxycarbonylamino, alkylsulfonylamino, alkenylsulfonylamino, alkynylsulfonylamino, aminocarbonylamino, alkylsulfonylaminoimino, alkenylsulfonylaminoimino, and alkynylsulfonylaminoimino, wherein:

1. **(a)** the amino portion of such substituents optionally is substituted with a substituent independently selected from the group consisting of carbocyclylalkyl, heterocyclylalkyl, alkylcarbonyloxy, aminocarbonylalkyl, alkyl, alkenyl, alkynyl, alkylcarbonyl, alkenylcarbonyl, alkynylcarbonyl, alkyloxycarbonyl, alkyloxyalkyloxycarbonyl, alkylcarbonyloxyalkyl, and alkylsulfonyl, wherein:
   1. **(1)** the carbocyclyl portion of the carbocyclylalkyl and the heterocyclyl portion of the heterocyclylalkyl optionally are substituted with one or more substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, carboxy, hydroxy, alkyloxy, alkenyloxy, alkynyloxy, halo, nitro, cyano, azido, oxo, and amino, and
   2. **(2)** the amino portion of the aminocarbonylalkyl optionally is substituted with one or two substituents independently selected from the group consisting of alkyl, alkenyl, and alkynyl,
2. **(b)** the alkyl, alkenyl, and alkynyl portion of such substituents optionally is substituted with one or more substituents independently selected from the group consisting of carboxy, halo, oxo, amino, alkyloxycarbonyl, alkylcarbonyloxy, hydroxy, alkyloxy, carbocyclyl, heterocyclyl, and cyano, wherein:

   the amino optionally is substituted with one or two substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, alkyloxy, alkenyloxy, and alkynyloxy, wherein:

   the alkyl optionally is substituted with one or more hydroxy;

3. **(c)** the carbocyclyl and heterocyclyl portions of such substituents optionally are substituted with one or more substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, carboxy, hydroxy, alkyloxy, alkenyloxy, alkynyloxy, halo, nitro, cyano, azido, and amino, wherein:

   the amino optionally is substituted with one or two substituents independently selected from the group consisting of alkyl, alkenyl, and alkynyl; and

[0212] In some of the above embodiments, each R^J is independently selected from the group consisting of carbocyclylsulfonylamino, heterocyclylsulfonylamino, alkylcarbonylamino, alkenylcarbonylamino, alkynylcarbonylamino, alkyloxycarbonylamino, alkenyloxycarbonylamino, alkynyloxycarbonylamino, alkylsulfonylamino, alkenylsulfonylamino, alkynylsulfonylamino, aminocarbonylamino, alkylsulfonylaminoimino, alkenylsulfonylaminoimino, and alkynylsulfonylaminoimino, wherein such substituents are not substituted.

[0213] In some embodiments, each R^J is independently selected from the group consisting of carbocyclylsulfonylamino, heterocyclylsulfonylamino, alkylcarbonylamino, alkyloxycarbonylamino, alkylsulfonylamino, aminocarbonylamino, and alkylsulfonylaminoimino, wherein:

1. **(a)** the amino portion of such substituents optionally is substituted with a substituent independently selected from the group consisting of carbocyclylalkyl, heterocyclylalkyl, alkylcarbonyloxy, aminocarbonylalkyl, alkyl, alkylcarbonyl, alkyloxycarbonyl, alkyloxyalkyloxycarbonyl, alkylcarbonyloxyalkyl, and alkylsulfonyl, wherein:
   1. **(1)** the carbocyclyl portion of the carbocyclylalkyl and the heterocyclyl portion of the heterocyclylalkyl optionally are substituted with one or two substituents independently selected from the group consisting of alkyl, carboxy, hydroxy, alkyloxy, halo, nitro, cyano, oxo, and amino, and
   2. **(2)** the amino portion of the aminocarbonylalkyl optionally is substituted with one or two substituents independently

selected from the group consisting of alkyl, alkenyl, and alkynyl,

2. **(b)** the alkyl portion of such substituents optionally is substituted with one or two substituents independently selected from the group consisting of carboxy, halo, oxo, amino, alkyloxycarbonyl, alkylcarbonyloxy, hydroxy, alkyloxy, carbocyclyl, heterocyclyl, and cyano, wherein:

   the amino optionally is substituted with one or two substituents independently selected from the group consisting of alkyl and alkyloxy, wherein:

   the alkyl optionally is substituted with one or more hydroxy;

3. **(c)** the carbocyclyl and heterocyclyl portions of such substituents optionally are substituted with one or two substituents independently selected from the group consisting of alkyl, carboxy, hydroxy, alkyloxy, halo, nitro, cyano, and amino, wherein:

   the amino optionally is substituted with one or two substituents independently selected alkyl.

[0214] In some embodiments, each R^J is independently selected from the group consisting of carbocyclylsulfonylamino, heterocyclylsulfonylamino, alkylsulfonylamino, and alkylsulfonylaminoimino, wherein:

1. **(a)** the amino portion of such substituents optionally is substituted with a substituent independently selected from the group consisting of carbocyclylalkyl, heterocyclylalkyl, alkylcarbonyloxy, aminocarbonylalkyl, alkyl, alkylcarbonyl, alkyloxycarbonyl, alkyloxyalkyloxycarbonyl, alkylcarbonyloxyalkyl, and alkylsulfonyl, wherein:
   1. **(1)** the carbocyclyl portion of the carbocyclylalkyl and the heterocyclyl portion of the heterocyclylalkyl optionally are substituted with one or two substituents independently selected from the group consisting of alkyl, carboxy, hydroxy, alkyloxy, halo, nitro, cyano, oxo, and amino, and
   2. **(2)** the amino portion of the aminocarbonylalkyl optionally is substituted with one or two substituents independently selected from the group consisting of alkyl, alkenyl, and alkynyl,
2. **(b)** the alkyl portion of such substituents optionally is substituted with one or two substituents independently selected from the group consisting of carboxy, halo, oxo, amino, alkyloxycarbonyl, alkylcarbonyloxy, hydroxy, alkyloxy, carbocyclyl, heterocyclyl, and cyano, wherein:

   the amino optionally is substituted with one or two substituents independently selected from the group consisting of alkyl and alkyloxy, wherein:

   the alkyl optionally is substituted with one or more hydroxy;

3. **(c)** the carbocyclyl and heterocyclyl portions of such substituents optionally are substituted with one or two substituents independently selected from the group consisting of alkyl, carboxy, hydroxy, alkyloxy, halo, nitro, cyano, and amino, wherein:

   the amino optionally is substituted with one or two substituents independently selected alkyl.

[0215] In some embodiments, each R^J is independently selected from the group consisting of carbocyclylsulfonylamino, heterocyclylsulfonylamino, alkylsulfonylamino, and alkylsulfonylaminoimino, wherein:

the amino portion of such substituents optionally is substituted with a substituent independently selected from the group consisting of carbocyclylalkyl, heterocyclylalkyl, alkylcarbonyloxy, aminocarbonylalkyl, alkyl, alkylcarbonyl, alkyloxycarbonyl, alkyloxyalkyloxycarbonyl, alkylcarbonyloxyalkyl, and alkylsulfonyl, wherein:

1. **(1)** the carbocyclyl portion of the carbocyclylalkyl and the heterocyclyl portion of the heterocyclylalkyl optionally are substituted with one or two substituents independently selected from the group consisting of alkyl, carboxy, hydroxy, alkyloxy, halo, nitro, cyano, oxo, and amino, and
2. **(2)** the amino portion of the aminocarbonylalkyl optionally is substituted with one or two substituents independently selected from the group consisting of alkyl, alkenyl, and alkynyl.

[0216] In some embodiments, each R^J is independently selected from the group consisting of carbocyclylsulfonylamino,

heterocyclylsulfonylamino, alkylsulfonylamino, and alkylsulfonylaminoimino, wherein:

the alkyl portion of the alkylsulfonylamino and alkylsulfonylaminoimino optionally is substituted with one or two substituents independently selected from the group consisting of carboxy, halo, oxo, amino, alkyloxycarbonyl, alkylcarbonyloxy, hydroxy, alkyloxy, carbocyclyl, heterocyclyl, and cyano, wherein:

the amino optionally is substituted with one or two substituents independently selected from the group consisting of alkyl and alkyloxy, wherein:

the alkyl optionally is substituted with one or more hydroxy.

[0217] In some embodiments, each R^J is independently selected from the group consisting of carbocyclylsulfonylamino, heterocyclylsulfonylamino, alkylsulfonylamino, and alkylsulfonylaminoimino, wherein:

the carbocyclyl and heterocyclyl portions of such substituents optionally are substituted with one or two substituents independently selected from the group consisting of alkyl, carboxy, hydroxy, alkyloxy, halo, nitro, cyano, and amino.

[0218] In some embodiments, each R^J is independently selected from the group consisting of carbocyclylsulfonylamino and heterocyclylsulfonylamino, wherein:

the carbocyclyl and heterocyclyl portions of such substituents optionally are substituted with one or two substituents independently selected from the group consisting of alkyl, carboxy, hydroxy, alkyloxy, halo, nitro, cyano, and amino.

[0219] In some embodiments, each R^J is independently selected from the group consisting of alkylsulfonylamino, alkenylsulfonylamino, alkynylsulfonylamino, and alkylsulfonylaminoimino, wherein:

1. **(a)** the amino portion of such substituents optionally is substituted with a substituent independently selected from the group consisting of carbocyclylalkyl, heterocyclylalkyl, alkylcarbonyloxy, aminocarbonylalkyl, alkyl, alkylcarbonyl, alkyloxycarbonyl, alkyloxyalkyloxycarbonyl, alkylcarbonyloxyalkyl, and alkylsulfonyl, wherein:
    1. **(1)** the carbocyclyl portion of the carbocyclylalkyl and the heterocyclyl portion of the heterocyclylalkyl optionally are substituted with one or two substituents independently selected from the group consisting of alkyl, carboxy, hydroxy, alkyloxy, halo, nitro, cyano, oxo, and amino, and
    2. **(2)** the amino portion of the aminocarbonylalkyl optionally is substituted with one or two substituents independently selected from the group consisting of alkyl, alkenyl, and alkynyl,
2. **(b)** the alkyl, alkenyl, and alkynyl portion of such substituents optionally is substituted with one or two substituents independently selected from the group consisting of carboxy, halo, oxo, amino, alkyloxycarbonyl, alkylcarbonyloxy, hydroxy, alkyloxy, carbocyclyl, heterocyclyl, and cyano, wherein:

    the amino optionally is substituted with one or two substituents independently selected from the group consisting of alkyl and alkyloxy, wherein:

    the alkyl optionally is substituted with one or more hydroxy.

[0220] In some embodiments, each R^J is an independently selected alkylsulfonylamino, wherein:

1. (**a**) the amino portion of the alkylsulfonylamino optionally is substituted with a substituent independently selected from the group consisting of carbocyclylalkyl, heterocyclylalkyl, alkylcarbonyloxy, aminocarbonylalkyl, alkyl, alkylcarbonyl, alkyloxycarbonyl, alkyloxyalkyloxycarbonyl, alkylcarbonyloxyalkyl, and alkylsulfonyl, wherein:
    1. **(1)** the carbocyclyl portion of the carbocyclylalkyl and the heterocyclyl portion of the heterocyclylalkyl optionally are substituted with one or two substituents independently selected from the group consisting of alkyl, carboxy, hydroxy, alkyloxy, halo, nitro, cyano, oxo, and amino, and
    2. **(2)** the amino portion of the aminocarbonylalkyl optionally is substituted with one or two substituents independently selected from the group consisting of alkyl, alkenyl, and alkynyl,

2. **(b)** the alkyl portion of the alkylsulfonylamino optionally is substituted with one or two substituents independently selected from the group consisting of carboxy, halo, oxo, amino, alkyloxycarbonyl, alkylcarbonyloxy, hydroxy, alkyloxy, carbocyclyl, heterocyclyl, and cyano, wherein:

   the amino optionally is substituted with one or two substituents independently selected from the group consisting of alkyl and alkyloxy, wherein:

   the alkyl optionally is substituted with one or more hydroxy.

[0221] In some embodiments, each R^J is an independently selected alkylsulfonylamino, wherein:

the amino portion of the alkylsulfonylamino optionally is substituted with a substituent independently selected from the group consisting of carbocyclylalkyl, heterocyclylalkyl, alkylcarbonyloxy, aminocarbonylalkyl, alkyl, alkylcarbonyl, alkyloxycarbonyl, alkyloxyalkyloxycarbonyl, alkylcarbonyloxyalkyl, and alkylsulfonyl, wherein:

1. **(1)** the carbocyclyl portion of the carbocyclylalkyl and the heterocyclyl portion of the heterocyclylalkyl optionally are substituted with one or two substituents independently selected from the group consisting of alkyl, carboxy, hydroxy, alkyloxy, halo, nitro, cyano, oxo, and amino, and
2. **(2)** the amino portion of the aminocarbonylalkyl optionally is substituted with one or two substituents independently selected from the group consisting of alkyl, alkenyl, and alkynyl.

[0222] In some embodiments, each R^J is an independently selected alkylsulfonylamino, wherein:

the amino portion of the alkylsulfonylamino optionally is substituted with a substituent independently selected from the group consisting of carbocyclylalkyl, heterocyclylalkyl, alkylcarbonyloxy, aminocarbonylalkyl, alkyl, alkylcarbonyl, alkyloxycarbonyl, alkyloxyalkyloxycarbonyl, alkylcarbonyloxyalkyl, and alkylsulfonyl.

[0223] In some embodiments, each R^J is an independently selected alkylsulfonylamino, wherein:

the alkyl portion of the alkylsulfonylamino optionally is substituted with one or two substituents independently selected from the group consisting of carboxy, halo, oxo, amino, alkyloxycarbonyl, alkylcarbonyloxy, hydroxy, alkyloxy, carbocyclyl, heterocyclyl, and cyano, wherein:

the amino optionally is substituted with one or two substituents independently selected from the group consisting of alkyl and alkyloxy, wherein:

the alkyl optionally is substituted with one or more hydroxy.

[0224] In some embodiments, each R^J is an independently selected alkylsulfonylamino, wherein:

the alkyl portion of the alkylsulfonylamino optionally is substituted with one or two substituents independently selected from the group consisting of carboxy, halo, oxo, amino, alkyloxycarbonyl, alkylcarbonyloxy, hydroxy, alkyloxy, carbocyclyl, heterocyclyl, and cyano.

[0225] In some embodiments, each R^J is an independently selected alkylsulfonylamino. In some such embodiments, each R^J is methylsulfonylamino.

[0226] In some embodiments, each R^J is an independently selected alkylsulfonylaminoimino, wherein:

1. **(a)** the amino portion of the alkylsulfonylaminoimino optionally is substituted with a substituent independently selected from the group consisting of carbocyclylalkyl, heterocyclylalkyl, alkylcarbonyloxy, aminocarbonylalkyl, alkyl, alkylcarbonyl,

alkyloxycarbonyl, alkyloxyalkyloxycarbonyl, alkylcarbonyloxyalkyl, and alkylsulfonyl, wherein:

1. **(1)** the carbocyclyl portion of the carbocyclylalkyl and the heterocyclyl portion of the heterocyclylalkyl optionally are substituted with one or two substituents independently selected from the group consisting of alkyl, carboxy, hydroxy, alkyloxy, halo, nitro, cyano, oxo, and amino, and
2. **(2)** the amino portion of the aminocarbonylalkyl optionally is substituted with one or two substituents independently selected from the group consisting of alkyl, alkenyl, and alkynyl,

2. **(b)** the alkyl portion of the alkylsulfonylaminoimino optionally is substituted with one or two substituents independently selected from the group consisting of carboxy, halo, oxo, amino, alkyloxycarbonyl, alkylcarbonyloxy, hydroxy, alkyloxy, carbocyclyl, heterocyclyl, and cyano, wherein:

   the amino optionally is substituted with one or two substituents independently selected from the group consisting of alkyl and alkyloxy, wherein:

   the alkyl optionally is substituted with one or more hydroxy.

[0227] In some embodiments, each R^J is an independently selected alkylsulfonylaminoimino, wherein:

the amino portion of the alkylsulfonylaminoimino optionally is substituted with a substituent independently selected from the group consisting of carbocyclylalkyl, heterocyclylalkyl, alkylcarbonyloxy, aminocarbonylalkyl, alkyl, alkylcarbonyl, alkyloxycarbonyl, alkyloxyalkyloxycarbonyl, alkylcarbonyloxyalkyl, and alkylsulfonyl, wherein:

1. **(1)** the carbocyclyl portion of the carbocyclylalkyl and the heterocyclyl portion of the heterocyclylalkyl optionally are substituted with one or two substituents independently selected from the group consisting of alkyl, carboxy, hydroxy, alkyloxy, halo, nitro, cyano, oxo, and amino, and
2. **(2)** the amino portion of the aminocarbonylalkyl optionally is substituted with one or two substituents independently selected from the group consisting of alkyl, alkenyl, and alkynyl.

[0228] In some embodiments, each R^J is an independently selected alkylsulfonylaminoimino, wherein:

the amino portion of the alkylsulfonylaminoimino optionally is substituted with a substituent independently selected from the group consisting of carbocyclylalkyl, heterocyclylalkyl, alkylcarbonyloxy, aminocarbonylalkyl, alkyl, alkylcarbonyl, alkyloxycarbonyl, alkyloxyalkyloxycarbonyl, alkylcarbonyloxyalkyl, and alkylsulfonyl.

[0229] In some embodiments, each R^J is an independently selected alkylsulfonylaminoimino, wherein:

the alkyl portion of the alkylsulfonylaminoimino optionally is substituted with one or two substituents independently selected from the group consisting of carboxy, halo, oxo, amino, alkyloxycarbonyl, alkylcarbonyloxy, hydroxy, alkyloxy, carbocyclyl, heterocyclyl, and cyano, wherein:

the amino optionally is substituted with one or two substituents independently selected from the group consisting of alkyl and alkyloxy, wherein:

the alkyl optionally is substituted with one or more hydroxy.

[0230] In some embodiments, each R^J is an independently selected alkylsulfonylaminoimino, wherein:

the alkyl portion of the alkylsulfonylaminoimino optionally is substituted with one or two substituents independently selected from the group consisting of carboxy, halo, oxo, amino, alkyloxycarbonyl, alkylcarbonyloxy, hydroxy, alkyloxy, carbocyclyl, heterocyclyl, and cyano.

[0231] In some embodiments, each R^J is an independently selected alkylsulfonylaminoimino. In some such embodiments, each

R^J is methylsulfonylaminoimino.

[0232] In some embodiments, each R^J is independently selected from the group consisting of alkylcarbonylamino and alkyloxycarbonylamino, wherein:

the alkyl portion of such substituents optionally is substituted with one or two substituents independently selected from the group consisting of carboxy, halo, oxo, amino, alkyloxycarbonyl, alkylcarbonyloxy, hydroxy, alkyloxy, carbocyclyl, heterocyclyl, and cyano.

B14. Substituent R^K.

[0233] Each R^K is independently selected from the group consisting of aminosulfonyl, alkylsulfonyl, alkenylsulfonyl, and alkynylsulfonyl, wherein:

1. (**a**) the alkylsulfonyl, alkenylsulfonyl, and alkynylsulfonyl optionally are substituted with one or more substituents independently selected from the group consisting of carboxy, hydroxy, halo, amino, nitro, azido, oxo, aminosulfonyl, alkyloxycarbonyl, alkenyloxycarbonyl, alkynyloxycarbonyl, alkylcarbonyloxy, alkenylcarbonyloxy, alkynylcarbonyloxy, alkyloxy, alkenyloxy, alkynyloxy, carbocyclyl, heterocyclyl, cyano, and aminocarbonyl, wherein:

   the amino, aminosulfonyl, and aminocarbonyl optionally are substituted with one or two substituents independently selected from the group consisting of alkyl, alkenyl, and alkynyl; and

2. **(b)** the aminosulfonyl optionally is substituted with one or two substituents independently selected from the group consisting of alkyl, alkenyl, and alkynyl.

[0234] In some of the above embodiments, each R^K is independently selected from the group consisting of aminosulfonyl, alkylsulfonyl, alkenylsulfonyl, and alkynylsulfonyl, wherein such substituents are not substituted.

[0235] In some embodiments, each R^K is independently selected from the group consisting of aminosulfonyl and alkylsulfonyl, wherein:

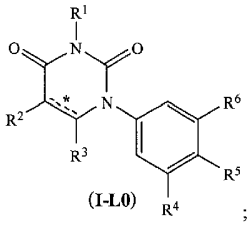
1. **(a)** the alkylsulfonyl optionally is substituted with one or two substituents independently selected from the group consisting of carboxy, hydroxy, halo, amino, nitro, oxo, aminosulfonyl, alkyloxycarbonyl, alkylcarbonyloxy, alkyloxy, carbocyclyl, heterocyclyl, cyano, and aminocarbonyl; and
2. **(b)** the aminosulfonyl optionally is substituted with one or two substituents independently selected alkyl.

[0236] In some embodiments, each R^K is independently selected from the group consisting of aminosulfonyl and alkylsulfonyl.

C. Embodiments of Compounds of Formula I.

[0237] Various embodiments of substituents R^1, R^2, R^3, R^4, R^5, L, R^A, R^B, R^C, R^D, R^6, R^E, R^F, R^G, R^H, R^I, R^J, and R^K have been discussed above. These substituent embodiments can be combined to form various embodiments of compounds of formula **I**. All embodiments of compounds of formula I formed by combining the substituent embodiments discussed above are within the scope of Applicants' invention, and some illustrative embodiments of the compounds of formula **I** are provided below.

[0238] In some embodiments, the compounds of formula **I** correspond in structure to formula **I-L0:**



(I-L0) ;

-.*.-
is selected from the group consisting of single carbon-carbon bond and double carbon-carbon bond;

R^1 is selected from the group consisting of hydrogen and methyl;

R^2 is selected from the group consisting of hydrogen and halo

R^3 is selected from the group consisting of hydrogen and halo;

R^4 is selected from the group consisting of C_1-C_4-alkyl, C_3-C_6-carbocyclyl, and 5-6-membered heterocyclyl, wherein:

1. **(a)** the C_1-C_4-alkyl optionally is substituted with up to three substituents independently selected from the group consisting of halo, oxo, hydroxy, alkyloxy, and trimethylsilyl, and
2. **(b)** the C_3-C_6-carbocyclyl and 5-6-membered heterocyclyl optionally are substituted with one or two substituents independently selected from the group consisting of alkyl, halo, and alkylsulfonylamino;

R^5 is selected from the group consisting of hydrogen, hydroxy, alkyloxy, and halo;

R^6 is selected from the group consisting of fused 2-ring heterocyclyl and fused 2-ring carbocyclyl, wherein each such substituent is substituted with one, two, or three substituents independently selected from the group consisting of **R^E**, **R^F**, **R^I**, **R^J**, and **R^K**;

each **R^E** is independently selected from the group consisting of chloro, fluoro, nitro, hydroxy, oxo, carboxy, amino, imino, aldehydo, and alkylamino;

each **R^F** is an independently selected alkyl optionally substituted with a substituent selected from the group consisting of carboxy, halo, amino, imino, and aminosulfonyl, wherein:

the amino, imino, and aminosulfonyl optionally are substituted with one or two substituents independently selected from the group consisting of alkyl, alkylsulfonyl, and alkylsulfonylamino;

each **R^I** is independently selected from the group consisting of alkylcarbonyl and aminocarbonyl, wherein:

the aminocarbonyl optionally is substituted with a substituent selected from the group consisting of alkyl, alkyloxyalkyl, alkylsulfonyl, and alkylsulfonylamino;

each **R^J** is independently selected from the group consisting of alkylsulfonylamino, alkenylsulfonylamino, alkynylsulfonylamino, and alkylsulfonylaminoimino, wherein:

1. **(a)** the amino portion of such substituents optionally is substituted with a substituent independently selected from the group consisting of carbocyclylalkyl, heterocyclylalkyl, alkylcarbonyloxy, aminocarbonylalkyl, alkyl, alkylcarbonyl, alkyloxycarbonyl, alkyloxyalkyloxycarbonyl, alkylcarbonyloxyalkyl, and alkylsulfonyl, wherein:
    1. **(1)** the carbocyclyl portion of the carbocyclylalkyl and the heterocyclyl portion of the heterocyclylalkyl optionally are substituted with one or two substituents independently selected from the group consisting of alkyl, carboxy, hydroxy, alkyloxy, halo, nitro, cyano, oxo, and amino, and
    2. **(2)** the amino portion of the aminocarbonylalkyl optionally is substituted with one or two substituents independently selected from the group consisting of alkyl, alkenyl, and alkynyl,
2. **(b)** the alkyl, alkenyl, and alkynyl portion of such substituents optionally is substituted with one or two substituents independently selected from the group consisting of carboxy, halo, oxo, amino, alkyloxycarbonyl, alkylcarbonyloxy, hydroxy, alkyloxy, carbocyclyl, heterocyclyl, and cyano, wherein:

    the amino optionally is substituted with one or two substituents independently selected from the group consisting of alkyl

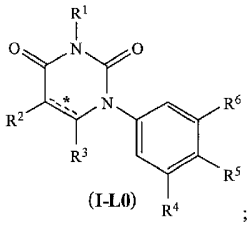
and alkyloxy, wherein:

the alkyl optionally is substituted with one or more hydroxy; and

each R^K is independently selected from the group consisting of aminosulfonyl and alkylsulfonyl, wherein:

1. **(a)** the alkylsulfonyl optionally is substituted with one or two substituents independently selected from the group consisting of carboxy, hydroxy, halo, amino, nitro, oxo, aminosulfonyl, alkyloxycarbonyl, alkylcarbonyloxy, alkyloxy, carbocyclyl, heterocyclyl, cyano, and aminocarbonyl; and
2. **(b)** the aminosulfonyl optionally is substituted with one or two substituents independently selected alkyl.

[0239] In some embodiments, the compounds of formula **I** correspond in structure to formula **I-L0:**



(I-L0) ;

is selected from the group consisting of single carbon-carbon bond and double carbon-carbon bond;

R^1 is hydrogen;

R^2 is selected from the group consisting of hydrogen and halo

R^3 is hydrogen;

R^4 is tert-butyl;

R^5 is selected from the group consisting of hydrogen, hydroxy, methoxy, and halo;

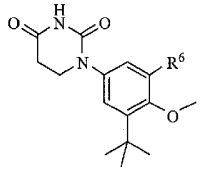
R^6 is a fused 2-ring carbocyclyl selected from the group consisting of naphthalenyl, dihydronaphthalenyl, tetrahydronaphthalenyl, hexahydronaphthalenyl, octahydronaphthalenyl, decahydronaphthalenyl, indenyl, dihydroindenyl, hexahydroindenyl, octahydroindenyl, pentalenyl, octahydropentalenyl, and hexahydropentalenyl, wherein each such substituent is substituted with a substituent selected from the group consisting of R^F and R^J;

R^F is alkylsulfonylaminoalkyl; and

R^J is alkylsulfonylamino.

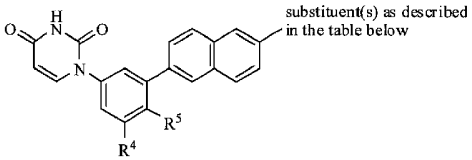
[0240] Examples of compounds of formula **I** (and salts thereof) are shown in Tables **1-9** below. The synthesis examples below provide step-by-step preparation instructions for some of these compounds. The remaining compounds were prepared utilizing the general method-of-preparation discussion, specific synthesis examples below, and/or the discussion throughout this application.

TABLE 1

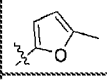


compound	R^6	
	ring/ring structure	substituent(s)
IA-L0-2.1	benzimidazol-2-yl	-5-N(H)S(O)$_2$CH$_3$
IA-L0-2.2	benzthiazol-2-yl	-6-N(H)S(O)$_2$CH$_3$
IA-L0-2.3	benzthiazol-2yl	---
IA-L0-2.4	benzthiazol-2-yl	-5-N(H)S(O)$_2$CH$_3$
IA-L0-2.5	benzoxazol-2-yl	-6-N(H)S(O)$_2$CH$_3$
IA-L0-2.6	benzoxazol-2-yl	-6-NO$_2$
IA-L0-2.7	benzoxazol-2-yl	-5-NO$_2$
IA-L0-2.8	benzoxazol-2-yl	-5-N(H)S(O)$_2$CH$_3$
IA-L0-2.9	naphthalen-2-yl	-6-N(H)S(O)$_2$CH$_3$
IA-L0-2.10	benzimidazol-2-yl	-5-N[S(O)$_2$CH$_3$]$_2$

TABLE 2



substituent(s) as described in the table below

compound	R^4	R^5	substituent(s)
IB-L0-2.1	-C(CH$_3$)$_3$	-OCH$_3$	-H
IB-L0-2.2	-C(CH$_3$)$_3$	-OCH$_3$	-OCH$_3$
IB-L0-2.3	-C(CH$_3$)$_3$	-OCH$_3$	-N(H)S(O)$_2$CH$_3$
IB-L0-2.8	-C(CH$_3$)$_3$	-H	-N(H)S(O)$_2$CH$_3$
IB-L0-2.14	-C(CH$_3$)$_3$	-Cl	-N(H)S(O)$_2$CH$_3$
IB-L0-2.23	-C(CH$_3$)$_3$	-OC(H)$_2$CH$_3$	-N(H)S(O)$_2$CH$_3$
IB-L0-2.52	-C(CH$_3$)$_2$C(H)$_2$C(H)$_3$	-OCH$_3$	-N(H)S(O)$_2$CH$_3$
IB-L0-2.53		-OCH$_3$	-N(H)S(O)$_2$CH$_3$
IB-L0-2.54	-C(CH$_3$)$_2$C(H)$_2$OH	-OCH$_3$	-N(H)S(O)$_2$CH$_3$
IB-L0-2.56	-CF$_3$	-OCH$_3$	-N(H)S(O)$_2$CH$_3$
IB-L0-2.57	-I	-OCH$_3$	-N(H)S(O)$_2$CH$_3$
IB-L0-2.58		-OCH$_3$	-N(H)S(O)$_2$CH$_3$
IB-L0-2.59	furan-2-yl	-OCH$_3$	-N(H)S(O)$_2$CH$_3$
IB-L0-2.60	-C(F)$_2$CF$_3$	-OCH$_3$	-N(H)S(O)$_2$CH$_3$
IB-L0-2.61		-OCH$_3$	-N(H)S(O)$_2$CH$_3$
IB-L0-2.64	furan-3-yl	-OCH$_3$	-N(H)S(O)$_2$CH$_3$
IB-L0-2.66	-C(CH$_3$)$_2$C(H)$_2$OCH$_3$	-OCH$_3$	-N(H)S(O)$_2$CH$_3$

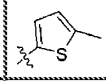
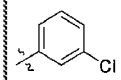
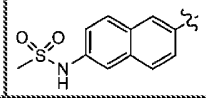
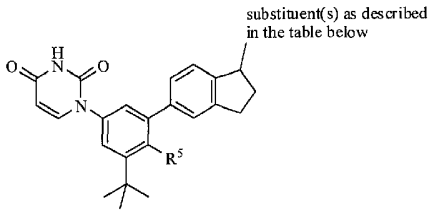
compound	R^4	R^5	substituent(s)
IB-L0-2.68	$-S(O)_2CH_3$	$-OCH_3$	$-N(H)S(O)_2CH_3$
IB-L0-2.69	-Br	$-OCH_3$	$-N(H)S(O)_2CH_3$
IB-L0-2.70	$-C(CH_3)_2C(O)OCH_3$	$-OCH_3$	$-N(H)S(O)_2CH_3$
IB-L0-2.71	phenyl	$-OCH_3$	$-N(H)S(O)_2CH_3$
IB-L0-2.72	$-C(O)OCH_3$	$-OCH_3$	$-N(H)S(O)_2CH_3$
IB-L0-2.73		$-OCH_3$	$-N(H)S(O)_2CH_3$
IB-L0-2.74		$-OCH_3$	$-N(H)S(O)_2CH_3$
IB-L0-2.75	$-N(H)S(O)_2CH_3$	$-OCH_3$	$-N(H)S(O)_2CH_3$
IB-L0-2.76		$-OCH_3$	$-N(H)S(O)_2CH_3$
IB-L0-2.77	$-C(CH_3)_2C(O)OH$	$-OCH_3$	$-N(H)S(O)_2CH_3$
IB-L0-2.78	$-C\equiv CSi(CH_3)_3$	$-OCH_3$	$-N(H)S(O)_2CH_3$

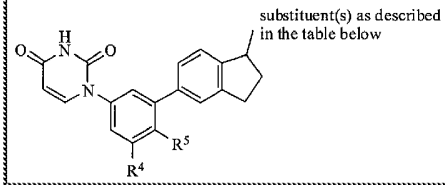
TABLE 3



compound	R^5	substituent(s)
IB-L0-2.4	$-OCH_3$	$=NN(H)S(O)_2CH_3$
IB-L0-2.7	-H	$=NN(H)S(O)_2CH_3$
IB-L0-2.9	$-OCH_3$	$(S)-C(H)_2N(H)S(O)_2CH_3$
IB-L0-2.10	$-OCH_3$	(R) -F and $-C(H)_2N(H)S(O)_2CH_3$
IB-L0-2.12	$-OCH_3$	-F and $-C(H)_2N(H)S(O)_2CH_3$
IB-L0-2.15	$-OCH_3$	(R) $-C(H)_2N(H)S(O)_2CH_3$
IB-L0-2.17	$-OCH_3$	$-C(H)_2N(H)S(O)_2CH_3$
IB-L0-2.20	$-OCH_3$	(S) -F and $-C(H)_2N(H)S(O)_2CH_3$
IB-L0-2.22	$-OCH_3$	(S) $-C(CH_3)_2N(H)S(O)_2CH_3$
IB-L0-2.24	$-OCH_3$	$=NN(H)C(O)OCH_3$
IB-L0-2.25	$-OCH_3$	$-CH_3$ and $-C(H)_2N(H)S(O)_2CH_3$
IB-L0-2.29	$-OCH_3$	$-C(CH_3)_2N(H)S(O)_2CH_3$
IB-L0-2.31	$-OCH_3$	$-N(H)N(H)S(O)_2CH_3$
IB-L0-2.34	$-OCH_3$	$-C(O)N(H)S(O)_2CH_3$
IB-L0-2.36	$-OCH_3$	-OH

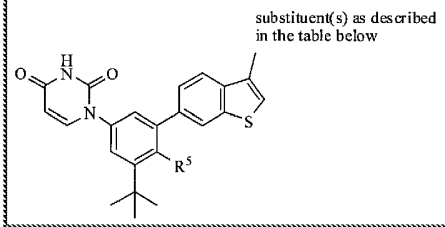
compound	R^5	substituent(s)
IB-L0-2.37	$-OCH_3$	(R) $-C(CH_3)_2N(H)S(O)_2CH_3$
IB-L0-2.44	$-OCH_3$	$-N(H)S(O)_2CH_3$
IB-L0-2.50	$-OCH_3$	=O

TABLE 4



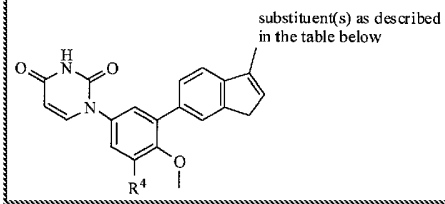
compound	R^4	R^5	substituent(s)
IB-L0-2.51		$-OCH_3$	$=NN(H)S(O)_2CH_3$
IB-L0-2.55	furan-2-yl	$-OCH_3$	$=NN(H)S(O)_2CH_3$

TABLE 5



compound	R^5	substituent(s)
IB-L0-2.11	$-OCH_3$	$C(H)_2N(H)S(O)_2CH_3$
IB-L0-2.21	$-OCH_3$	$-C(H)_2N(CH_3)S(O)_2CH_3$
IB-L0-2.35	-C1	$-C(H)_2N(H)S(O)_2CH_3$

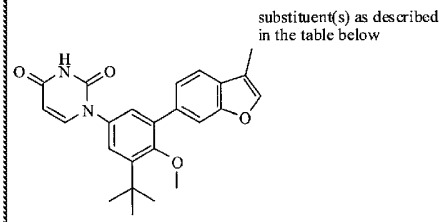
TABLE 6



compound	R^4	substituent(s)
IB-L0-2.13	$-C(CH_3)_3$	$-C(H)_2N(H)S(O)_2CH_3$
IB-L0-2.16	$-C(CH_3)_3$	$-C(H)_2N(CH_3)S(O)_2CH_3$
IB-L0-2.41	$-C(CH_3)_3$	$-C(CH_3)_2N(H)S(O)_2CH_3$
IB-L0-2.62		$-C(H)_2N(H)S(O)_2CH_3$

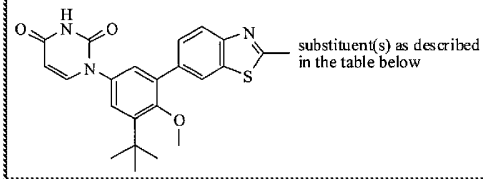
compound	R^4	substituent(s)
IB-L0-2.63		$-C(H)_2N(H)S(O)_2CH_3$
IB-L0-2.65	furan-2-yl	$-C(H)_2N(H)S(O)_2CH_3$
IB-L0-2.67	furan-3-yl	$-C(H)_2N(H)S(O)_2CH_3$

TABLE 7



compound	substituent(s)
IB-L0-2.18	$-C(H)_2N(H)S(O)_2CH_3$
IB-L0-2.42	$-CH_3$

TABLE 8



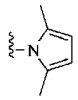
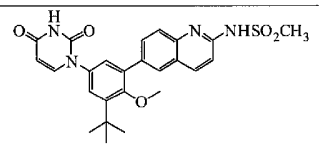
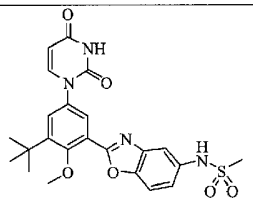
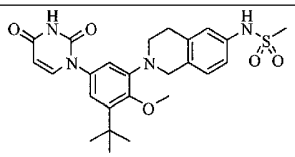
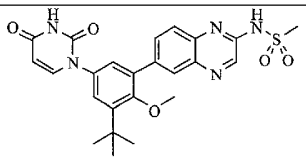
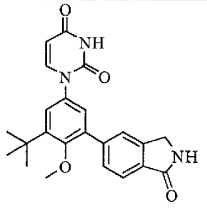
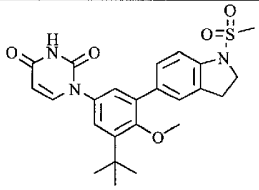
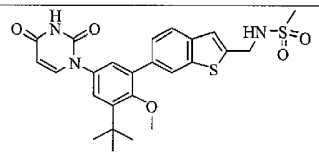
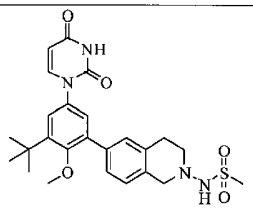
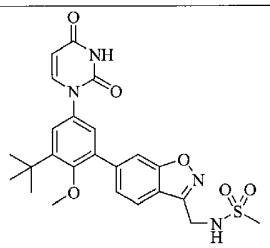
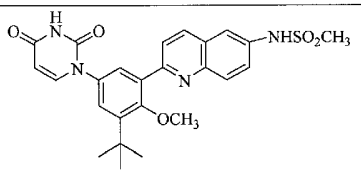
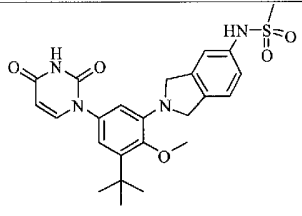
compound	substituent(s)
IB-L0-2.27	$-NH_2$
IB-L0-2.28	$-N(H)S(O)_2CH_3$
IB-L0-2.33	-H
IB-L0-2.38	-Cl
IB-L0-2.39	$-NH_2$
IB-L0-2.46	$-N(H)C(H)_2\ C(H)_2CH_3$
IB-L0-2.47	
IB-L0-2.49	$-N(H)C(O)CH_3$

TABLE 9

 IB-L0-2.5	 IB-L0-2.6
 IB-L0-2.19	 IB-L0-2.26
 IB-L0-2.30	 IB-L0-2.32
 IB-L0-2.40	 IB-L0-2.43

 IB-L0-2.45	 IB-L0-2.48
 IB-L0-2.79	

D. Isomers.

[0241] This invention also is directed, in part, to all isomers of the compounds of formula **I** (and their salts) (*i.e.,* structural and stereoisomers). Structural isomers include chain and position isomers. Stereoisomers include E/Z isomers (*i.e.,* isomers with regard to one or more double bonds), enantiomers (*i.e.,* stereo- isomers that have opposite configurations at all stereogenic

centers), and diastereoisomers (*i.e.,* stereo- isomers that have the same configuration at one or more stereogenic centers, but differ at other stereogenic centers).

E. Salts.

[0242] This invention also is directed, in part, to all salts of the compounds of formula **I**. A salt of a compound may be advantageous due to one or more of the salt's properties, such as, for example, enhanced pharmaceutical stability in differing temperatures and humidities, or a desirable solubility in water or other solvents. Where a salt is intended to be administered to a patient (as opposed to, for example, being in use in an *in vitro* context), the salt preferably is pharmaceutically acceptable and/or physiologically compatible. The term "pharmaceutically acceptable" is used adjectivally in this patent application to mean that the modified noun is appropriate for use as a pharmaceutical product or as a part of a pharmaceutical product. Pharmaceutically acceptable salts include salts commonly used to form alkali metal salts and to form addition salts of free acids or free bases. In general, these salts typically may be prepared by conventional means by reacting, for example, the appropriate acid or base with a compound of the invention.

[0243] Pharmaceutically acceptable acid addition salts of the compounds of formula **I** can be prepared from an inorganic or organic acid. Examples of often suitable inorganic acids include hydrochloric, hydrobromic, hydroiodic, nitric, carbonic, sulfuric, and phosphoric acid. Suitable organic acids generally include, for example, aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic, and sulfonic classes of organic acids. Specific examples of often suitable organic acids include acetate, trifluoroacetate, formate, propionate, succinate, glycolate, gluconate, digluconate, lactate, malate, tartaric acid, citrate, ascorbate, glucuronate, maleate, fumarate, pyruvate, aspartate, glutamate, benzoate, anthranilic acid, mesylate, stearate, salicylate, p-hydroxybenzoate, phenylacetate, mandelate, embonate (pamoate), ethanesulfonate, benzenesulfonate, pantothenate, 2-hydroxyethanesulfonate, sulfanilate, cyclohexylaminosulfonate, algenic acid, beta-hydroxybutyric acid, galactarate, galacturonate, adipate, alginate, bisulfate, butyrate, camphorate, camphorsulfonate, cyclopentanepropionate, dodecylsulfate, glycoheptanoate, glycerophosphate, heptanoate, hexanoate, nicotinate, oxalate, palmoate, pectinate, 2-naphthalesulfonate, 3-phenylpropionate, picrate, pivalate, thiocyanate, tosylate, and undecanoate.

[0244] Pharmaceutically acceptable base addition salts of the compounds of formula **I** include, for example, metallic salts and organic salts. Preferred metallic salts include alkali metal (group Ia) salts, alkaline earth metal (group IIa) salts, and other physiologically acceptable metal salts. Such salts may be made from aluminum, calcium, lithium, magnesium, potassium, sodium, and zinc. Preferred organic salts can be made from amines, such as tromethamine, diethylamine, N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine), and procaine. Basic nitrogen-containing groups can be quaternized with agents such as lower alkyl (C_1-C_6) halides (*e.g.,* methyl, ethyl, propyl, and butyl chlorides, bromides, and iodides), dialkyl sulfates (*e.g.,* dimethyl, diethyl, dibutyl, and diamyl sulfates), long chain halides (*e.g.*, decyl, lauryl, myristyl, and stearyl chlorides, bromides, and iodides), arylalkyl halides (*e.g.*, benzyl and phenethyl bromides), and others.

[0245] In some embodiments, the salt is sodium salt of N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydro-pyrimidin-1(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methanesulfonamide.

[0246] In some embodiments, the salt is monosodium salt of N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methanesulfonamide.

[0247] In some embodiments, the salt is disodium salt of N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydro-pyrimidin-1(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methanesulfonamide.

[0248] In some embodiments, the salt is potassium salt of N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydro-pyrimidin-1(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methanesulfonamide.

[0249] In some embodiments, the salt is monopotassium salt of N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methanesulfonamide.

[0250] In some embodiments, the salt is choline salt of N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydro-pyrimidin-1(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methanesulfonamide.

[0251] In some embodiments, the salt is monocholine salt of N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-

methoxyphenyl)naphthalen-2-yl)methanesulfonamide.

F. Purity.

[0252] Compounds of formula **I** (and salts thereof) with any level of purity (including pure and substantially pure) are within the scope of Applicants' invention. The term "substantially pure" in reference to a compound/salt/isomer, means that the preparation/composition containing the compound/salt/isomer contains more than about 85% by weight of the compound/salt/isomer, preferably more than about 90% by weight of the compound/salt/isomer, preferably more than about 95% by weight of the compound/salt/isomer, preferably more than about 97% by weight of the compound/salt/isomer, and preferably more than about 99% by weight of the compound/salt/isomer.

G. Crystalline Forms of Some Specific Compounds and Salts of The Invention.

G1. Crystalline Forms of N-(6-(3-Tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)yl)-2-methoxyphenyl)naphthalen-2-yl)methanesulfonamide (compound IB-L0-2.3).

[0253] This invention also relates, in part, to crystalline forms of N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methanesulfonamide (compound **IB-L0-2.3**), namely the solvate, hydrate, and solvent-free crystalline forms discussed below.

G1A. IB-L0-2.3 Solvates.

[0254] This invention also relates, in part, to an ethanol solvate of compound **IB-L0-2.3.**

[0255] In some embodiments, the ethanol solvate has an X-ray powder diffraction pattern comprising one or more peaks selected from the group consisting of 8.3±0.2, 9.7±0.2, 10.6±0.2, 13.6±0.2, 17.2±0.2, 19.2±0.2, 22.7±0.2, 26.9±0.2, and 29.4±0.2 degrees two theta (2θ). In some such embodiments, the ethanol solvate has an X-ray powder diffraction pattern comprising three or more peaks selected from the group consisting of 8.3±0.2, 9.7±0.2, 10.6±0.2, 13.6±0.2, 17.2±0.2, 19.2±0.2, 22.7±0.2, 26.9±0.2, and 29.4±0.2 degrees 2θ. In other such embodiments, the ethanol solvate has an X-ray powder diffraction pattern comprising five or more peaks selected from the group consisting of 8.3±0.2, 9.7±0.2, 10.6±0.2, 13.6±0.2, 17.2±0.2, 19.2±0.2, 22.7±0.2, 26.9±0.2, and 29.4±0.2 degrees 2θ.

[0256] In some embodiments, the ethanol solvate has an X-ray powder diffraction pattern comprising one or more peaks selected from the group consisting of 8.3±0.2, 9.7±0.2, 10.0±0.2, 10.6±0.2, 13.6±0.2, 17.2±0.2, 17.5±0.2, 19.2±0.2, 19.4±0.2, 22.7±0.2, 26.9±0.2, and 29.4±0.2 degrees 2θ. In some such embodiments, the ethanol solvate has an X-ray powder diffraction pattern comprising three or more peaks selected from the group consisting of 8.3±0.2, 9.7±0.2, 10.0±0.2, 10.6±0.2, 13.6±0.2, 17.2±0.2, 17.5±0.2, 19.2±0.2, 19.4±0.2, 22.7±0.2, 26.9±0.2, and 29.4±0.2 degrees 2θ. In other embodiments, the ethanol solvate has an X-ray powder diffraction pattern comprising five or more peaks selected from the group consisting of 8.3±0.2, 9.7±0.2, 10.0±0.2, 10.6±0.2, 13.6±0.2, 17.2±0.2, 17.5±0.2, 19.2±0.2, 19.4±0.2, 22.7±0.2, 26.9±0.2, and 29.4±0.2 degrees 2θ.

[0257] In some embodiments, the ethanol solvate has an X-ray powder diffraction pattern substantially as shown in Figure **1.** The 2θ values for the peaks in Figure **1** (and their intensities) are as follows: 8.25 (54), 9.67 (74), 9.92 (63), 10.59 (21), 13.64 (49), 17.25 (40), 17.51 (20), 19.19 (66), 19.43 (100), 22.75 (19), 26.92 (25), and 29.39 (18).

[0258] This invention also relates, in part, to an acetonitrile solvate of compound **IB-L0-2.3**.

[0259] In some embodiments, the acetonitrile solvate has an X-ray powder diffraction pattern comprising one or more peaks selected from the group consisting of 5.3±0.2, 8.3±0.2, 9.7±0.2, 10.5±0.2, 13.8±0.2, 17.2±0.2, 19.1±0.2, and 19.5±0.2 degrees 2θ. In some such embodiments, the acetonitrile solvate has an X-ray powder diffraction pattern comprising three or more peaks selected from the group consisting of 5.3±0.2, 8.3±0.2, 9.7±0.2, 10.5±0.2, 13.8±0.2, 17.2±0.2, 19.1±0.2, and 19.5±0.2 degrees 2θ. In other such embodiments, the acetonitrile solvate has an X-ray powder diffraction pattern comprising five or more peaks selected from the group consisting of 5.3±0.2, 8.3±0.2, 9.7±0.2, 10.5±0.2, 13.8±0.2, 17.2±0.2, 19.1±0.2, and 19.5±0.2 degrees

2θ.

[0260] In some embodiments, the acetonitrile solvate has an X-ray powder diffraction pattern comprising one or more peaks selected from the group consisting of 5.3±0.2, 8.3±0.2, 9.7±0.2, 10.5±0.2, 13.8±0.2, 17.2±0.2, 17.7±0.2, 19.1±0.2, 19.5±0.2, 22.0±0.2, 22.8±0.2, and 27.2±0.2 degrees 20. In some such embodiments, the acetonitrile solvate has an X-ray powder diffraction pattern comprising three or more peaks selected from the group consisting of 5.3±0.2, 8.3±0.2, 9.7±0.2, 10.5±0.2, 13.8±0.2, 17.2±0.2, 17.7±0.2, 19.1±0.2, 19.5±0.2, 22.0±0.2, 22.8±0.2, and 27.2±0.2 degrees 20. In other such embodiments, the acetonitrile solvate has an X-ray powder diffraction pattern comprising five or more peaks selected from the group consisting of 5.3±0.2, 8.3±0.2, 9.7±0.2, 10.5±0.2, 13.8±0.2, 17.2±0.2, 17.7±0.2, 19.1±0.2, 19.5±0.2, 22.0±0.2, 22.8±0.2, and 27.2±0.2 degrees 2θ.

[0261] In some embodiments, the acetonitrile solvate has an X-ray powder diffraction pattern substantially as shown in Figure 3. The 20 values for the peaks in Figure 3 (and their intensities) are as follows: 5.27 (14), 8.29 (33), 9.72 (100), 10.53 (20), 13.77 (67), 17.25 (38), 17.69 (17), 19.05 (63), 19.47 (58), 22.05 (19), 22.75 (16), and 27.17 (21).

[0262] This invention also relates, in part, to an ethyl acetate solvate of compound **IB-L0-2.3.**

[0263] In some embodiments, the ethyl acetate solvate has an X-ray powder diffraction pattern comprising one or more peaks selected from the group consisting of 7.9±0.2, 9.3±0.2, 9.7±0.2, 10.6±0.2, 18.7±0.2, 38.5±0.2, and 44.7±0.2 degrees 2θ**.** In some such embodiments, the ethyl acetate solvate has an X-ray powder diffraction pattern comprising three or more peaks selected from the group consisting of 7.9±0.2, 9.3±0.2, 9.7±0.2, 10.6±0.2, 18.7±0.2, 38.5±0.2, and 44.7±0.2 degrees 20. In other such embodiments, the ethyl acetate solvate has an X-ray powder diffraction pattern comprising five or more peaks selected from the group consisting of 7.9±0.2, 9.3±0.2, 9.7±0.2, 10.6±0.2, 18.7±0.2, 38.5±0.2, and 44.7±0.2 degrees 2θ.

[0264] In some embodiments, the ethyl acetate solvate has an X-ray powder diffraction pattern comprising one or more peaks selected from the group consisting of 7.9±0.2, 9.3±0.2, 9.7±0.2, 10.6±0.2, 13.7±0.2, 17.4±0.2, 18.7±0.2, 21.7±0.2, 22.0±0.2, 28.2±0.2, 38.5±0.2, and 44.7±0.2 degrees 2θ. In some such embodiments, the ethyl acetate solvate has an X-ray powder diffraction pattern comprising three or more peaks selected from the group consisting of 7.9±0.2, 9.3±0.2, 9.7±0.2, 10.6±0.2, 13.7±0.2, 17.4±0.2, 18.7±0.2, 21.7±0.2, 22.0±0.2, 28.2±0.2, 38.5±0.2, and 44.7±0.2 degrees 20. In other such embodiments, the ethyl acetate solvate has an X-ray powder diffraction pattern comprising five or more peaks selected from the group consisting of 7.9±0.2, 9.3±0.2, 9.7±0.2, 10.6±0.2, 13.7±0.2, 17.4±0.2, 18.7±0.2, 21.7±0.2, 22.0±0.2, 28.2±0.2, 38.5±0.2, and 44.7±0.2 degrees 20.

[0265] In some embodiments, the ethyl acetate has an X-ray powder diffraction pattern substantially as shown in Figure **4.** The 2θ values for the peaks in Figure **4** (and their intensities) are as follows: 7.94 (24), 9.33 (26), 9.72 (13), 10.58 (23), 13.71 (19), 17.40 (28), 18.72 (44), 21.69 (8), 22.04 (10), 28.23 (8), 38.45 (100), and 44.66 (95).

[0266] This invention also relates, in part, to a 2-propanol solvate of compound **IB-L0-2.3.**

[0267] In some embodiments, the 2-propanol solvate has an X-ray powder diffraction pattern comprising one or more peaks selected from the group consisting of 8.2±0.2, 9.3±0.2, 10.1±0.2, 16.3±0.2, 18.1±0.2, 18.6±0.2, 19.4±0.2, 21.6±0.2, and 22.5±0.2 degrees 20. In some such embodiments, the 2-propanol solvate has an X-ray powder diffraction pattern comprising three or more peaks selected from the group consisting of 8.2±0.2, 9.3±0.2, 10.1±0.2, 16.3±0.2, 18.1±0.2, 18.6±0.2, 19.4±0.2, 21.6±0.2, and 22.5±0.2 degrees 20. In other such embodiments, the 2-propanol solvate has an X-ray powder diffraction pattern comprising five or more peaks selected from the group consisting of 8.2±0.2, 9.3+0.2, 10.1±0.2, 16.3±0.2, 18.1±0.2, 18.6±0.2, 19.4±0.2, 21.6±0.2, and 22.5±0.2 degrees 20.

[0268] In some embodiments, the 2-propanol solvate has an X-ray powder diffraction pattern comprising one or more peaks selected from the group consisting of 8.2±0.2, 9.3±0.2, 10.1±0.2, 16.3±0.2, 18.1±0.2, 18.6±0.2, 19.4±0.2, 21.6±0.2, 22.5±0.2, 23.8±0.2, 26.0±0.2, and 28.0±0.2 degrees 20. In some such embodiments, the 2-propanol solvate has an X-ray powder diffraction pattern comprising three or more peaks selected from the group consisting of 8.2±0.2, 9.3±0.2, 10.1±0.2, 16.3±0.2, 18.1±0.2, 18.6±0.2, 19.4±0.2, 21.6±0.2, 22.5±0.2, 23.8±0.2, 26.0±0.2, and 28.0±0.2 degrees 2θ. In other such embodiments, the 2-propanol solvate has an X-ray powder diffraction pattern comprising five or more peaks selected from the group consisting of 8.2±0.2, 9.3±0.2, 10.1±0.2, 16.3±0.2, 18.1±0.2, 18.6±0.2, 19.4±0.2, 21.6±0.2, 22.5±0.2, 23.8±0.2, 26.0±0.2, and 28.0±0.2 degrees 2θ.

[0269] In some embodiments, the 2-propanol solvate has an X-ray powder diffraction pattern substantially as shown in Figure **5.** The 2θ values for the peaks in Figure **5** (and their intensities) are as follows: 8.18 (32), 9.26 (100), 10.12 (81), 16.28 (93), 18.11

(30), 18.59 (63), 19.40 (67), 21.57 (60), 22.51 (31), 23.82 (29), 25.94 (24), and 28.05 (29).

[0270] This invention also relates, in part, to a methanol solvate of compound **IB-L0-2.3.**

[0271] In some embodiments, the methanol solvate has an X-ray powder diffraction pattern comprising one or more peaks selected from the group consisting of 8.4±0.2, 9.7±0.2, 10.1±0.2, 13.8±0.2, 17.4±0.2, 19.3±0.2, and 19.6±0.2 degrees 2θ. In some such embodiments, the methanol solvate has an X-ray powder diffraction pattern comprising three or more peaks selected from the group consisting of 8.4±0.2, 9.7±0.2, 10.1±0.2, 13.8±0.2, 17.4±0.2, 19.3±0.2, and 19.6±0.2 degrees 2θ. In other such embodiments, the methanol solvate has an X-ray powder diffraction pattern comprising five or more peaks selected from the group consisting of 8.4±0.2, 9.7±0.2, 10.1±0.2, 13.8±0.2, 17.4±0.2, 19.3±0.2, and 19.6±0.2 degrees 2θ.

[0272] In some embodiments, the methanol solvate has an X-ray powder diffraction pattern comprising one or more peaks selected from the group consisting of 8.4±0.2, 9.7±0.2, 10.1±0.2, 13.5±0.2, 13.8±0.2, 17.4±0.2, 19.3±0.2, 19.6±0.2, and 27.1±0.2 degrees 2θ. In some such embodiments, the methanol solvate has an X-ray powder diffraction pattern comprising three or more peaks selected from the group consisting of 8.4±0.2, 9.7±0.2, 10.1±0.2, 13.5±0.2, 13.8±0.2, 17.4±0.2, 19.3±0.2, 19.6±0.2, and 27.1±0.2 degrees 2θ. In other such embodiments, the methanol solvate has an X-ray powder diffraction pattern comprising five or more peaks selected from the group consisting of 8.4±0.2, 9.7±0.2, 10.1±0.2, 13.5±0.2, 13.8±0.2, 17.4±0.2, 19.3±0.2, 19.6±0.2, and 27.1±0.2 degrees 2θ.

[0273] In some embodiments, the methanol solvate has an X-ray powder diffraction pattern substantially as shown in Figure **6.** The 2θ values for the peaks in Figure **6** (and their intensities) are as follows: 8.36 (48), 9.74 (65), 10.05 (74), 13.55 (24), 13.79 (69), 17.40 (32), 19.30 (80), 19.58 (100), and 27.08 (24).

[0274] This invention also relates, in part, to a 1-propanol solvate of compound **IB-L0-2.3.**

[0275] In some embodiments, the 1-propanol solvate has an X-ray powder diffraction pattern comprising one or more peaks selected from the group consisting of 8.2±0.2, 9.3±0.2, 10.1±0.2, 15.7±0.2, 16.2 ±0.2, 18.4±0.2, 19.3±0.2, 21.6±0.2, and 22.8±0.2 degrees 2θ. In some such embodiments, the 1-propanol solvate has an X-ray powder diffraction pattern comprising three or more peaks selected from the group consisting of 8.2±0.2, 9.3±0.2, 10.1±0.2, 15.7±0.2, 16.2 ±0.2, 18.4±0.2, 19.3±0.2, 21.6±0.2, and 22.8±0.2 degrees 2θ. In other such embodiments, the 1-propanol solvate has an X-ray powder diffraction pattern comprising five or more peaks selected from the group consisting of 8.2±0.2, 9.3±0.2, 10.1±0.2, 15.7±0.2, 16.2 ±0.2, 18.4±0.2, 19.3±0.2, 21.6±0.2, and 22.8±0.2 degrees 2θ.

[0276] In some embodiments, the 1-propanol solvate has an X-ray powder diffraction pattern comprising one or more peaks selected from the group consisting of 8.2±0.2, 9.3±0.2, 10.1±0.2, 10.5±0.2, 15.7±0.2, 16.2 ±0.2, 18.4±0.2, 18.6±0.2, 19.3±0.2, 21.0±0.2, 21.6±0.2, and 22.8±0.2 degrees 2θ. In some such embodiments, the 1-propanol solvate has an X-ray powder diffraction pattern comprising three or more peaks selected from the group consisting of 8.2±0.2, 9.3±0.2, 10.1±0.2, 10.5±0.2, 15.7±0.2, 16.2 ±0.2, 18.4±0.2, 18.6±0.2, 19.3±0.2, 21.0±0.2, 21.6±0.2, and 22.8±0.2 degrees 2θ. In other such embodiments, the 1-propanol solvate has an X-ray powder diffraction pattern comprising five or more peaks selected from the group consisting of 8.2±0.2, 9.3±0.2, 10.1±0.2, 10.5±0.2, 15.7±0.2, 16.2 ±0.2, 18.4±0.2, 18.6±0.2, 19.3±0.2, 21.0±0.2, 21.6±0.2, and 22.8±0.2 degrees 2θ.

[0277] In some embodiments, the 1-propanol solvate has an X-ray powder diffraction pattern substantially as shown in Figure 7. The 2θ values for the peaks in Figure 7 (and their intensities) are as follows: 8.15 (27), 9.26 (87), 10.08 (84), 10.47 (62), 15.73 (40), 16.24 (100), 18.37 (41), 18.59 (49), 19.33 (50), 20.97 (28), 21.65 (71), and 22.81 (44).

[0278] This invention also relates, in part, to a process for preparing the above solvates by suspending compound **IB-L0-2.3** in the corresponding solvent.

G1B. Solvent Free IB-L0-2.3.

[0279] This invention also relates, in part, to a solvent free crystalline form of compound **IB-L0-2.3.**

[0280] In some embodiments, the solvent free compound **IB-L0-2.3** has an X-ray powder diffraction pattern comprising one or more peaks selected from the group consisting of 6.2±-0.2, 7.9±0.2, 9.9±0.2, 16.2±0.2, and 18.3±0.2 degrees two theta (2θ). In some such embodiments, the solvent free compound **IB-L0-2.3** has an X-ray powder diffraction pattern comprising three or more

peaks selected from the group consisting of 6.2±0.2, 7.9±0.2, 9.9±0.2, 16.2±0.2, and 18.3±0.2 degrees 2θ. In other such embodiments, the solvent free compound **IB-L0-2.3** has an X-ray powder diffraction pattern comprising five or more peaks selected from the group consisting of 6.2±0.2, 7.9±0.2, 9.9±0.2, 16.2±0.2, and 18.3±0.2 degrees 2θ.

[0281] In some embodiments, the solvent free compound **IB-L0-2.3** has an X-ray powder diffraction pattern comprising one or more peaks selected from the group consisting of 6.2±0.2, 7.9±0.2, 9.9±0.2, 10.1±0.2, 14.9±0.2, 16.2±0.2, 18.3±0.2, 19.8±0.2, and 26.5±0.2 degrees 2θ. In some such embodiments, the solvent free compound **IB-L0-2.3** has an X-ray powder diffraction pattern comprising three or more peaks selected from the group consisting of 6.2±0.2, 7.9±0.2, 9.9±0.2, 10.1±0.2, 14.9±0.2, 16.2±0.2, 18.3±0.2, 19.8±0.2, and 26.5±0.2 degrees 2θ. In other such embodiments, the solvent free compound **IB-L0-2.3** has an X-ray powder diffraction pattern comprising five or more peaks selected from the group consisting of 6.2±0.2, 7.9±0.2, 9.9±0.2, 10.1±0.2, 14.9±0.2, 16.2±0.2, 18.3±0.2, 19.8±0.2, and 26.5±0.2 degrees 2θ. In yet other such embodiments, the solvent free compound **IB-L0-2.3** has an X-ray powder diffraction pattern comprising eight or more peaks selected from the group consisting of 6.2±0.2, 7.9±0.2, 9.9±0.2, 10.1±0.2, 14.9±0.2, 16.2±0.2, 18.3±0.2, 19.8±0.2, and 26.5±0.2 degrees 2θ.

[0282] In some embodiments, the solvent free compound **IB-L0-2.3** has an X-ray powder diffraction pattern substantially as shown in Figure **8.** The 2θ values for the peaks in Figure **8** (and their intensities) are as follows: 6.20 (36), 7.85 (66), 9.89 (61), 10.12 (75), 14.87 (27), 16.19 (89), 18.32 (100), 19.82 (77), and 26.53 (34).

[0283] This invention also relates, in part, to a process for preparing the solvent free crystalline form of compound **IB-L0-2.3** by desolvating one of **IB-L0-2.3** solvates discussed above. A solvate can be desolvated by heating the solvate solid for about 10min at ~125^{0}C.

G1C. IB-L0-2.3 Hydrate.

[0284] This invention also relates, in part, to a hydrate of compound **IB-L0-2.3.**

[0285] In some embodiments, the hydrate has an X-ray powder diffraction pattern comprising one or more peaks selected from the group consisting of 6.4±0.2, 12.9±0.2, 17.9±0.2, and 18.9±0.2 degrees 2θ. In some such embodiments, the hydrate has an X-ray powder diffraction pattern comprising three or more peaks selected from the group consisting of 6.4±0.2, 12.9±0.2, 17.9±0.2, and 18.9±0.2 degrees 2θ.

[0286] In some embodiments, the hydrate has an X-ray powder diffraction pattern comprising one or more peaks selected from the group consisting of 6.4±0.2, 12.9±0.2, 17.5±0.2, 17.9±0.2, 18.9±0.2, and 24.4±0.2 degrees 2θ. In some such embodiments, the hydrate has an X-ray powder diffraction pattern comprising three or more peaks selected from the group consisting of 6.4±0.2, 12.9±0.2, 17.5±0.2, 17.9±0.2, 18.9±0.2, and 24.4±0.2 degrees 2θ. In other such embodiments, the hydrate has an X-ray powder diffraction pattern comprising five or more peaks selected from the group consisting of 6.4±0.2, 12.9±0.2, 17.5±0.2, 17.9±0.2, 18.9±0.2, and 24.4±0.2 degrees 2θ.

[0287] In some embodiments, the hydrate has an X-ray powder diffraction pattern comprising one or more peaks selected from the group consisting of 6.4±0.2, 12.7±0.2, 12.9±0.2, 14.1±0.2, 15.7±0.2, 17.2±0.2, 17.5±0.2, 17.9±0.2, 18.9±0.2, 21.2±0.2, 24.4±0.2, and 25.0±0.2 degrees 2θ. In some such embodiments, the hydrate has an X-ray powder diffraction pattern comprising three or more peaks selected from the group consisting of 6.4±0.2, 12.7±0.2, 12.9±0.2, 14.1±0.2, 15.7±0.2, 17.2±0.2, 17.5±0.2, 17.9±0.2, 18.9±0.2, 21.2±0.2, 24.4±0.2, and 25.0±0.2 degrees 2θ. In other such embodiments, the hydrate has an X-ray powder diffraction pattern comprising five or more peaks selected from the group consisting of 6.4±0.2, 12.7±0.2, 12.9±0.2, 14.1±0.2, 15.7±0.2, 17.2±0.2, 17.5±0.2, 17.9±0.2, 18.9±0.2, 21.2±0.2, 24.4±0.2, and 25.0±0.2 degrees 2θ.

[0288] In some embodiments, the hydrate has an X-ray powder diffraction pattern substantially as shown in Figure **9.** The 2θ values for the peaks in Figure **9** (and their intensities) are as follows: 6.42 (60), 12.71 (33), 12.89 (58), 14.05 (17), 15.68 (18), 17.22 (44), 17.53 (100), 17.86 (51), 18.87 (77), 21.25 (17), 24.35 (28), and 24.95 (20).

[0289] This invention also relates, in part, to a process for preparing the hydrate by suspending the above-described solvent free crystalline compound in water. The hydrate was prepared by suspending 300mg of the solvent free crystalline compound in 2ml of water at 45^{0}C for four days.

G2. Crystalline Forms of N-(6-(3-Tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methanesulfonamide, Monosodium Salt.

[0290] This invention also relates, in part, to crystalline forms of N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methanesulfonamide, monosodium salt, namely the pattern A, pattern B, and pattern C crystalline forms discussed below.

[0291] This invention relates, in part, to a pattern A crystalline monosodium salt.

[0292] In some embodiments, the pattern A monosodium salt has an X-ray powder diffraction pattern comprising one or more peaks selected from the group consisting of 4.6±0.2, 10.4±0.2, 12.0±0.2, 15.6±0.2, 18.6±0.2, 22.8±0.2, and 23.9±0.2 degrees 2θ. In some such embodiments, the pattern A monosodium salt has an X-ray powder diffraction pattern comprising three or more peaks selected from the group consisting of 4.6±0.2, 10.4±0.2, 12.0±0.2, 15.6±0.2, 18.6±0.2, 22.8±0.2, and 23.9±0.2 degrees 2θ. In other such embodiments, the pattern A monosodium salt has an X-ray powder diffraction pattern comprising five or more peaks selected from the group consisting of 4.6±0.2, 10.4±0.2, 12.0±0.2, 15.6±0.2, 18.6±0.2, 22.8±0.2, and23.9±0.2 degrees 2θ.

[0293] In some embodiments, the pattern A monosodium salt has an X-ray powder diffraction pattern comprising one or more peaks selected from the group consisting of 4.6±0.2, 10.4±0.2, 12.0±0.2, 15.6±0.2, 18.6±0.2, 22.8±0.2, 23.3±0.2, and 23.9±0.2 degrees 2θ. In some such embodiments, the pattern A monosodium salt has an X-ray powder diffraction pattern comprising three or more peaks selected from the group consisting of 4.6±0.2, 10.4±0.2, 12.0±0.2, 15.6±0.2, 18.6±0.2, 22.8±0.2, 23.3±0.2, and 23.9±0.2 degrees 2θ. In other such embodiments, the pattern A monosodium salt has an X-ray powder diffraction pattern comprising five or more peaks selected from the group consisting of 4.6±0.2, 10.4±0.2, 12.0±0.2, 15.6±0.2, 18.6±0.2, 22.8±0.2, 23.3±0.2, and 23.9±0.2 degrees 2θ.

[0294] In some embodiments, the pattern A monosodium salt has an X-ray powder diffraction pattern comprising one or more peaks selected from the group consisting of 4.6±0.2, 10.4±0.2, 12.0±0.2, 15.6±0.2, 16.0±0.2, 18.6±0.2, 22.8±0.2, 23.3±0.2, 23.9±0.2, and 28.3±0.2 degrees 2θ. In some such embodiments, the pattern A monosodium salt has an X-ray powder diffraction pattern comprising three or more peaks selected from the group consisting of 4.6±0.2, 10.4±0.2, 12.0±0.2, 15.6±0.2, 16.0±0.2, 18.6±0.2, 22.8±0.2, 23.3±0.2, 23.9±0.2, and 28.3±0.2 degrees 2θ. In other such embodiments, the pattern A monosodium salt has an X-ray powder diffraction pattern comprising five or more peaks selected from the group consisting of 4.6±0.2, 10.4±0.2, 12.0±0.2, 15.6±0.2, 16.0±0.2, 18.6±0.2, 22.8±0.2, 23.3±0.2, 23.9±0.2, and 28.3±0.2 degrees 2θ. In other such embodiments, the pattern A monosodium salt has an X-ray powder diffraction pattern comprising eight or more peaks selected from the group consisting of 4.6±0.2, 10.4±0.2, 12.0±0.2, 15.6±0.2, 16.0±0.2, 18.6±0.2, 22.8±0.2, 23.3±0.2, 23.9±0.2, and 28.3±0.2 degrees 2θ.

[0295] In some embodiments, the pattern A monosodium salt has an X-ray powder diffraction pattern substantially as shown in Figure **10.** The 20 values for the peaks in Figure **10** (and their intensities) are as follows: 4.64 (62), 10.41 (38), 12.04 (38), 15.62 (44), 15.99 (44), 18.63 (49), 22.77 (60), 23.29 (40), 23.93 (100), and 28.31 (56).

[0296] This invention also relates, in part, to a process for preparing the pattern A monosodium salt. The pattern A monosodium salt was prepared by adding 1M aqueous NaOH (0.548ml) to compound **IB-L0-2.3** (225.72mg), seeding the resulting suspension with crystalline N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methanesulfonamide, disodium salt (prepared as discussed below), and equilibrating the resulting suspension at ambient conditions. The pattern A monosodium salt was formed on the following day through a solution-mediated process. The stoichiometry of the salt was presumed to be 1:1 based on the crystallization procedure. This invention also relates, in part, to a pattern B crystalline monosodium salt.

[0297] In some embodiments, the pattern B monosodium salt has an X-ray powder diffraction pattern comprising one or more peaks selected from the group consisting of 5.4±0.2, 10.8±0.2, 14.4±0.2, 16.3±0.2, 17.0±0.2, 21.6±0.2, 22.1±0.2, and 23.7±0.2 degrees 2θ. In some such embodiments, the pattern B monosodium salt has an X-ray powder diffraction pattern comprising three or more peaks selected from the group consisting of 5.4±0.2, 10.8±0.2, 14.4±0.2, 16.3±0.2, 17.0±0.2, 21.6±0.2, 22.1±0.2, and 23.7±0.2 degrees 2θ. In other such embodiments, the pattern B monosodium salt has an X-ray powder diffraction pattern comprising five or more peaks selected from the group consisting of 5.4±0.2, 10.8±0.2, 14.4±0.2, 16.3±0.2, 17.0±0.2, 21.6±0.2, 22.1±0.2, and 23.7±0.2 degrees 2θ.

[0298] In some embodiments, the pattern B monosodium salt has an X-ray powder diffraction pattern comprising one or more peaks selected from the group consisting of 5.4±0.2, 10.8±0.2, 14.4±0.2, 16.3±0.2, 17.0±0.2, 18.8±0.2, 19.2±0.2, 19.6±0.2, 21.6±0.2, 22.1±0.2, 23.7±0.2, 28.8±0.2, 29.1±0.2, and 31.8±0.2 degrees 2θ. In some such embodiments, the pattern B monosodium salt has an X-ray powder diffraction pattern comprising three or more peaks selected from the group consisting of 5.4±0.2, 10.8±0.2, 14.4±0.2, 16.3±0.2, 17.0±0.2, 18.8±0.2, 19.2±0.2, 19.6±0.2, 21.6±0.2, 22.1±0.2, 23.7±0.2, 28.8±0.2,

29.1±0.2, and 31.8±0.2 degrees 2θ. In other such embodiments, the pattern B monosodium salt has an X-ray powder diffraction pattern comprising five or more peaks selected from the group consisting of 5.4±0.2, 10.8±0.2, 14.4±0.2, 16.3±0.2, 17.0±0.2, 18.8±0.2, 19.2±0.2, 19.6±0.2, 21.6±0.2, 22.1±0.2, 23.7±0.2, 28.8±0.2, 29.1±0.2, and 31.8±0.2 degrees 2θ. In other such embodiments, the pattern B monosodium salt has an X-ray powder diffraction pattern comprising eight or more peaks selected from the group consisting of 5.4±0.2, 10.8±0.2, 14.4±0.2, 16.3±0.2, 17.0±0.2, 18.8±0.2, 19.2±0.2, 19.6±0.2, 21.6±0.2, 22.1±0.2, 23.7±0.2, 28.8±0.2, 29.1±0.2, and 31.8±0.2 degrees 2θ.

[0299] In some embodiments, the pattern B monosodium salt has an X-ray powder diffraction pattern comprising one or more peaks selected from the group consisting of 5.4±0.2, 10.8±0.2, 14.4±0.2, 16.3±0.2, 17.0±0.2, 18.8±0.2, 19.2±0.2, 19.6±0.2, 21.6±0.2, 22.1±0.2, 23.7±0.2, 28.8±0.2, 29.1±0.2, and 31.8±0.2 degrees 2θ. In some such embodiments, the pattern B monosodium salt has an X-ray powder diffraction pattern comprising two or more peaks selected from the group consisting of 5.4±0.2, 10.8±0.2, 14.4±0.2, 16.3±0.2, 17.0±0.2, 18.8±0.2, 19.2±0.2, 19.6±0.2, 21.6±0.2, 22.1±0.2, 23.7±0.2, 29.1±0.2, and 31.8±0.2 degrees 2θ. In other such embodiments, the pattern B monosodium salt has an X-ray powder diffraction pattern comprising two or more peaks selected from the group consisting of 5.4±0.2, 10.8±0.2, 14.4±0.2, 16.3±0.2, 17.0±0.2, 18.8±0.2, 19.2±0.2, 19.6±0.2, 21.6±0.2, 22.1±0.2, 23.7±0.2, 28.8±0.2, and 31.8±0.2 degrees 2θ. In yet other such embodiments, the pattern B monosodium salt has an X-ray powder diffraction pattern comprising three or more peaks selected from the group consisting of 5.4±0.2, 10.8±0.2, 14.4±0.2, 16.3±0.2, 17.0±0.2, 18.8±0.2, 19.2±0.2, 19.6±0.2, 21.6±0.2, 22.1±0.2, 23.7±0.2, and 31.8±0.2 degrees 2θ. In yet other such embodiments, the pattern B monosodium salt has an X-ray powder diffraction pattern comprising three or more peaks selected from the group consisting of 5.4±0.2, 10.8±0.2, 14.4±0.2, 16.3±0.2, 17.0±0.2, 18.8±0.2, 19.2±0.2, 21.6±0.2, 22.1±0.2, and 23.7±0.2 degrees 20. In yet other such embodiments, the pattern B monosodium salt has an X-ray powder diffraction pattern comprising three or more peaks selected from the group consisting of 5.4±0.2, 10.8±0.2, 14.4±0.2, 16.3±0.2, 17.0±0.2, 19.2±0.2, 21.6±0.2, 22.1±0.2, and 23.7±0.2 degrees 2θ. In yet other such embodiments, the pattern B monosodium salt has an X-ray powder diffraction pattern comprising three or more peaks selected from the group consisting of 5.4±0.2, 10.8±0.2, 14.4±0.2, 16.3±0.2, 17.0±0.2, 18.8±0.2, 21.6±0.2, 22.1±0.2, and 23.7±0.2 degrees 2θ. In yet other such embodiments, the pattern B monosodium salt has an X-ray powder diffraction pattern comprising three or more peaks selected from the group consisting of 5.4±0.2, 10.8±0.2, 14.4±0.2, 16.3±0.2, 17.0±0.2, 21.6±0.2, 22.1±0.2, and 23.7±0.2 degrees 2θ. In yet other such embodiments, the pattern B monosodium salt has an X-ray powder diffraction pattern comprising three or more peaks selected from the group consisting of 5.4±0.2, 10.8±0.2, 16.3±0.2, 22.1±0.2, and 23.7±0.2 degrees 2θ.

[0300] In some embodiments, the pattern B monosodium salt has an X-ray powder diffraction pattern comprising peaks at 5.4±0.2, 10.8±0.2, and 16.3±0.2 degrees 2θ. In some such embodiments, the pattern B monosodium salt has an X-ray powder diffraction pattern comprising peaks at 5.4±0.2, 10.8±0.2, 16.3±0.2, and 22.1±0.2 degrees 28. In other such embodiments, the pattern B monosodium salt has an X-ray powder diffraction pattern comprising peaks at 5.4±0.2, 10.8±0.2, 16.3±0.2, 22.1±0.2, and 23.7±0.2 degrees 2θ. In yet other such embodiments, the pattern B monosodium salt has an X-ray powder diffraction pattern comprising peaks at 5.4±0.2, 10.8±0.2, 14.4±0.2, 16.3±0.2, 17.0±0.2, 21.6±0.2, 22.1±0.2, and 23.7±0.2 degrees 2θ. In yet other such embodiments, the pattern B monosodium salt has an X-ray powder diffraction pattern comprising peaks at 5.4±0.2, 10.8±0.2, 14.4±0.2, 16.3±0.2, 17.0±0.2, 18.8±0.2, 21.6±0.2, 22.1±0.2, and 23.7±0.2 degrees 2θ. In yet other such embodiments, the pattern B monosodium salt has an X-ray powder diffraction pattern comprising peaks at 5.4±0.2, 10.8±0.2, 14.4±0.2, 16.3±0.2, 17.0±0.2, 19.2±0.2, 21.6±0.2, 22.1±0.2, and 23.7±0.2 degrees 2θ. In yet other such embodiments, the pattern B monosodium salt has an X-ray powder diffraction pattern comprising peaks at 5.4±0.2, 10.8±0.2, 14.4±0.2, 16.3±0.2, 17.0±0.2, 18.8±0.2, 19.2±0.2, 21.6±0.2, 22.1±0.2, and 23.7±0.2 degrees 2θ. In further such embodiments, the pattern B monosodium salt has an X-ray powder diffraction pattern comprising peaks at 5.4±0.2, 10.8±0.2, 14.4±0.2, 16.3±0.2, 17.0±0.2, 18.8±0.2, 19.2±0.2, 19.6±0.2, 21.6±0.2, 22.1±0.2, 23.7±0.2, and 31.8±0.2 degrees 2θ. In yet further such embodiments, the pattern B monosodium salt has an X-ray powder diffraction pattern comprising peaks at 5.4±0.2, 10.8±0.2, 14.4±0.2, 16.3±0.2, 17.0±0.2, 18.8±0.2, 19.2±0.2, 19.6±0.2, 21.6±0.2, 22.1±0.2, 23.7±0.2, 28.8±0.2, and 31.8±0.2 degrees 2θ. In yet further such embodiments, the pattern B monosodium salt has an X-ray powder diffraction pattern comprising peaks at 5.4±0.2, 10.8±0.2, 14.4±0.2, 16.3±0.2, 17.0±0.2, 18.8±0.2, 19.2±0.2, 19.6±0.2, 21.6±0.2, 22.1±0.2, 23.7±0.2, 29.1±0.2, and 31.8±0.2 degrees 20. In yet further such embodiments, the pattern B monosodium salt has an X-ray powder diffraction pattern comprising peaks at 5.4±0.2, 10.8±0.2, 14.4±0.2, 16.3±0.2, 17.0±0.2, 18.8±0.2, 19.2±0.2, 19.6±0.2, 21.6±0.2, 22.1±0.2, 23.7±0.2, 28.8±0.2, 29.1±0.2, and 31.8±0.2 degrees 2θ.

[0301] In some embodiments, the pattern B monosodium salt has an X-ray powder diffraction pattern substantially as shown in Figure **12.** The 2θ values for the peaks in Figure **12** (and their intensities) are as follows: 5.36 (100), 10.75 (42), 14.43 (20), 16.34 (60), 17.00 (25), 18.83 (18), 19.24 (18), 19.66 (12), 21.64 (29), 22.12 (41), 23.73 (32), 28.83 (9), 29.10 (9), and 31.78 (10).

[0302] This invention also relates, in part, to a process for preparing the pattern B monosodium salt. The pattern B monosodium

salt can prepared by suspending the pattern A monosodium salt (for example, ~ 30mg) in various organic solvents (e.g., ~ 125ul acetonitrile, ethanol, 1-propanol, or 2-propanol) at room temperature. The pattern B monosodium salt was also prepared by seeding a solution with pattern B monosodium salt. Compound **IB-L0-2.3** (12.5g) was dissolved in DMSO (37.5ml) at ~68^{0}C. 1.04g NaOH dissolved in 6.3ml of water, 6.3ml 2-propanol, and 12.5my 35.2:1 v/v 2-propanol/water was added. The solution was seeded with 125mg of pattern B seeds slurried in 12.5ml of 35.2:1 v/v 2-propanol/water, and the crystallization slurry was incubated at ~68°C for ~1.5h. 175ml 35.2:1 v/v 2-propanol/water at ~68°C was added over ~7h, and the crystallization slurry was cooled to ~0°C over no less than 7h. The crystals were isolated by filtration and analyzed by PXRD. The crystals were then dried at ~50°C under vacuum (approximately 3 inches of mercury). The dried crystals were analyzed by PXRD, which showed no change in comparison to the pre-drying sample. The stoichiometry of the pattern B monosodium salt was confirmed by ion chromatography.

[0303] This invention also relates, in part, to a pattern C crystalline monosodium salt.

[0304] In some embodiments, the pattern C monosodium salt has an X-ray powder diffraction pattern comprising one or more peaks selected from the group consisting of 5.0±0.2, 12.0±0.2, 17.5±0.2, 18.8±0.2, and 22.7±0.2 degrees 2θ. In some such embodiments, the pattern C monosodium salt has an X-ray powder diffraction pattern comprising three or more peaks selected from the group consisting of 5.0±0.2, 12.0±0.2, 17.5±0.2, 18.8±0.2, and 22.7±0.2 degrees 2θ.

[0305] In some embodiments, the pattern C monosodium salt has an X-ray powder diffraction pattern comprising one or more peaks selected from the group consisting of 5.0±0.2, 12.0±0.2, 17.5±0.2, 17.8±0.2, 18.8±0.2, and 22.7±0.2 degrees 2θ. In some such embodiments, the pattern A monosodium salt has an X-ray powder diffraction pattern comprising three or more peaks selected from the group consisting of 5.0±0.2, 12.0±0.2, 17.5±0.2, 17.8±0.2, 18.8±0.2, and 22.7±0.2 degrees 2θ. In other such embodiments, the pattern A monosodium salt has an X-ray powder diffraction pattern comprising five or more peaks selected from the group consisting of 5.0±0.2, 12.0±0.2, 17.5±0.2, 17.8±0.2, 18.8±0.2, and 22.7±0.2 degrees 2θ.

[0306] In some embodiments, the pattern C monosodium salt has an X-ray powder diffraction pattern substantially as shown in Figure **14.** The 2θ values for the peaks in Figure **14** (and their intensities) are as follows: 4.97 (100), 12.03 (24), 17.55 (32), 17.80 (77), 18.79 (23), and 22.74 (33).

[0307] This invention also relates, in part, to a process for preparing the pattern C monosodium salt. The pattern C monosodium salt was prepared as follows. Pattern B monosodium salt (100mg) was dissolved in 400ul DMSO and 2ml 12:1 v/v 2-propanol/H_2O at 70°C. Pattern B monosodium salt seed crystals were added to the solution, and the solution was then cooled to ambient temperature over 20min. Filtration yielded crystals of the pattern C monosodium salt.

G3. Crystalline Form of N-(6-(3-Tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methanesulfonamide, Disodium Salt.

[0308] This invention also relates, in part, to a crystalline form of N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methanesulfonamide, disodium salt.

[0309] In some embodiments, the disodium salt has an X-ray powder diffraction pattern comprising one or more peaks selected from the group consisting of 4.8±0.2, 9.6±0.2, 10.5±0.2, 13.0±0.2, 14.6±0.2, 15.4±0.2, 16.8 ±0.2, and 23.0±0.2 degrees 2θ. In some such embodiments, the disodium salt has an X-ray powder diffraction pattern comprising three or more peaks selected from the group consisting of 4.8±0.2, 9.6±0.2, 10.5±0.2, 13.0±0.2, 14.6±0.2, 15.4±0.2, 16.8±0.2, and 23.0±0.2 degrees 2θ. In other such embodiments, the disodium salt has an X-ray powder diffraction pattern comprising five or more peaks selected from the group consisting of 4.8±0.2, 9.6±0.2, 10.5±0.2, 13.0±0.2, 14.6±0.2, 15.4±0.2, 16.8±0.2, and 23.0±0.2 degrees 2θ.

[0310] In some embodiments, the disodium salt has an X-ray powder diffraction pattern comprising one or more peaks selected from the group consisting of 4.8±0.2, 9.6±0.2, 10.5±0.2, 13.0±0.2, 14.6±0.2, 15.4±0.2, 16.8 ±0.2, 22.7±0.2, 23.0±0.2, and 23.3±0.2 degrees 2θ. In some such embodiments, the disodium salt has an X-ray powder diffraction pattern comprising three or more peaks selected from the group consisting of 4.8±0.2, 9.6±0.2, 10.5±0.2, 13.0±0.2, 14.6±0.2, 15.4±0.2, 16.8 ±0.2, 22.7±0.2, 23.0±0.2, and 23.3±0.2 degrees 2θ. In other such embodiments, the disodium salt has an X-ray powder diffraction pattern comprising five or more peaks selected from the group consisting of 4.8±0.2, 9.6±0.2, 10.5±0.2, 13.0±0.2, 14.6±0.2, 15.4±0.2, 16.8 ±0.2, 22.7±0.2, 23.0±0.2, and 23.3±0.2 degrees 2θ.

[0311] In some embodiments, the disodium salt has an X-ray powder diffraction pattern substantially as shown in Figure **15.** The

2θ values for the peaks in Figure **15** (and their intensities) are as follows: 4.80 (100), 9.59 (10), 10.51 (13), 12.98 (11), 14.56 (8), 15.38 (12), 16.84 **(6),** 22.68 (10), 23.04 **(6),** and 23.33 (4).

[0312] This invention also relates, in part, to a process for preparing the disodium salt. The disodium salt was prepared by suspending compound **IB-L0-2.3** (52.83mg) in 1M aqueous NaOH (1.1ml) (the molar ratio compound:NaOH was 1:10). The solution was heated to 36°C, and the solid dissolved completely to yield a clear solution. The solution was naturally cooled to ambient temperature, and the salt crystallized in 24h. Alternatively, the disodium salt was prepared by suspending compound **IB-L0-2.3** (51mg) in EtOH (1ml). NaOH in 1.2ml of 5:1 v/v EtOH/H_2O (2.1 molar equivalent) was added. The reaction mixture was concentrated and 2ml acetonitrile was added to induce crystallization. The stoichiometry of this solid was determined by ion chromatography.

G4. Crystalline Form of N-(6-(3-Tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)naphthalen-2yl)methanesulfonamide, Monopotassium Salt.

[0313] This invention also relates, in part, to a crystalline form of N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methanesulfonamide, monopotassium salt.

[0314] In some embodiments, the monopotassium salt has an X-ray powder diffraction pattern comprising one or more peaks selected from the group consisting of 5.0±0.2, 9.9±0.2, 11.3±0.2, 13.3±0.2, 16.9±0.2, 18.1±0.2, 19.1±0.2, 20.0±0.2, 21.1±0.2, 23.5±0.2, 24.8±0.2, and 25.7±0.2 degrees 2θ. In some such embodiments, the monopotassium salt has an X-ray powder diffraction pattern comprising three or more peaks selected from the group consisting of 5.0±0.2, 9.9±0.2, 11.3±0.2, 13.3±0.2, 16.9±0.2, 18.1±0.2, 19.1±0.2, 20.0±0.2, 21.1±0.2, 23.5±0.2, 24.8±0.2, and 25.7±0.2 degrees 2θ. In other such embodiments, the monopotassium salt has an X-ray powder diffraction pattern comprising five or more peaks selected from the group consisting of 5.0±0.2, 9.9±0.2, 11.3±0.2, 13.3±0.2, 16.9±0.2, 18.1±0.2, 19.1±0.2, 20.0±0.2, 21.1±0.2, 23.5±0.2, 24.8±0.2, and 25.7±0.2degrees 2θ.

[0315] In some embodiments, the monopotassium salt has an X-ray powder diffraction pattern comprising one or more peaks selected from the group consisting of 5.0±0.2, 9.9±0.2, 11.3±0.2, 13.3±0.2, 16.9±0.2, 18.1±0.2, 19.1±0.2, 20.0±0.2, 21.1±0.2, 21.5±0.2, 23.5±0.2, 24.8±0.2, and 25.7±0.2 degrees 2. In some such embodiments, the monopotassium salt has an X-ray powder diffraction pattern comprising three or more peaks selected from the group consisting of 5.0±0.2, 9.9±0.2, 11.3±0.2, 13.3±0.2, 16.9±0.2, 18.1±0.2, 19.1±0.2, 20.0±0.2, 21.1±0.2, 21.5±0.2, 23.5±0.2, 24.8±0.2, and 25.7±0.2 degrees 2θ. In other such embodiments, the monopotassium salt has an X-ray powder diffraction pattern comprising five or more peaks selected from the group consisting of 5.0±0.2, 9.9±0.2, 11.3±0.2, 13.3±0.2, 16.9±0.2, 18.1±0.2, 19.1±0.2, 20.0±0.2, 21.1±0.2, 21.5±0.2, 23.5±0.2, 24.8±0.2, and 25.7±0.2degrees 20.

[0316] In some embodiments, the monopotassium salt has an X-ray powder diffraction pattern substantially as shown in Figure **17.** The 2θ values for the peaks in Figure **17** (and their intensities) are as follows: 4.97 (100), 9.94 (7), 11.33 (15), 13.28 (7), 16.91 (5), 18.13 (7), 19.14 (4), 20.00 (4), 21.13 (4), 21.45 (4), 23.54 (4), 24.84 (3), and 25.67 (6).

[0317] This invention also relates, in part, to a process for preparing the monopotassium salt. The monopotassium salt was prepared in aqueous medium. 0.366ml of 1M aqueous KOH was added to 150.56mg of compound **IB-L0-2.3** (molar ratio 1:1.2). The resulting suspension was equilibrated at ambient conditions. The monopotassium salt was formed on the following day through a solution-mediated process. Alternatively, the monopotassium salt was prepared by suspending compound **IB-L0-2.3** (300mg) in 3ml acetonitrile. KOH in 1.3mL of H_2O (2.1 molar equivalent) was added. Additional 1ml H_2O was added to dissolve all solids. Afterwards, 12ml acetonitrile was added to induce crystallization. The stoichiometry of the salt was confirmed by ion chromatograph.

G5. Crystalline Forms of N-(6-(3-Tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methanesulfonamide, Monocholine Salt.

[0318] This invention also relates, in part, to crystalline forms of N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methanesulfonamide, monocholine salt, namely the pattern A and pattern B crystalline forms discussed below.

[0319] This invention relates, in part, to a pattern A crystalline monocholine salt.

[0320] In some embodiments, the pattern A monocholine salt has an X-ray powder diffraction pattern comprising one or more peaks selected from the group consisting of 10.9±0.2, 12.1±0.2, 13.4±0.2, 15.5±0.2, 17.0±0.2, 17.8±0.2, 18.3±0.2, 19.5±0.2, and 21.9±0.2 degrees 2θ. In some such embodiments, the pattern A monocholine salt has an X-ray powder diffraction pattern comprising three or more peaks selected from the group consisting of 10.9±0.2, 12.1±0.2, 13.4±0.2, 15.5±0.2, 17.0±0.2, 17.8±0.2, 18.3±0.2, 19.5±0.2, and 21.9±0.2 degrees 2θ. In other such embodiments, the pattern A monocholine salt has an X-ray powder diffraction pattern comprising five or more peaks selected from the group consisting of 10.9±0.2, 12.1±0.2, 13.4±0.2, 15.5±0.2, 17.0±0.2, 17.8±0.2, 18.3±0.2, 19.5±0.2, and 21.9±0.2 degrees 2θ.

[0321] In some embodiments, the pattern A monocholine salt has an X-ray powder diffraction pattern comprising one or more peaks selected from the group consisting of 10.9±0.2, 12.1±0.2, 13.0±0.2, 13.4±0.2, 13.6±0.2, 15.5±0.2, 17.0±0.2, 17.8±0.2, 18.3±0.2, 19.5±0.2, 19.7±0.2, and 21.9±0.2 degrees 2θ. In some such embodiments, the pattern A monocholine salt has an X-ray powder diffraction pattern comprising three or more peaks selected from the group consisting of degrees 2θ. In other such embodiments, the pattern A monocholine salt has an X-ray powder diffraction pattern comprising five or more peaks selected from the group consisting of degrees 2θ.

[0322] In some embodiments, the pattern A monocholine salt has an X-ray powder diffraction pattern substantially as shown in Figure **19.** The 2θ values for the peaks in Figure **19** (and their intensities) are as follows: 10.94 (42), 12.06 (20), 12.96 (26), 13.42 (64), 13.64 (27), 15.51 (18), 16.98 (78), 17.81 (26), 18.32 (100), 19.49 (48), 19.70 (33), and 21.91 (22).

[0323] This invention also relates, in part, to a process for preparing the pattern A monocholine salt. It was prepared in a solvent mixture of tetrahydrofuran (THF) and methanol. Compound **IB-L0-2.3** (56.79mg) was dissolved in THF at 60°C, 40.01mg of choline hydroxide solution (45wt% in methanol) was added resulting in a molar ratio of 1:1.2. The crystals formed upon natural cooling to ambient temperature.

[0324] This invention also relates, in part, to a pattern B crystalline monocholine salt.

[0325] In some embodiments, the pattern B monocholine salt has an X-ray powder diffraction pattern comprising one or more peaks selected from the group consisting of 8.0±0.2, 9.4±0.2, 11.0±0.2, 13.0±0.2, 13.7±0.2, 15.9±0.2, 17.0±0.2, 18.3±0.2, 18.9±0.2, 19.8±0.2, and 22.1±0.2 degrees 2θ. In some such embodiments, the pattern B monocholine salt has an X-ray powder diffraction pattern comprising three or more peaks selected from the group consisting of 8.0±0.2, 9.4±0.2, 11.0±0.2, 13.0±0.2, 13.7±0.2, 15.9±0.2, 17.0±0.2, 18.3±0.2, 18.9±0.2, 19.8±0.2, and 22.1±0.2 degrees 2θ. In other such embodiments, the pattern B monocholine salt has an X-ray powder diffraction pattern comprising five or more peaks selected from the group consisting of 8.0±0.2, 9.4±0.2, 11.0±0.2, 13.0±0.2, 13.7±0.2, 15.9±0.2, 17.0±0.2, 18.3±0.2, 18.9±0.2, 19.8±0.2, and 22.1±0.2 degrees 2θ.

[0326] In some embodiments, the pattern B monocholine salt has an X-ray powder diffraction pattern comprising one or more peaks selected from the group consisting of 8.0±0.2, 9.4±0.2, 11.0±0.2, 13.0±0.2, 13.3±0.2, 13.7±0.2, 15.9±0.2, 17.0±0.2, 17.4±0.2, 18.3±0.2, 18.9±0.2, 19.8±0.2, 21.8±0.2, and 22.1±0.2 degrees 2θ. In some such embodiments, the pattern B monocholine salt has an X-ray powder diffraction pattern comprising three or more peaks selected from the group consisting of 8.0±0.2, 9.4±0.2, 11.0±0.2, 13.0±0.2, 13.3±0.2, 13.7±0.2, 15.9±0.2, 17.0±0.2, 17.4±0.2, 18.3±0.2, 18.9±0.2, 19.8±0.2, 21.8±0.2, and 22.1±0.2 degrees 2θ. In other such embodiments, the pattern B monocholine salt has an X-ray powder diffraction pattern comprising five or more peaks selected from the group consisting of 8.0±0.2, 9.4±0.2, 11.0±0.2, 13.0±0.2, 13.3±0.2, 13.7±0.2, 15.9±0.2, 17.0±0.2, 17.4±0.2, 18.3±0.2, 18.9±0.2, 19.8±0.2, 21.8±0.2, and 22.1±0.2 degrees 2θ.

[0327] In some embodiments, the pattern B monocholine salt has an X-ray powder diffraction pattern substantially as shown in Figure **21.** The 2θ values for the peaks in Figure **21** (and their intensities) are as follows: 7.96 (41), 9.38 (34), 10.96 (24), 12.98 (76), 13.34 (33), 13.72 (37), 15.90 (100), 17.03 (60), 17.42 (37), 18.30 (31), 18.85 (93), 19.82 (90), 21.76 (38), and 22.06 (46).

[0328] This invention also relates, in part, to a process for preparing the pattern B monocholine salt. It was prepared by suspending amorphous choline salt in ethyl acetate for seven days.

G6. Crystalline Form of N-(6-(3-Tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)naphthalen-2yl)methanesulfonamide, Dicholine Salt.

[0329] This invention also relates, in part, to a crystalline form of N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methanesulfonamide, dicholine salt.

[0330] In some embodiments, the dicholine salt has an X-ray powder diffraction pattern comprising one or more peaks selected from the group consisting of 8.6±0.2, 11.0±0.2, 12.9±0.2, 17.0±0.2, 17.5±0.2, 18.9±0.2, 19.8±0.2, and 21.9±0.2 degrees 2θ. In some such embodiments, the dicholine salt has an X-ray powder diffraction pattern comprising three or more peaks selected from the group consisting of 8.6±0.2, 11.0±0.2, 12.9±0.2, 17.0±0.2, 17.5±0.2, 18.9±0.2, 19.8±0.2, and 21.9±0.2 degrees 2θ. In other such embodiments, the dicholine salt has an X-ray powder diffraction pattern comprising five or more peaks selected from the group consisting of 8.6±0.2, 11.0±0.2, 12.9±0.2, 17.0±0.2, 17.5±0.2, 18.9±0.2, 19.8±0.2, and 21.9±0.2 degrees 2θ.

[0331] In some embodiments, the dicholine salt has an X-ray powder diffraction pattern comprising one or more peaks selected from the group consisting of 8.6±0.2, 11.0±0.2, 12.9±0.2, 17.0±0.2, 17.5±0.2, 18.9±0.2, 19.8±0.2, 21.9±0.2, and 22.1±0.2 degrees 2θ. In some such embodiments, the dicholine salt has an X-ray powder diffraction pattern comprising three or more peaks selected from the group consisting of 8.6±0.2, 11.0±0.2, 12.9±0.2, 17.0±0.2, 17.5±0.2, 18.9±0.2, 19.8±0.2, 21.9±0.2, and 22.1±0.2 degrees 2θ. In other such embodiments, the dicholine salt has an X-ray powder diffraction pattern comprising five or more peaks selected from the group consisting of 8.6±0.2, 11.0±0.2, 12.9±0.2, 17.0±0.2, 17.5±0.2, 18.9±0.2, 19.8±0.2, 21.9±0.2, and 22.1±0.2 degrees 2θ.

[0332] In some embodiments, the dicholine salt has an X-ray powder diffraction pattern substantially as shown in Figure **23.** The 2θ values for the peaks in Figure **23** (and their intensities) are as follows: 8.62 (28), 10.98 (29), 12.93 (50), 15.88 (100), 17.03 (42), 17.47 (29), 18.88 (66), 19.82 (57), 21.89 (42), 2.07 (41).

[0333] This invention also relates, in part, to a process for preparing the dicholine salt. It was prepared by suspending compound **IB-L0-2.3** (200mg) in 0.75ml MeOH. Choline hydroxide in MeOH (210ml, 45wt%, 2.10 molar equivalent) was added. The reaction mixture was concentrated, and 4ml acetonitrile and 6ml isopropyl acetate were added. The reaction mixture was then seeded with trace amount of the compound **IB-L0-2.3** monopotassium salt seed crystals (discussed above). The reaction mixture started to crystallize shortly after. The stoichiometry of the salt was determined by solution ^{1}H NMR.

H. Compositions.

[0334] This invention also is directed, in part, to compositions comprising one or more compounds and/or salts of the invention (including the crystalline compounds and salts discussed in section G above). In some embodiments, the compositions comprise one or more substantially phase pure crystalline forms (compounds/salts/solvates/hydrates) discussed in section G above. The compositions can be pharmaceutical compositions.

[0335] The compositions further comprise one or more additional therapeutic agents selected from the group consisting of interferon agents, ribavirin, HCV inhibitors, and anti-HIV agents.

[0336] The preferred composition depends on the method of administration, and typically comprises one or more conventional pharmaceutically acceptable carriers, adjuvants, and/or vehicles (together referred to as "excipients"). Formulation of drugs is generally discussed in, for example, Hoover, J., Remington's Pharmaceutical Sciences (Mack Publishing Co., 1975) and Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems (Lippincott Williams & Wilkins, 2005).

[0337] Solid dosage forms for oral administration include, for example, capsules, tablets, pills, powders, and granules. In such solid dosage forms, the compounds or salts are ordinarily combined with one or more excipients. If administered per os, the compounds or salts can be mixed with, for example, lactose, sucrose, starch powder, cellulose esters of alkanoic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, gelatin, acacia gum, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, and then tableted or encapsulated for convenient administration. Such capsules or tablets can contain a controlled-release formulation, as can be provided in, for example, a dispersion of the compound or salt in hydroxypropylmethyl cellulose. In the case of capsules, tablets, and pills, the dosage forms also can comprise buffering agents, such as sodium citrate, or magnesium or calcium carbonate or bicarbonate. Tablets and pills additionally can be prepared with enteric coatings.

[0338] Liquid dosage forms for oral administration include, for example, pharmaceutically acceptable emulsions (including both oil-in-water and water-in-oil emulsions), solutions (including both aqueous and non-aqueous solutions), suspensions (including both aqueous and non-aqueous suspensions), syrups, and elixirs containing inert diluents commonly used in the art (*e.g.*, water). Such compositions also can comprise, for example, wetting, emulsifying, suspending, flavoring (*e.g.*, sweetening), and/or perfuming agents.

[0339] Parenteral administration includes subcutaneous injections, intravenous injections, intramuscular injections, intrasternal injections, and infusion. Injectable preparations (*e.g.*, sterile injectable aqueous or oleaginous suspensions) can be formulated according to the known art using suitable dispersing, wetting agents, and/or suspending agents. Acceptable vehicles and solvents include, for example, water, 1,3-butanediol, Ringer's solution, isotonic sodium chloride solution, bland fixed oils (*e.g.*, synthetic mono- or diglycerides), fatty acids (*e.g.,* oleic acid), dimethyl acetamide, surfactants (*e.g.,* ionic and non-ionic detergents), and/or polyethylene glycols.

[0340] Formulations for parenteral administration may, for example, be prepared from sterile powders or granules having one or more of the excipients mentioned for use in the formulations for oral administration. A compound or salt of the invention can be dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, and/or various buffers. The pH may be adjusted, if necessary, with a suitable acid, base, or buffer.

[0341] Suppositories for rectal administration can be prepared by, for example, mixing a compound or salt of the invention with a suitable nonirritating excipient that is solid at ordinary temperatures, but liquid at the rectal temperature, and will therefore melt in the rectum to release the drug. Suitable excipients include, for example, cocoa butter; synthetic mono-, di-, or triglycerides, fatty acids, and/or polyethylene glycols.

[0342] Topical administration includes the use of transdermal administration, such as transdermal patches or iontophoresis devices.

[0343] Other excipients and modes of administration known in the pharmaceutical art also may be used.

[0344] The preferred total daily dose of the compound or salt (administered in single or divided doses) is typically from about 0.001 to about 100mg/kg, more preferably from about 0.001 to about 30mg/kg, and even more preferably from about 0.01 to about 10mg/kg (*i.e.*,mg of the compound or salt per kg body weight). Dosage unit compositions can contain such amounts or submultiples thereof to make up the daily dose. In many instances, the administration of the compound or salt will be repeated a plurality of times. Multiple doses per day typically may be used to increase the total daily dose, if desired.

[0345] Factors affecting the preferred dosage regimen include the type, age, weight, sex, diet, and condition of the patient; the severity of the pathological condition; the severity of the pathological condition; the route of administration; pharmacological considerations, such as the activity, efficacy, pharmacokinetic, and toxicology profiles of the particular compound or salt used; whether a drug delivery system is utilized; and whether the compound or salt is administered as part of a drug combination. Thus, the dosage regimen actually employed can vary widely, and therefore, can derive from the preferred dosage regimen set forth above.

I. Product for Use.

[0346] This invention also is directed, in part, to a product for use in inhibiting replication of an RNA virus. The method comprises exposing the virus to one or more compounds and/or salts of this invention. In some embodiments, replication of the RNA virus is inhibited *in vitro.* In other embodiments, replication of the RNA virus is inhibited *in vivo.* In some embodiments, the RNA virus whose replication is being inhibited is a single-stranded, positive sense RNA virus. In some such embodiments, the RNA virus whose replication is being inhibited is a virus from the *Flaviviridae* family. In some such embodiments, the RNA virus whose replication is being inhibited is HCV.

[0347] This invention also is directed, in part, to a method for inhibiting HCV RNA polymerase. The method comprises exposing the polymerase with one or more compounds and/or salts of this invention. In some embodiments, HCV RNA polymerase activity is inhibited *in vitro.* In other embodiments, HCV RNA polymerase activity is inhibited *in vivo.*

[0348] The term "inhibiting" means reducing the level of RNA virus replication/HCV polymerase activity either *in vitro* or *in vivo.* For example, if a compound/salt of the invention reduces the level of RNA virus replication by at least about 10% compared to the level of RNA virus replication before the virus was exposed to the compound/salt, then the compound/salt inhibits RNA virus replication. In some embodiments, the compound/salt can inhibit RNA virus replication by at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, or at least about 95%.

[0349] This invention also is directed, in part, to a method for treating a disease that can be treated by inhibiting HCV RNA polymerase. Thus, this invention also is directed, in part, to a method for treating hepatitis C in an animal in need of such treatment. These uses comprise administering to the animal one or more compounds and/or salts of the invention, and one or more additional therapeutic agents. In some embodiments, a therapeutically effective amount of the compound(s) and/or salt(s) is administered to the animal. "Treating" means ameliorating, suppressing, eradicating, preventing, reducing the risk of, and/or delaying the onset of the disease being treated. Applicants specifically intend that the term "treating" encompass administration of the compounds and/or salts of the invention to an HCV-negative patient that is a candidate for an organ transplant. The uses of treatment are particularly suitable for use with humans, but may be used with other animals, particularly mammals. A "therapeutically-effective amount" or "effective amount" is an amount that will achieve the goal of treating the targeted condition.

[0350] The uses comprise combination therapy, wherein the compound(s) and/or salt(s) of the invention is/are co-administered with a second (or even a third, fourth, etc.) compound, such as, for example, another therapeutic agent used to treat hepatitis C (*e.g.*, interferon or interferon/ribavirin combination, or an HCV inhibitor such as, for example, an HCV polymerase inhibitr or an HCV protease inhibitor). The compound(s) and/or salt(s) of this invention can also be co-administered with therapeutic agents other than therapeutic agents used to treat hepatitis C (*e.g.*, anti-HIV agents). In these co-administration embodiments, the compound(s) and/or salt(s) of the invention and the second, etc. therapeutic agent(s) may be administered in a substantially simultaneous manner (*e.g.*, or within about 5 minutes of each other), in a sequential manner, or both. It is contemplated that such combination therapies may include administering one therapeutic agent multiple times between the administrations of the other. The time period between the administration of each agent may range from a few seconds (or less) to several hours or days, and will depend on, for example, the properties of each composition and active ingredient (*e.g.*, potency, solubility, bioavailability, half-life, and kinetic profile), as well as the condition of the patient. The compound(s) and/or salt(s) of this invention and the second, etc. therapeutic agent may also be administered in a single formulation.

[0351] This invention also is directed, in part, to a use of one or more compounds and/or salts of the invention, and one or more additional therapeutic agents to prepare a medicament. In some embodiments, the medicament is for co-administration with one or more additional therapeutic agents.

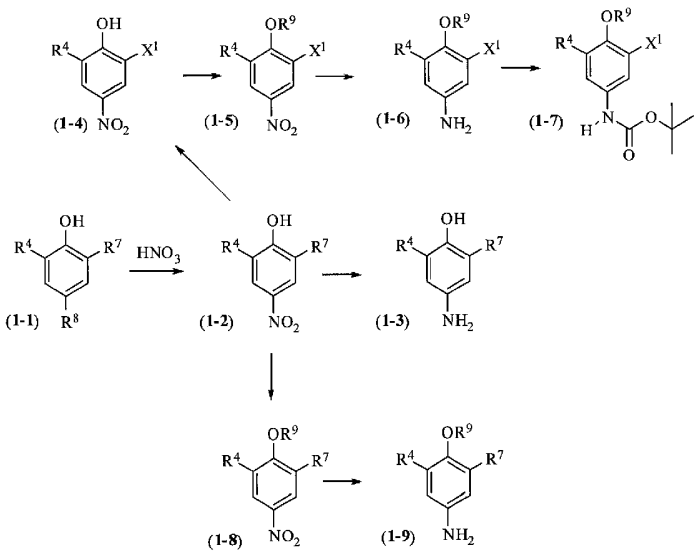
[0352] In some embodiments, the medicament is for inhibiting replication of an RNA virus.

[0353] In some embodiments, the medicament is for treating hepatitis C.

[0354] This invention also is directed, in part, to one or more compounds and/or salts of the invention, and one or more additional therapeutic agents, for use as a medicament. In some embodiments, the medicament is for inhibiting replication of an RNA virus. In other embodiments, the medicament is for treating hepatitis C.

[0355] Information about the preparation of compounds of formulas **I** and **II** (and their salts) is provided in the general discussion and/or specific synthesis examples below. In the discussion below, R^1, R^2, R^3, R^4, R^5, L, R^A, R^B, R^C, R^D, R^6, R^E, R^F, R^G, R^H, R^I, R^J, R^K, X^1, and X^2 have the meaning discussed above unless otherwise stated.

SCHEME 1



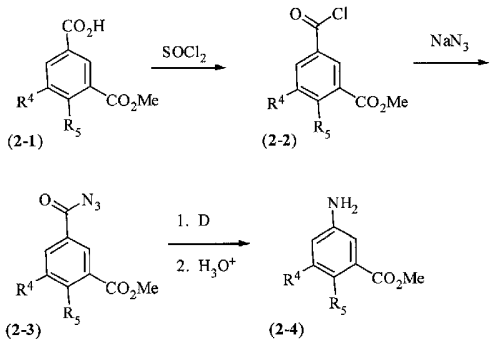
[0356] Compound **(1-1),** wherein R^7 is, for example, hydrogen or $-CO_2Me$, and R^8 is, for example, hydrogen or t-butyl, may be treated with nitric acid in solvents such as, for example, acetic acid or water in a temperature range of about 0 to about 35°C over about 1 to about 5h to provide compound **(1-2).** Compound **(1-2)** may then be reduced using conditions known to those skilled in the art to furnish the corresponding aniline **(1-3).** Typical conditions for this reduction include using hydrogen at a pressure of about 1 to about 5 atmospheres in the presence of a catalyst such as, for example, palladium or platinum on charcoal in a solvent such as, for example, tetrahydrofuran, ethyl acetate, ethanol, or hexane at or near ambient temperature over a period of about 1 to about 12h. Dependent on the functional groups present, an alternative reduction procedure may be more appropriate such as, for example, using iron powder in the presence of a mild acid such as, for example, ammonium chloride or dilute hydrochloric acid at reflux temperatures in a mixture of solvents containing, for example, methanol, water, and/or tetrahydrofuran over about 1 to about 12h. Another set of reduction conditions includes the use of sodium borohydride in a solvent mixture such as, for example, water and tetrahydrofuran. Yet another set of reduction conditions includes the use of tin(II) chloride in the presence of hydrochloric acid in such solvents as, for example, water and methanol or mixtures thereof.

[0357] Compound **(1-2)** may be modified prior to reduction. For example, treatment of compound **(1-2),** wherein R^7 is hydrogen, with iodine monochloride in a mixture of methanol and water at or near ambient temperature over a period of about 8 to about 24h supplies compound **(1-4),** wherein X^1 is iodine. Alternatively, compound **(1-2)** can be treated with pyridinium hydrobromide perbromide in a solvent such as, for example, acetic acid at or near ambient temperature over a period of about 2 to about 16h to provide compound **(1-4),** wherein X^1 is bromine. Modifications may be introduced at the phenol moiety in compound **(1-4).** For example, the phenol may be alkylated with alkyl halides (*e.g.*, methyl iodide), alkyl sulfates (e.g., methyl sulfate), alkenyl halides (*e.g.*, allyl bromide), alkynyl halides (e.g., propargyl bromide) in the presence of a base such as, for example, potassium carbonate in acetone, sodium hydride in dimethylformamide, or potassium t-butoxide in tetrahydrofuran, at temperatures from about 0 to about 35°C over a period of about 1 to about 24h to provide compound **(1-5),** wherein R^9 is, for example, alkyl, alkenyl, or alkynyl. Alternatively, alkylation may be achieved by using a reagent such as (trimethylsilyl) diazomethane in solvents such as, for example, methanol or t-butyl methyl ether, or mixtures thereof in a sealed tube at or near room temperature over about 8 to about 24h. Compound **(1-5)** may subsequently be reduced to compound **(1-6)** using the iron powder or tin(II) chloride conditions described above. An alternative reduction procedure employs hydrogenation at approximately 1 atmosphere pressure with a catalyst such as 5% platinum on sulfided carbon in a solvent such as methanol. Protection of the resultant aniline of compound **(1-6)** with, for example, a t-butyl carbamate can be achieved by treatment with di-tert-butyl dicarbonate in a solvent such as, for example, tetrahydrofuran or dioxane at a temperature of about 50 to about 65°C for about 1 to about 8h provides compound **(1-7).**

[0358] Modifications may also occur at the phenol moiety in compound **(1-2).** One skilled in the art may alkylate the phenol of compound **(1-2)** using, for example, the conditions described above to obtain compound **(1-8).** Compound **(1-8)** is transformed into compound **(1-9)** using, for example, one or more of the appropriate reduction conditions described above.

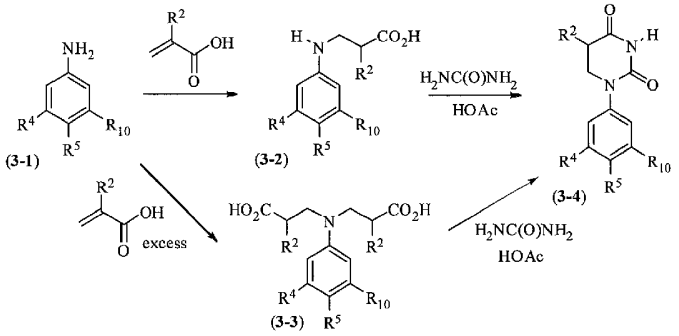
[0359] Another modification of the phenol group in compound **(1-2)** is sulfonylation to furnish compound **(1-8),** wherein R^9 is alkylsulfonyl, carbocyclylsulfonyl, or haloalkylsulfonyl. Such a compound may be prepared by exposing compound **(1-2)** to sulfonyl chlorides such as, for example, methanesulfonyl chloride, cyclohexanesulfonyl chloride, benzenesulfonyl chloride, or 3-chloropropane sulfonyl chloride in the presence of a base such as, for example, triethylamine, diisopropylethylamine, or pyridine in a solvent such as, for example, dichloromethane at or near ambient temperature for a period of about 1 to about 24h. One skilled in the art can then transform compound **(1-8)** into compound **(1-9)** with an appropriate set of reduction conditions.

SCHEME 2



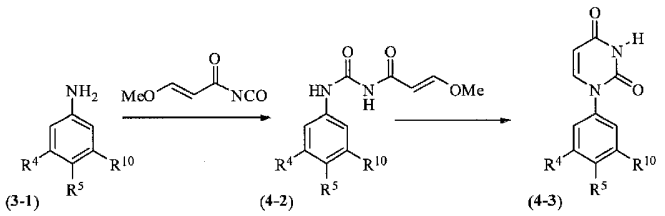
[0360] Aniline **(2-4)** can be prepared through use of the Curtius rearrangement. To this end, compound **(2-1),** wherein R^4 is not amino, can be treated in refluxing thionyl chloride with a catalytic amount of dimethylformamide for about 1 to about 4h to obtain acid chloride **(2-2).** Treatment with thionyl chloride at the reflux temperature in solvents such as, for example, chloroform or toluene also furnishes compound **(2-2).** Compound **(2-2)** can be reacted with an aqueous solution of sodium azide in a solvent such as, for example, acetone over about 1 to about 8h to provide acyl azide **(2-3).** Compound **(2-3)** can then undergo a Curtius rearrangement in refluxing solvents such as dioxane or toluene. The intermediate isocyanate is hydrolyzed with an aqueous acid such as dilute hydrochloric acid in a solvent such as dimethoxyethane to provide compound **(2-4).**

SCHEME 3



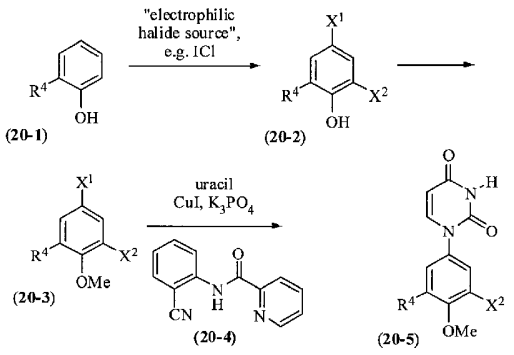
[0361] Compound **(3-1),** wherein R^{10} is, for example, hydrogen, bromine, iodine, or $-CO_2Me$, can be treated with an acrylic acid either neat at or near ambient temperature in a solvent such as, for example, toluene and heated to reflux over a period of about 15 to about 48h to supply compound **(3-2).** When excess of an acrylic acid is used, compound **(3-3)** is produced. Compound **(3-2)** or **(3-3)** can be treated with urea in a solvent such as, for example, acetic acid at about 100 to about 120°C over about 2 to about 48h to supply compound **(3-4).**

SCHEME 4



[0362] Compound **(4-2)** can be prepared from compound **(3-1)** dissolved in solvents such as, for example, dimethylformamide or dimethylacetamide by the addition of a benzene solution of (E)-3-methoxyacryloyl isocyanate (prepared as described by Santana, L.; et al. J. Heterocyclic Chem. 1999, 36, 293-295.) at a temperature of about -40 to about -15°C under an inert atmosphere and then warming to ambient temperature for from about 30 min to about 4h. Compound **(4-2)** can be treated with an acid such as, for example, sulfuric acid in mixtures of water and ethanol in a temperature range of from about 90 to about 110°C for about 1 to about 8h to supply compound **(4-3).** Alternatively, compound **(4-2)** can be cyclized to uracil **(4-3)** under the basic conditions described by Ueno, Y.; et al. J. Org. Chem. 70:7925-7935 (2005).

SCHEME 5

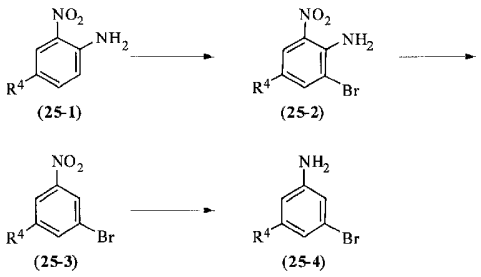


[0363] Phenol **(20-1),** wherein R^4 is other than amino, is treated with a source of electrophilic halide, such as, for example, iodine

monochloride to provide dihalogenated compound **(20-2),** wherein X^1 and X^2 are independently bromine or iodine. Compound **(20-2)** is transformed to compound **(20-3)** by reaction of an alkylating agent such as, for example, methyl sulfate with a base such as, for example, potassium carbonate in refluxing acetone. Alternatively, methyl iodide in the presence of a base such as, for example, potassium *t*-butoxide in a solvent such as, for example, tetrahydrofuran, or dimethylformamide also furnish compound **(20-3).** In yet another alternative, compound **(20-2)** can be methylated with (trimethylsilyl)diazomethane in a solvent such as, for example, t-butyl methyl ether. Compound **(20-3)** can be reacted with uracil, ligand **(20-4),** copper (I) iodide, and potassium phosphate in dimethyl sulfoxide at about 40°C to about 100°C to supply compound **(20-5).**

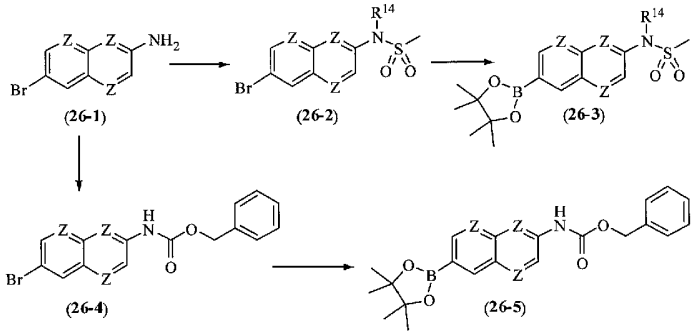
[0364] For example, when in compound **(20-3),** R^4 is tert-butyl, X^1 is iodo, and X^2 is iodo or bromo, compound (20-3) can be stirred with uracil and compound **(20-4)** in the presence of CuI and K_2PO_4 in DMSO for about 15 to about 24h at about 60°C to supply compound **(20-5).** Alternatives to ligand **(20-4)** for making **(20-5)** are 8-hydroxyquinoline and 2-(2-pyridyl)-benzimidazole.

SCHEME 6



[0365] Compound **(25-1)** can be brominated by treatment with, for example, pyridinium hydrobromide perbromide in a solvent such as, for example, acetic acid at or near ambient temperature over a period of about 1 to about 8h to give compound **(25-2).** The amino group of compound **(25-2)** can be removed by exposure to t-butyl nitrite in a solvent such as, for example, dimethylformamide at a temperature initially at ambient temperature and then increased to the range of about 50 to about 65 °C to give compound **(25-3).** Additional aliquots of t-butyl nitrite can be added at ambient temperature followed by heating until the transformation is complete. Compound **(25-3)** can be reduced to compound **(25-4)** by, for example, treatment with iron and ammonium chloride.

SCHEME 7



[0366] Compound **(26-1),** wherein each Z is independently N or CH can be converted to a boronic acid ester for use in Suzuki reactions. For example, compound of formula **(26-1)** can be converted to compound **(26-2),** wherein R^{14} is hydrogen or methanesulfonyl (when excess methanesulfonyl chloride is used) by treatment with methanesulfonyl chloride in pyridine at approximately ambient temperature in about 1 to about 8h.

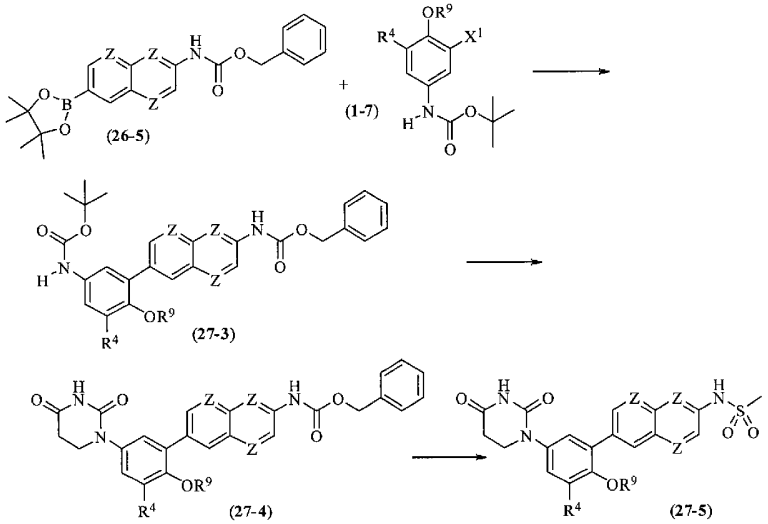
[0367] Compound **(26-2)** can be transformed to compound of **(26-3)** by treatment with pinacol-borane in the presence of a catalyst such as, for example, tris(dibenzylidineacetone)dipalladium (0), ligand such as, for example, tri-t-butylphosphine, and a base such as triethylamine in solvents such as, for example, tetrahydrofuran, dioxane, or toluene at temperatures ranging from ambient to about 130°C.

[0368] Alternatively, compound **(26-2)** can be reacted with bis(pinacolato)diboron in the presence of a catalyst such as, for example, Combiphos® Pd6, dichloro[1,1'-bis(diphenylphosphino)ferrocene] palladium (II) dichloromethane adduct, or palladium acetate in the presence of a ligand such as, for example, 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (XPhos), and a base such as, for example, potassium acetate in solvents such as, for example, toluene, dioxane, tetrahydrofuran,

dimethylformamide or dimethyl sulfoxide in temperatures from about 60 to about 130°C to give compound **(26-3).**

[0369] Compound **(26-3)** can be converted to protected compound **(26-4)** by treatment with benzyl chloroformate initially at about 0°C in the presence of saturated aqueous sodium bicarbonate in a mixture of acetone and water. This can be warmed to ambient temperature and maintained at that temperature for about 12 to about 24h. Subsequently, compound **(26-4)** can be converted to the boronic acid pinacol ester **(26-5)** using the reaction conditions described above.

SCHEME 9

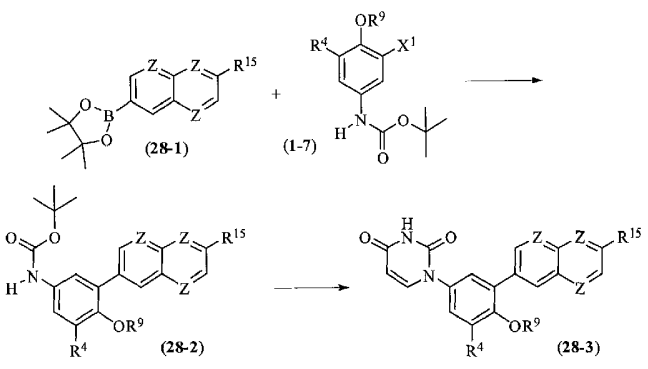


[0370] Compound **(26-5),** wherein each Z is independently N or CH, can be coupled with compound (1-7) under Suzuki reaction conditions to provide compound **(27-3).** Such conditions include, for example, use of a palladium catalyst such as, for example, tris(dibenzylidineacetone)palladium (0), palladium acetate, bis(triphenylphosphine)palladium (II) chloride, tetrakis(triphenylphosphine)palladium, or dichloro[1,1'-bis(diphenylphosphino)ferrocene] palladium (II) dichloromethane adduct; base such as, for example, potassium carbonate, potassium phosphate, potassium *t*-butoxide, sodium carbonate, cesium carbonate, or cesium fluoride; and solvent such as, for example, toluene, ethanol, water, or tetrahydrofuran, or mixtures thereof heated in the temperature range from about 40 to about 130°C.

[0371] Compound **(27-3)** can be transformed to compound **(27-4)** in a three-step process. The initial step involves removal of the t-butoxycarbonyl protecting group with an acid such as, for example, trifluoroacetic acid in solvent such as, for example, dichloromethane or hydrochloric acid in dioxane at room temperature over about 1 to about 24h. Subsequently, the dihydropyrimidinedione can be introduced as described in Scheme 3.

[0372] Compound **(27-5)** can be obtained from compound **(27-4)** in a two-step sequence. First, the protecting group is removed from the naphthyl amine under reductive conditions. Typically, hydrogenation (~1 atmosphere pressure) in the presence of a catalyst such as, for example, 10% palladium on charcoal in a solvent such as, for example, ethyl acetate at or near ambient temperature over a period of about 8 to about 24h. Second, the naphthyl amine can now be sulfonylated by treatment with methanesulfonyl chloride in the presence of a base such as triethylamine in a solvent (e.g., dichloromethane) at room temperature over about 20 min to about 4h.

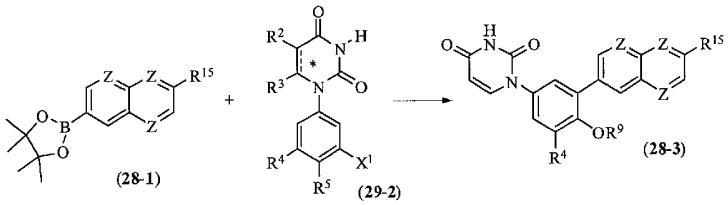
SCHEME 10



[0373] Compound **(28-1),** wherein each Z is independently N or CH, and R^{15} is, for example, hydrogen, -$NHSO_2Me$, -$N(SO_2Me)_2$ or methoxy can be coupled with compound (1-7) under Suzuki reaction conditions to provide compound **(28-2).** Such conditions include, for example, use of palladium catalyst such as, for example, tris(dibenzylidineacetone) palladium (0), palladium acetate, bis(triphenylphosphine)palladium (II) chloride, tetrakis(triphenylphosphine)palladium, or dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium (II) dichloromethane adduct; a base such as potassium carbonate, potassium phosphate, potassium *t*-butoxide, sodium carbonate, cesium carbonate, or cesium fluoride; and solvent such as, for example, toluene, ethanol, water or tetrahydrofuran, or mixtures thereof heated in the temperature range from about 40 to about 130°C. The reaction is typically deoxygenated with an inert gas such as nitrogen prior to heating. The heating may occur in conventional glassware, a sealed tube, or in a microwave reactor over about 1 to about 24h.

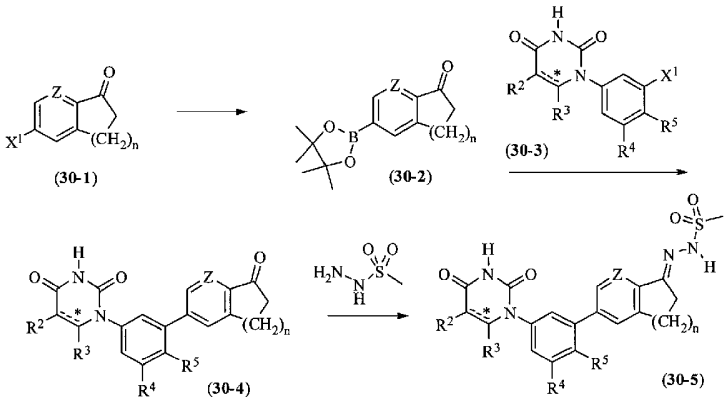
[0374] Compound **(28-2)** can be transformed to compound **(28-3)** in a three-step process. The initial step involves removal of the t-butoxycarbonyl protecting group with an acid such as, for example, trifluoroacetic acid in solvent such as, for example, dichloromethane or hydrochloric acid in dioxane at room temperature over about 1 to about 24h. Subsequently, the uracil can be introduced as described in Scheme 4.

SCHEME 11



[0375] Compound **(28-1),** wherein each Z is independently N or CH, and R^{15} is, for example, hydrogen, -$NHSO_2Me$, -$N(SO_2Me)_2$, or methoxy can be coupled with compound of formula **(29-2),** wherein X^1 is, for example, bromine or iodine, under Suzuki reaction conditions to provide compound of formula **(28-3).** Such conditions include, for example, use of palladium catalyst such as, for example, tris(dibenzylidineacetone)palladium (0), palladium acetate, bis(triphenylphosphine)palladium (II) chloride, tetrakis(triphenylphosphine) palladium , dichloro[1,1'-bis(diphenylphosphino)ferrocene] palladium (II) dichloromethane adduct, or bis(diphenylphosphino)ferrocene]palladium (II) dichloromethane; base such as, for example, potassium carbonate, potassium phosphate, potassium *t*-butoxide, sodium carbonate, cesium carbonate, or cesium fluoride; and solvent such as, for example, toluene, ethanol, water, or tetrahydrofuran, or mixtures thereof heated in the temperature range from about 40 to about 130°C. The reaction is typically deoxygenated with an inert gas such as nitrogen prior to heating. The heating may occur in conventional glassware, a sealed tube, or in a microwave reactor over about 1 to about 24h.

SCHEME 12

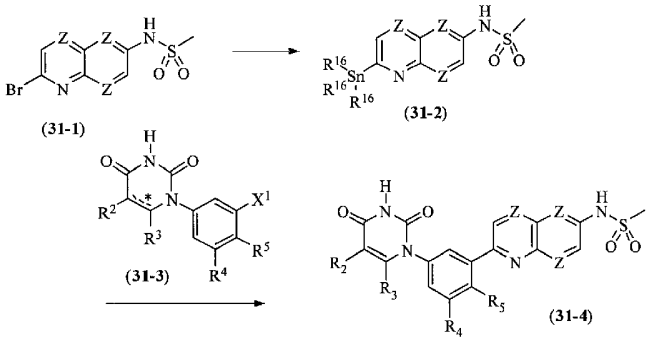


[0376] Compound **(30-1),** wherein X^1 is bromine or iodine, n is 1 or 2, and Z is CH or N, can be reacted with bis(pinacolato)diboron in the presence of a catalyst such as, for example, Combiphos® Pd6, dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium (II) dichloromethane adduct, or palladium acetate in the presence of a ligand such as 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (XPhos), and a base such as potassium acetate in solvents such as, for example, toluene, dioxane, tetrahydrofuran, dimethylformamide or dimethyl sulfoxide in temperatures from 60-130°C to give compound **(30-2).** The reaction is typically deoxygenated with an inert gas such as nitrogen prior to heating. The heating may occur in conventional glassware, a sealed tube, or in a microwave reactor over 1 to 24h. Compound **(30-3)** can be reacted with

compound **(30-2)** to give compound **(30-4)** employing the conditions described in Scheme **11.**

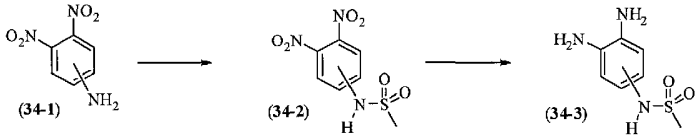
[0377] Treatment of compound **(30-4)** with methanesulfonylhydrazide in solvent such as, for example, tetrahydrofuran, methanol, or ethanol, or a mixture thereof at ambient temperature to about 100°C over a period of 8 to 48h provides compound **(30-5).**

SCHEME 13



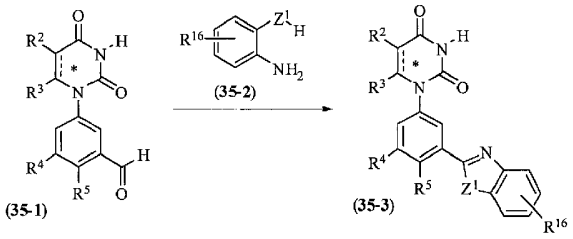
[0378] Compound **(31-1)** can be treated with hexamethylditin or hexabutylditin in the presence of a catalyst such as, for example, bis(triphenylphosphine)palladium (II) chloride in a solvent such as, for example, toluene or dioxane heated to about 50 to about 130°C to supply compound **(31-2).** Compound **(31-2)** can be treated with compound **(31-3)** in presence of catalyst such as, for example, tris(dibenzylidine acetone)palladium (0) and ligand such as tri(2-furyl)phosphine in solvent such as, for example, toluene, dioxane, or tetrahydrofuran heated to about 40 to about 130°C to give compound **(31-4).**

SCHEME 14



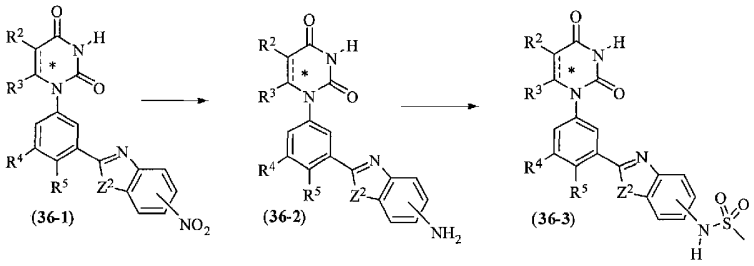
[0379] Dinitroaniline (34-1) can be sulfonylated with methanesulfonyl chloride in the presence of a base like, for example, pyridine in a solvent such as, for example, dichloromethane at room temperature over a period of about 8 to about 36h to give compound **(34-2).** Compound **(34-2)** can be converted to compound **(34-3)** using iron powder in the presence of a mild acid such as, for example, ammonium chloride or dilute hydrochloric acid at reflux temperatures in a mixture of solvents, such as, for example, methanol, water, and tetrahydrofuran over about 1 to about 12h.

SCHEME 15



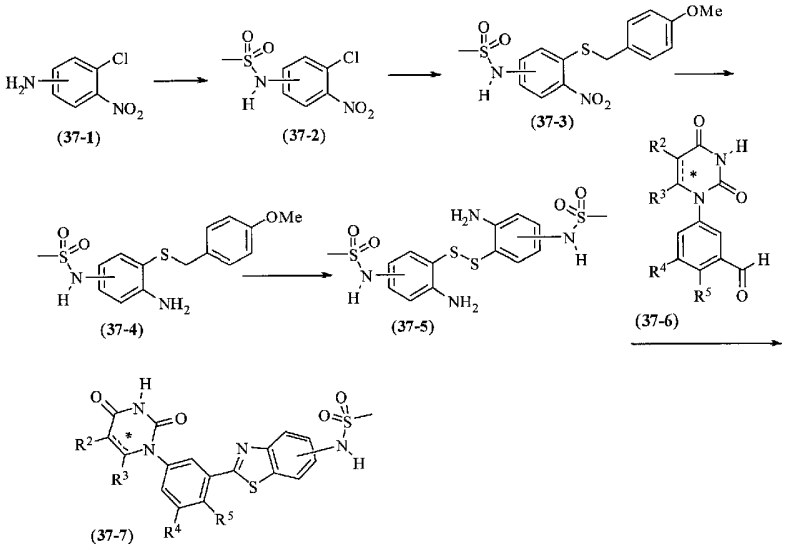
[0380] Compound **(35-1)** can be reacted with compound **(35-2),** wherein Z^1 is O, S, or NH and R^{16} is hydrogen, -$NHSO_2Me$, or NO_2, in the presence of charcoal exposed to air in solvent such as, for example, toluene heated from about 90 to about 110°C for about 24 to about 72h to give compound **(35-3).**

SCHEME 16



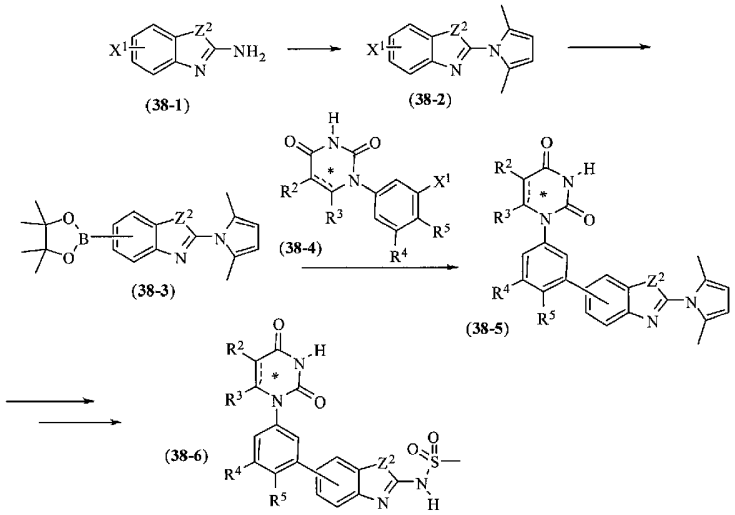
[0381] Compound **(36-1),** wherein Z^2 is O or S, can be reduced to compound **(36-2)** using iron powder in the presence of a mild acid such as, for example, ammonium chloride or dilute hydrochloric acid at temperatures of about 60 to about 90°C in solvents such as, for example, methanol, ethanol, water, and tetrahydrofuran, or mixtures thereof over about 30 min to about 12h. Compound **(39-2)** can be sulfonylated with methanesulfonyl chloride in the presence of a base like, for example, pyridine in a solvent such as, for example, dichloromethane at room temperature over a period of about 8 to about 36h.

SCHEME 17



[0382] Compound **(37-1)** can be sulfonylated with methanesulfonyl chloride in the presence of a base like, for example, pyridine in a solvent such as, for example, dichloromethane at room temperature over a period of about 8 to about 36h to give compound **(37-2).** Compound (37-2) can be reacted with (4-methoxyphenyl)methanethiol in the presence of a base such as, for example, potassium carbonate in a solvent such as, for example, dimethylformamide heated to about 90 to about 110°C for about 8 to about 24h to give compound **(37-3).** Compound **(37-3)** can be reduced to compound **(37-4)** using iron powder in the presence of a mild acid such as, for example, ammonium chloride or dilute hydrochloric acid at temperatures of about 60 to about 90°C in solvent such as, for example, methanol, ethanol, water, and tetrahydrofuran, or mixtures thereof over about 30 min to about 12h. Compound **(37-4)** can be transformed to compound **(37-5)** in the presence of mercury(II) acetate, anisole, and trifluoroacetic acid at about 0 °C for about 30 to about 90 min and subsequently bubbling hydrogen sulfide through the mixture. Compound **(37-5)** can be treated with compound **(37-6)** in the presence of p-toluenesulfonic acid and triphenylphosphine in a solvent such as, for example, toluene heated to reflux for about 2 to about 16h to supply compound **(37-7).**

SCHEME 18



[0383] Compound **(38-1),** wherein X^1 is bromine or iodine and Z^2 is O or S, can be reacted with 2,5-hexanedione in the presence of a p-toluenesulfonic acid and pyridine heated in benzene to give compound of formula **(38-2).** Compound **(38-2)** can be reacted with bis(pinacolato)diboron in the presence of a catalyst such as, for example, Combiphos® Pd6, dichloro[1,1'-bis(diphenylphosphino)ferrocene] palladium (II) dichloromethane adduct, or palladium acetate in the presence of a ligand such as, for example, 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (XPhos), and a base such as, for example, potassium acetate in a solvent such as, for example, toluene, dioxane, tetrahydrofuran, dimethylformamide or dimethyl sulfoxide at a temperature from about 60 to about 130°C to give compound **(38-3).** Compound **(38-3)** can be reacted with compound **(38-4)** to give compound **(38-5)** under Suzuki reaction conditions. Such conditions include, for example, use of a palladium catalyst such as, for example, dihydrogen dichlorobis(di-t-butylphosphinito-KP)palladate(2-), tris(dibenzylidineacetone) palladium (0), palladium acetate, bis(triphenylphosphine)palladium (II) chloride, tetrakis (triphenylphosphine)palladium, or dichloro[1,1'-bis(diphenylphosphino)ferrocene] palladium (II) dichloromethane adduct; a base such as, for example, potassium acetate, potassium carbonate, potassium phosphate, potassium *t*-butoxide, sodium carbonate, cesium carbonate, or cesium fluoride; and solvent such as, for example, toluene, ethanol, water or tetrahydrofuran, or mixtures thereof heated in the temperature range from about 40 to about 130°C.

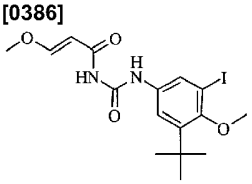
[0384] Compound **(38-5)** can be treated with hydroxylamine hydrochloride in heated ethanol to remove the pyrrole-protecting group. Then treatment with methanesulfonyl chloride in the presence of a base such as, for example, pyridine in a solvent such as, for example, dichloromethane at or near ambient temperature supplies compound **(38-6).**

EXAMPLES

[0385] The following examples are merely illustrative, and not limiting to this disclosure in any way.

Example A. Preparation of (E)-N-(3-tert-butyl-5-iodo-4-methoxyphenylcarbamoyl)-3-methoxy acrylamide.

[0386]



Part A. Preparation of 2-tert-butyl-4-nitrophenol.

[0387] To a vigorously stirred solution of 2-tert-butylphenol (10g, 66.6mmol) in heptane (67ml) was added at a fast drip a solution of 70% nitric acid (4.25ml, 66.6mmol) diluted with water (4.25ml). The resulting dark red/brown mixture was stirred vigorously for 2h. The suspended solid was collected by filtration washed with hexane (300mL), water (200mL) and once again with hexane (200mL) to give a cocoa colored powder that was dried to constant mass (4.65g, 35.6%).

Part B. Preparation of 2-tert-butyl-6-iodo-4-nitrophenol.

[0388] To the product from **Part A** (4.5g, 23.05mmol) dissolved in MeOH (120ml) and water (30mL) was added iodine monochloride (1.155ml, 23.05mmol) drop wise over a period of 10min. The mixture was stirred for 2h and diluted into 1L of water and allowed to stand overnight. The solid material was collected by filtration and washed 3x50mL with water and dried under vacuum overnight to give a tan solid (7.14g, 96%).

Part C. Preparation of 1-tert-butyl-3-iodo-2-methoxy-5-nitrobenzene.

[0389] To an ice bath cooled solution of the product from **Part B** (5.5g, 17.13mmol) in MTBE (15ml) in a 50mL pressure vessel was added 2.0M TMS diazomethane (12.85ml, 25.7mmol) followed by drop-wise addition of methanol (1.0mL) resulting in calm bubbling. The vessel was sealed and stirred at room temperature for 16h, cooled and the pressure was released. The solution was partitioned between EtOAc and water. The organic layer was washed with 1.0M HCl, saturated potassium carbonate solution, and saturated NaCl. The organic layer was dried over sodium sulfate, filtered and concentrated to give a red oil that was used without purification (5.4g, 84%).

Part D. Preparation of 3-tert-butyl-5-iodo-4-methoxyaniline.

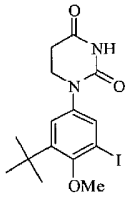
[0390] A mixture of the product from **Part C** (5.80g, 17.31mmol), ammonium chloride (1.389g, 26.0mmol), and iron (4.83g, 87mmol) in THF/MeOH/water (200mL total, 2/2/1) was refluxed for 2h, cooled and filtered through Celite. The filtrate was evaporated and the residue was partitioned between water and EtOAc. The organic layer was washed with saturated brine, dried with sodium sulfate, filtered and evaporated to give a brown oil (5.28g, 100% yield).

Part E. Preparation of (E)-N-(3-tert-butyl-5-iodo-4-methoxyphenylcarbamoyl)-3-methoxy acrylamide.

[0391] To a solution of the product from **Part E** (3.05g, 10mmol) in DMF (50ml) at -20°C under N_2 was added at a fast drip a 0.4M solution in benzene of (E)-3-methoxyacryloyl isocyanate (50.0ml, 20.00mmol, prepared by the method of Santana et al., J. Heterocyclic Chem. 36:293 (1999). The solution was stirred for 15min at -20°C, warmed to room temperature for 45min and diluted into EtOAc. The EtOAc layer was washed 4 x 300mL with water, 2 x 100mL with brine, dried (Na_2SO_4) and concentrated to a brown solid. The residue was triturated in Et_2O/hexane to give a fine powder that was collected by filtration and dried to give a tan powder (2.46g, 57%).

Example B. Preparation of 1-(3-tert-butyl-5-iodo-4-methoxyphenyl)dihydropyrimidine-2,4(1H,3H)-dione.

[0392]

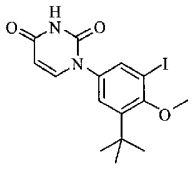


[0393] To a suspension of the product from **Example A** (2.46g, 5.69mmol) in ethanol (50ml) was added a solution of 5.5mL of

H_2SO_4 in 50mL water and the mixture was heated at 110°C for 2.5h to give a clear solution. The solution was cooled and diluted with 50mL of water while stirring to give an off-white solid that was collected by filtration, washed with water and dried (2.06g, 90%).

Example C. Preparation of 1-(3-tert-butyl-5-iodo-4-methoxyphenyl)pyrimidine-2,4(1H,3H)-dione.

[0394]



Part A. Preparation of 2-tert-butyl-4,6-diiodophenol.

[0395] A solution of 2-tert-butylphenol (20.0g, 133mmol) in methanol (266mL) was treated with sodium hydroxide pellets (6.39g, 160mmol). The mixture was stirred until all the sodium hydroxide had dissolved and was then cooled in an ice-salt bath to -2°C. Sodium iodide (15.0g, 100mmol) was added and then 10 % sodium hypochlorite solution (45mL, 73.3mmol) was added drop wise at a rate such that the solution temperature rose no higher than 1.3°C. This sequence of events was repeated (3x) until a total of 60g (400mmol) of sodium iodide had been added and the sodium hypochlorite solution was added until the solution color changed from a light green-yellow color to the color of weak iced tea. This required all but 16mL of the 180mL total sodium hypochlorite solution measured out. With continued cooling at ca. 2°C, a solution of sodium thiosulfate pentahydrate (20g) in water (100mL) was added drop wise over 20min. After addition, the solution was acidified to pH 3 by drop wise addition of concentrated hydrochloric acid (ca. 35mL required of 40mL placed in the addition funnel). The precipitate was collected by filtration and washed with >1 liter of water. The salmon-colored solid was sucked as dry as possible, and dried in a vacuum oven at 50°C for 18h. These procedures afforded the product (49.61g, 93%) as a tan solid.

Part B. Preparation of 1-tert-butyl-3,5-diiodo-2-methoxybenzene.

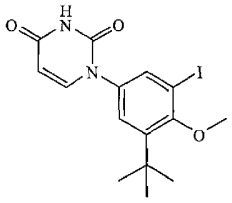
[0396] A solution of the product from **Part A** (20.0g, 49.7mmol) in acetone (140mL) was treated with methyl iodide (3.9mL, 8.83g, 62.2mmol) and 50 % (w/w) sodium hydroxide solution (3.02mL, 4.58g, 57.2mmol) followed by stirring at ambient temperature for 48h. The mixture was concentrated in vacuo to a volume of ca. 50-60mL, followed by dilution with heptane (80mL) and water (50mL). The layers were separated and the organic layer was extracted with saturated sodium chloride solution. Drying (Na_2SO_4) and concentration in vacuo afforded the product (20.59g, 99%) as a light yellow oil.

Part C. Preparation of 1-(3-tert-butyl-5-iodo-4-methoxyphenyl)pyrimidine-2,4(1H,3H)-dione.

[0397] A suspension of the product from **Part B** (12.04g, 28.9mmol), uracil (3.89g, 34.7mmol), N-(2-cyanophenyl)picolinamide (1.29g, 5.79mmol) and tribasic potassium phosphate (12.9g, 60.8mmol) in DMSO (181mL) was degassed by nitrogen sparge for 1 h. The mixture was then treated with copper (I) iodide (551mg, 2.89mmol) and degassing was continued for another 10min. The mixture was then warmed at 60°C for 18h. The mixture was then poured into water (600mL) and acidified to pH 3 by addition of 4N hydrochloric acid solution. The mixture was diluted with ethyl acetate, and the organic layer was extracted with water (3x), saturated ammonium chloride solution (1x) and saturated sodium chloride solution. The solution was dried and treated with (3-mercaptopropyl) silica gel, followed by stirring for 2h. The mixture was filtered and concentrated in vacuo. The solid obtained was triturated with ether-ethyl acetate (>10:1) and collected by filtration and washed with ether. After drying in a vacuum oven at 50°C for 2h, these procedures afforded the product (2.75 g) as a white solid. The mother liquors were concentrated in vacuo to afford an amber solid. This material was chromatographed over a Flash 65 silica gel cartridge, eluting with 20-100 % ethyl acetate in hexanes. These procedures afforded a nearly white solid, which was triturated with ether-hexanes and collected by filtration. After drying in a vacuum oven for 3h, these procedures afforded another 4.31g of the product as a white solid. Total yield: 7.06g (61 %).

Example D. Preparation of 1-(3-*tert*-Butyl-5-iodo-4-methoxyphenyl)pyrimidine-2,4(1H,3H)-dione.

[0398]



Part A. Preparation of 2-*tert*-butyl-4,6-diiodophenol.

[0399] 2-*tert*-Butylphenol (99.95g, 665.36mmol) was dissolved in 1250mL methanol and converted to the corresponding phenoxide with 31.96g (799.0mmol, 1.2equiv.) of sodium hydroxide by stirring the sodium hydroxide pellets at room temperature, and then cooling the reaction mixture in an ice/salt bath. Sodium iodide (299.34g, 1997.07mmol, 3.0equiv.) and 8.3% bleach (1265.83g, 1411.39mmol, 2.1equiv.) were added to the cold reaction solution in four equal portions, the bleach being added while keeping the reaction mixture at <0°C. 500mL of 20% (w/w) sodium thiosulfate solution was added over an 18-minute period, with the temperature rising from -0.6°C to 2.5°C. The pH of the reaction mixture was adjusted to approximately 3 by adding 197.55mL of conc. HCl over a period of 97min with the reaction temperature going from 1.2°C to 4.1°C. The resulting slurry was filtered, and the wet cake washed with ~ 2L of water. The wet cake was left on the Buchner funnel under vacuum overnight (approximately 15h) to yield 289.33g (potency adjusted yield = 254.61g) of the title product.

Part B. Preparation of 1-*tert*-butyl-3,5-diiodo-2-methoxybenzene.

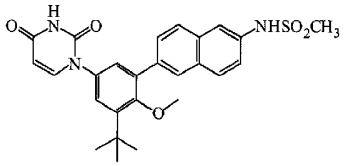
[0400] The product from **Part A** (93%assay, 21.6g, 50mmol) was dissolved in 140mL of acetone. Methyl iodide (4.2mL, 67.5mmol, 1.35equiv.) was added, followed by 50% aqueous sodium hydroxide (5.0g, 62.5mmol, 1.25equiv.). The reaction was stirred overnight, then concentrated to approximately 50-60mL. 80mL of heptanes was added followed by 50mL of water, and the layers were shaken and separated, and the aqueous layer was back extracted with 20mL of heptanes. The organic layers were combined and washed twice with 505mL each of 10% aqueous NaCl to afford 91.1 grams of a heptane solution, which assayed to 19.1g of the title compound.

Part C. Preparation of 1-(3-*tert*-Butyl-5-iodo-4-methoxyphenyl)pyrimidine-2,4(1H,3H)-dione.

[0401] Uracil (33.3g, 297mmol, 1.2equiv.), K_3PO_4 (106g, 500mmol, 2.1equiv.), CuI (4.6g, 24.2mmol, 0.1equiv.), and *N*-(2-cyanophenyl)picolinamide (6.4g, 28.7mmol, 0.12equiv.) were charged to a flask and inerted with argon. The 1-*tert*-butyl-3,5-diiodo-2-methoxybenzene was solvent switched into MeCN, dissolved in 1L DMSO and sparged with argon and added to the solids. The reaction was heated to 60°C for 16h. After cooling, the reaction was diluted with 2L EtOAc and washed with 2.6L water (back extracted with 3 x 1L EtOAc). The combined organic layers were washed with 2 x 1L of 0.25M $(CuOAc)_2$ then 2 x 830mL 15% NH_4Cl then 800mL brine. The organic layer was then concentrated and chased with 1L heptane, then triturated with refluxing 85:15 (v/v) heptane:iPrOAc for 4h. After cooling, the product was collected by filtration and washed with an additional 330mL of 85:15 v/v heptanes:EtOAc to yield after drying 66.9g (70% yield) of the product as a white solid.

Example E. Preparation of *N*-(6-(3-tert-Butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methanesulfonamide.

[0402]



[0403] A solution of 100mL of water and 300mL of THF was sparged with nitrogen and then transferred via canula and nitrogen pressure to a flask containing 19.9965g (49.96mmol) of the product from **Example D,** 20.8234g (59.97mmol, 1.20equivalents) of *N*-(6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-2-yl)methanesulfonamide, and 21.8711g (103.03mmol, 2.06equivalents) of potassium phosphate which had been purged with nitrogen. The resulting solution was again sparged with nitrogen.

[0404] THF (100mL) was sparged with nitrogen and then transferred via canula and nitrogen pressure to a flask containing 462.8mg (0.51mmol, 0.01equivalents) of Pd_2dba_3 and 735.8mg (2.52mmol, 0.05 equivalents) of 1,3,5,7-tetramethyl-6-phenyl-2,4,8-trioxa-6-phosphaadamantane, which had been purged with nitrogen. The resulting solution was again sparged with nitrogen.

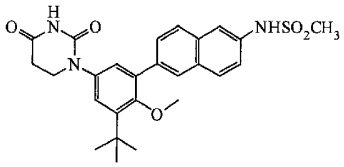
[0405] The initial THF/water solution was transferred via canula and nitrogen pressure to the flask containing the catalyst and ligand in THF. The reaction was warmed to 50°C and stirred overnight under positive nitrogen pressure. A sample of the reaction was taken the following morning. HPLC of the sample showed 0.28 PA% iodouracil starting material, 76.8 PA% product, and 5.2 PA% boronate.

[0406] The reaction was cooled to room temperature and washed, in three portions, with a solution of 5.84g of L-cysteine and 81.4g of sodium chloride in 550mL of water which had been sparged with nitrogen. The THF solution was filtered through a celite pad. The pad was rinsed with 100mL of THF, which was combined with the original THF solution. The THF solution was concentrated on the rotary evaporator to 136g. To the white slurry was added 405mL of ethyl acetate with good agitation. The slurry was filtered after stirring overnight. The wet cake was washed with 2X50mL of ethyl acetate. The solid, an ethyl acetate solvate, was dried in the vacuum oven at 50°C. It weighed 25.49g.

[0407] The solid and 8.7g of 3-mercaptopropyl derivatized silica gel was stirred in 500mL of THF then filtered through a celite pad. The filtrate was concentrated on the rotary evaporator to give 13.08g of white solid. The solid that had been filtered off on the celite pad was extracted with 500mL of THF at 60°C. The THF solution was concentrated to 66g and treated with 206mL of ethyl acetate. The solid which precipitated was filtered and dried, yielding 9.13g of product. This solid was combined with the original solid and slurried in 100mL of 200 proof 3A ethanol. It was filtered and dried in the vacuum oven at 50°C to give 20.74g of product.

Example 1. Preparation of N-(6-(3-tert-butyl-5-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methanesulfonamide (compound IA-L0-2.9).

[0408]



Part A. Preparation of 6-bromo-2-naphthoic acid.

[0409] A solution of methyl 6-bromo-2-naphthoate (7.70g, 29.0mmol) in 2:1 THF:water (150mL) was treated with lithium hydroxide hydrate (2.44g, 58.1mmol) followed by stirring at room temperature for 48h. Concentrated under vacuum, diluted with water and cooled to 0°C. Acidified to pH3 with 4N HCl. Solids were collected by filtration, dissolved in toluene-EtOAc (ca. 2L) and washed with brine. Dried over Na_2SO_4, filtered and concentrated under vacuum. Brown solid was triturated with ether, collected

by filtration, and dried under vacuum to give the title compound as a nearly white solid (5.07g, 70%).

Part B. Preparation of 6-bromonaphthalen-2-amine.

[0410] A solution of the product **Part A** (5.07g, 20.19mmol) and triethylamine (4.22mL, 3.07g, 30.3mmol) in dry DMF (155mL) was treated with the diphenylphosphoroyl azide (6.55mL, 8.34g, 30.3mmol) followed by stirring at room temperature for 3h. The solution was then treated with water (20mL) followed by warming at 100°C for 1h. The solution was cooled and the flask fitted with a short-path distillation head and the DMF removed by distillation under high vacuum. The solid residue was dissolved in EtOAc and washed with saturated sodium bicarbonate solution. Filtered through celite and the filtrate was washed with water (3x) and then with brine. Dried over Na_2SO_4, filtered and concentrated under vacuum to give the title compound as a beige solid (4.48g, 100 %).

Part C. Preparation of benzyl 6-bromonaphthalen-2-ylcarbamate.

[0411] A mixture of the product from **Part B** (1.79g, 8.06mmol) and saturated sodium bicarbonate solution (18mL) in acetone (40mL) at 0 °C was treated drop wise with benzyl chloroformate. The mixture was stirred at 0°C for 1h, and then allowed to gradually warm to room temperature over 18h. The mixture was diluted with EtOAc and water and the layers separated. The organic layer was extracted with water and washed with brine. Dried over Na_2SO_4, filtered and concentrated under vacuum. Purification by silica gel column chromatography eluting with EtOAc/hexanes gave the title compound as a pink solid (1.5g, 52%).

Part D. Preparation of benzyl 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-2-yl carbamate.

[0412] A resealable Schlenk tube containing a solution of the product from **Part C** (1.42g, 3.99mmol), bis(pinacolato)diboron (1.11g, 4.39mmol), and potassium acetate (1.17g, 11.96mmol) in DMF (28mL) was degassed by three freeze-thaw cycles. The solution was treated with 1,1'-bis(diphenyl phosphino)ferrocene palladium (II) chloride dichloromethane complex (98mg, 0.12mmol), followed by degassing by two additional freeze-thaw cycles. The Schlenk tube was then sealed and the mixture warmed at 80°C for 18h. Cooled and diluted with ethyl acetate and water. The mixture was treated with Darco G-60 and then filtered through celite. The filtrate was extracted with water (4x) and saturated sodium chloride solution. Dried over Na_2SO_4, filtered and concentrated under vacuum afforded a light brown oil. Purification by silica gel column chromatography eluting with EtOAc/hexane gave the title compound as a colorless oil (910mg, 57 %).

Part E. Preparation of 2-tert-butyl-4-nitrophenol.

[0413] To a vigorously stirred solution of 2-tert-butylphenol (10g, 66.6mmol) in heptane (67ml) was added at a fast drip a solution of 70% nitric acid (4.25ml, 66.6mmol) diluted with water (4.25ml). The resulting dark red/brown mixture was stirred vigorously for 2h. The suspended solid was collected by filtration washed with hexane (300mL), water (200mL) and once again with hexane (200mL) to give a cocoa colored powder that was dried to constant mass (4.65g, 35.6%).

Part F. Preparation of 2-bromo-6-tert-butyl-4-nitrophenol.

[0414] A solution of the product from **Part E** (1.0g, 5.12mmol) in glacial acetic acid (10.25mL) was treated portion wise with pyridine hydrobromide perbromide (1.80g, 5.63mmol) followed by stirring at room temperature for 2h. Additional pyridinium hydrobromide perbromide (3.6g) was added in two portions and after another 3h of stirring, the reaction was complete. The mixture was poured into ice water, and the mixture treated with a small amount of sodium sulfite. The resulting solid was filtered and dried under vacuum to give the title compound as a brown solid (1.40g, 100 %).

Part G. Preparation of 1-bromo-3-tert-butyl-2-methoxy-5-nitrobenzene.

[0415] A solution of the product from **Part F** (1.40g, 5.11mmol) in 10:1 t-butylmethylether-methanol (25.5mL) was treated with

2.0M trimethylsilyldiazomethane in ether (5.1mL, 10.21mmol), followed by stirring at room temperature for 18h. The mixture was concentrated under vacuum to afford a yellow oil, which was purified by silica gel column chromatography eluting with EtOAc/hexanes to give the title compound as a yellow oil (1.36g, 92 %).

Part H. Preparation of tert-butyl 3-bromo-5-tert-butyl-4-methoxyphenylcarbamate.

[0416] A solution of the product from **Part G** (960mg, 3.33mmol) in methanol (17mL) was treated with 5 % platinum on sulfided carbon (100mg), followed by hydrogenation under balloon pressure for 3h, and then filtered through celite and concentrated under vacuum to afford the 3-bromo-5-tert-butyl-4-methoxyaniline as a yellow oil (860mg, 3.33mmol, 100%). A solution of this material in THF (17mL) was treated with di-tert-butyl dicarbonate (800mg, 3.66mmol) followed by warming at reflux for 2h. Concentration under vacuum afforded a beige solid, which was purified by silica gel column chromatography eluting with EtOAc/hexanes. Solid was triturated with hexanes, collected by filtration, and dried under vacuum to give the title compound as a nearly white solid (890mg, 75 %).

Part I. Preparation of benzyl 6-(3-tert-butyl-5-(tert-butylcarbamoyl)-2-methoxyphenyl) naphthalen-2-yl carbamate.

[0417] Toluene (928ul) and EtOH (928ul) were combined with the product from **Part H** (133mg, 0.37mmol), the product from **Part D** (299mg, 0.74mmol) and 1M sodium carbonate (371ul, 0.37mmol) and de-gassed for 20min with nitrogen. Tetrakis(triphenylphosphine)palladium(0) (8.6mg, 7.4umol) was added and de-gassing continued 5-10min. Heated at 85-90°C for 18h, cooled and concentrated under vacuum. Purification by silica gel column chromatography eluting with EtOAc/hexanes gave the title compound (102mg, 49%).

Part J. Preparation of benzyl 6-(3-tert-butyl-5-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-2-methoxyphenyl)naphthalen-2-ylcarbamate.

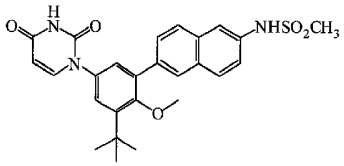
[0418] A solution of the product from **Part I** (100mg, 0.18mmol) in CH_2Cl_2 (1.0ml) was treated with trifluoroacetic acid (0.5ml, 6.5mmol) at room temperature for 1h. Concentrated under vacuum. Dissolved in ethyl acetate, washed with 10% $NaHCO_3$, brine. Dried over Na_2SO_4, filtered and concentrated under vacuum. Dissolved in toluene (1.0ml) and added Et_3N (25ul, 0.18mmol) and acrylic acid (13ul, 0.19mmol) and the mixture was refluxed for 16h. Concentrated under vacuum. Dissolved in acetic acid (1.0ml, 17.5mmol) and added urea (11.9mg, 0.20mmol) and refluxed for 72h. Cooled and poured into ice water, extracted three times with $CHCl_3$, combined extracts, dried over Na_2SO_4, filtered and concentrated under vacuum. Purification by silica gel column chromatography eluting with EtOAc/hexanes gave title compound (57.5mg, 58%).

Part K. Preparation of N-(6-(3-tert-butyl-5-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methanesulfonamide.

[0419] Combined the product from **Part J** (56mg, 0.10mmol) and EtOAc (1.0ml) and added 10% palladium on carbon (10mg). Stirred under a balloon of H_2 gas for 16h. Filtered through Celite and concentrated under vacuum. Dissolved in CH_2Cl_2 (1.0ml), added Et_3N (16ul, 0.115mmol) and methanesulfonyl chloride (8.7ul, 0.112mmol) and stirred at room temperature for 30min. Concentrated under vacuum and purification by silica gel column chromatography eluting with EtOAc/hexanes gave the title compound (10mg, 20%). ^1H NMR (300 MHz, DMSO-*d*6) δ 1.34 - 1.48 (m, 9 H) 2.71 (t, *J*=6.62 Hz, 2 H) 3.08 (s, 3 H) 3.21 (s, 3 H) 3.82 (t, *J*=6.62 Hz, 2 H) 7.26 (s, 2 H) 7.41 (dd, *J*=8.82, 1.84 Hz, 1 H) 7.59 - 7.76 (m, 2 H) 7.89 - 8.04 (m, 3 H) 10.03 (s, 1 H) 10.34 (s, 1 H); MS (ESI+) m/z 496 $(M+H)^+$; (ESI-) *m/z* 494 $(M-H)^-$.

Example 2A. Preparation of N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methanesulfonamide (compound IB-L0-2.3).

[0420]



Part A. Preparation of N-(6-bromonaphthalen-2-yl)methanesulfonamide.

[0421] A solution of the product from **Example 1, Part B** (4.48g, 20.17mmol) in pyridine (100mL) was treated drop wise with methanesulfonyl chloride (1.97mL, 2.89 g, 25.2mmol) followed by stirring at room temperature for 1h. Diluted with toluene and concentrated under vacuum twice. The residue was extracted with EtOAc and washed with water, 1M citric acid and brine. Treated with Darco G-60, dried over Na_2SO_4, filtered through celite and concentrated under vacuum. Solid was triturated with ether-hexane, collected by filtration and dried under vacuum to give the title compound as a faint pink solid (3.32g, 55 %).

Part B. Preparation of N-(6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-2-yl) methanesulfonamide.

[0422] A mixture of the product from **Part A** (1.00g, 3.33mmol), bis(pincolato)diboron (1.27g, 5.00mmol), potassium acetate (0.98 g, 9.99mmol) and Combiphos Pd6 (84mg, 0.17mmol) in toluene (22mL) was heated at reflux for 3h. Cooled and diluted with ethyl acetate and water. The mixture was treated with Darco G-60 and filtered through celite. The filtrate was washed with water and brine. Dried over Na_2SO_4, filtered and concentrated under vacuum. Oil was dissolved in ether and precipitated by addition of hexanes. The product was collected by filtration and washed with hexanes. Evaporation of the filtrate and purification by silica gel column chromatography eluting with EtOAc/hexanes. The title compound from crystallization and chromatography was obtained as a white solid (927mg, 80%).

Part C. Preparation of tert-butyl 3-tert-butyl-4-methoxy-5-(6-(methylsulfonamido) naphthalen-2-yl)phenylcarbamate.

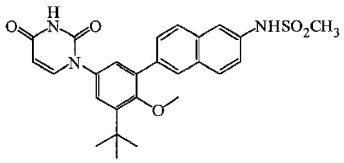
[0423] Combined the product from **Example 1, Part H** (87mg, 0.243mmol), the product from **Part B** (169mg, 0.486mmol), toluene (1.0ml), ethanol (1.0ml) and sodium carbonate (0.243ml, 0.243mmol) in a sealed tube and de-gassed with N_2 gas for 20min. Tetrakis(triphenylphosphine)palladium(0) (5.61mg, 4.86µmol) was added and de-gassing was continued another 5-10 min. Heated at 90-95°C for 16h. Cooled and concentrated under vacuum. Purification by silica gel column chromatography eluting with EtOAc/hexanes gave the title compound (92.2mg, 76 %).

Part D. Preparation of N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methanesulfonamide.

[0424] A solution of the product from **Part C** (90mg, 0.180mmol) in CH_2Cl_2 (2.0ml) was treated with trifluoroacetic acid (1.0ml, 12.98mmol) at room temperature for 1h. Concentrated under vacuum, dissolved residue in EtOAc, washed with 10% $NaHCO_3$, and brine. Dried over Na_2SO_4, filtered and concentrated under vacuum. Dissolved in DMF (1.4ml) and cooled to -25°C and added (E)-3-methoxy-acryloyl isocyanate (0.633ml, 0.361mmol) drop wise while maintaining the temperature below -10°C. Warmed to room temperature and stirred for 2h. Poured into ether, washed with water, and brine. Dried over Na_2SO_4, filtered and concentrated under vacuum. Added a mixture of H_2SO_4 (0.1ml, 1.876mmol), water (1.0ml) and EtOH (1.0ml) and stirred at 100°C 16h. Cooled and concentrated under vacuum. Poured into water, extracted with EtOAc, combined extracts and washed with brine. Dried over Na_2SO_4, filtered and concentrated under vacuum. Purification by silica gel column chromatography eluting with MeOH/$CHCl_3$ gave the title compound (53mg, 59%). ^{1}H NMR (300 MHz DMSO-*d*6) δ 1.42 (s, 9 H) 3.08 (s, 3 H) 3.25 (s, 3 H) 5.65 (d, *J*=7.72 Hz, 1 H) 7.34 (dd, *J*=15.81, 2.57 Hz, 2 H) 7.42 (dd, *J*=8.82, 1.84 Hz, 1 H) 7.65 - 7.76 (m, 2 H) 7.80 (d, *J*=8.09 Hz, 1 H) 7.96 (t, *J*= 8.27 Hz, 2 H) 8.02 (s, 1 H) 10.04 (s, 1 H) 11.41 (s, 1 H); MS (ESI+) *m/z* 494 $(M+H)^+$; (ESI-) *m/z* 492 $(M-H)^-$.

Example 2B. Preparation of N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methanesulfonamide (compound IB-L0-2.3).

[0425]



Part A. Preparation of 2-tert-butyl-6-iodo-4-nitrophenol.

[0426] To the product from **Example 1**, **Part E** (4.5g, 23.05mmol) dissolved in MeOH (120ml) and water (30mL) was added iodine monochloride (1.155ml, 23.05mmol) drop wise over a period of 10min. The mixture was stirred for 2h and diluted into 1L of water and allowed to stand overnight. The solid material was collected by filtration and washed 3 x 50mL with water and dried under vacuum overnight to give a tan solid (7.14g, 96%).

Part B. Preparation of 1-tert-butyl-3-iodo-2-methoxy-5-nitrobenzene.

[0427] To an ice bath cooled solution of the product from **Part A** (5.5g, 17.13mmol) in MTBE (15ml) in a 50mL pressure vessel was added 2.0M trimethylsilyl diazomethane (12.85ml, 25.7mmol) followed by drop-wise addition of methanol (1.0mL) resulting in calm bubbling. The vessel was sealed and stirred at room temperature for 16h, cooled and the pressure was released. The solution was partitioned between EtOAc and water. The organic layer was washed with 1.0M HCl, saturated potassium carbonate solution, and saturated NaCl. The organic layer was dried over sodium sulfate, filtered and concentrated to give a red oil that was used without purification (5.4g, 84%).

Part C. Preparation of 3-tert-butyl-5-iodo-4-methoxyaniline.

[0428] A mixture of the product from **Part B** (5.80g, 17.31mmol), ammonium chloride (1.389g, 26.0mmol), and iron (4.83g, 87mmol) in THF/MeOH/water (200mL total, 2/2/1) was refluxed for 2h, cooled and filtered through Celite. The filtrate was evaporated and the residue was partitioned between water and EtOAc. The organic layer was washed with saturated brine, dried with sodium sulfate, filtered and evaporated to give a brown oil (5.28g, 100% yield).

Part D. Preparation of (E)-N-(3-tert-butyl-5-iodo-4-methoxyphenylcarbamoyl)-3-methoxy acrylamide.

[0429] To a solution of the product from **Part C** (3.05g, 10mmol) in DMF (50ml) at -20 °C under N_2 was added at a fast drip a 0.4M solution in benzene of (E)-3-methoxyacryloyl isocyanate (50.0ml, 20.00mmol, prepared by the method of Santana et al., J. Heterocyclic. Chem. 36:293 (1999). The solution was stirred for 15min at -20 °C, warmed to room temperature for 45min and diluted with EtOAc. The organic was washed with water and brine. Dried over Na_2SO_4, filtered and concentrated to a brown solid. The residue was triturated in Et_2O/hexane to give a fine powder that was collected by filtration and dried under vacuum to give the title compound as a tan powder (2.46g, 57%).

Part E. Preparation of 1-(3-tert-butyl-5-iodo-4-methoxyphenyl)dihydropyrimidine-2,4(1H,3H)-dione.

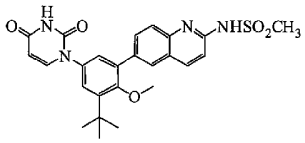
[0430] To a suspension of the product from **Part D** (2.46g, 5.69mmol) in ethanol (50ml) was added a solution of 5.5mL of H_2SO_4 in 50mL water and the mixture was heated at 110°C for 2.5h to give a clear solution. Cooled and diluted with 50mL of water while stirring to give an off-white solid that was collected by filtration, washed with water and dried under vacuum to give the title compound (2.06g, 90%).

Part F. Preparation of N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methanesulfonamide.

[0431] In a microwave tube, the product from **Part E** (104mg, 0.26mmol), the product from **Example 2A, Part B** (108mg, 0.31mmol), and 1.0M sodium carbonate solution (312µL, 0.31mmol) in 1:1 ethanol-toluene (1.7mL) was degassed by nitrogen sparge for 15min. 1,1'-Bis(diphenylphosphino) ferrocene palladium (II) chloride dichloromethane complex (9mg, 0.011mmol) was added, and degassing was continued for another 5min. The tube was sealed and heated in the microwave at 100°C for 1h. Diluted with dichloromethane and washed with 1M citric acid solution and brine. The organic layer was then stirred with (3-mercaptopropyl) silica gel for 1h. Filtered through celite and concentrated under vacuum. Triturated with ether, methanol, and then again with ether to give the title compound as a nearly white solid (32mg, 25 %). ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.41 (d, J=1.84 Hz, 1 H) 10.04 (s, 1 H) 8.03 (s, 1 H) 7.96 (t, J=8.09 Hz, 2 H) 7.80 (d, J=8.09 Hz, 1 H) 7.63 - 7.79 (m, 2 H) 7.35 - 7.45 (m, 1 H) 7.37 (d, J=2.57 Hz, 1 H) 7.32 (d, J=2.57 Hz, 1 H) 5.65 (dd, J=8.09, 2.21 Hz, 1 H) 3.25 (s, 3 H) 3.09 (s, 3 H) 1.43 (s, 9 H). MS (+ESI) m/z (rel abundance): 494 (100, M+H), 511 (90, M+NH4), 987 (20, 2M+H), 1009 (8, 2M+Na).

Example 3. Preparation of N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)quinolin-2-yl)methanesulfonamide (compound IB-L0-2.5).

[0432]



Part A. Preparation of (E)-N-(4-bromophenyl)-3-methoxyacrylamide.

[0433] Combined 4-bromoaniline (285mg, 1.659mmol), CH_2Cl_2 (2.0ml) and pyridine (0.25ml, 3.09mmol) and slowly added (E)-3-methoxyacryloyl chloride (200mg, 1.659mmol) and stirred at room temperature for 2h. The resulting yellow solid was filtered off and washed with water. The solid was dried under vacuum to give the title compound (406mg, 96 %).

Part B. Preparation of 6-Bromoquinolin-2(1H)-one.

[0434] The product from **Part A** (395mg, 1.542mmol) was added in portions to H_2SO_4 (4.5ml). Stirred for 3h at room temperature, poured onto crushed ice. Solid filtered, washed with water and dried under vacuum to give the title compound (203mg, 59 %).

Part C. Preparation of 6-bromo-2-chloroquinoline.

[0435] To phosphorus oxychloride (2.5ml, 26.8mmol) was added, in portions, the product from **Part B** (200mg, 0.893mmol). Refluxed for 1h, cooled to room temperature and poured onto crushed ice. Extracted with $CHCl_3$, extracts combined, dried overmgSO_4, filtered and concentrated under vacuum to give the title compound (173mg, 80%).

Part D. Preparation of 6-bromo-2-aminoquinoline.

[0436] The product from **Part C** (173mg, 0.713mmol), acetamide (843mg, 14.27mmol) and potassium carbonate (493mg, 3.57mmol) were combined and heated at 200 °C for 2h. Cooled to room temperature, whereupon it solidified. Dissolved in a mixture of $CHCl_3$ and water. Aqueous layer was extracted twice more with $CHCl_3$, extracts were combined, washed with brine, dried over Na_2SO_4, filtered and concentrated under vacuum. Purification by silica gel column chromatography eluting with MeOH/$CHCl_3$ gave title compound (92mg, 58 %).

Part E. Preparation of N-(6-bromoquinolin-2-yl)-N-(methylsulfonyl)methanesulfonamide.

[0437] Combined the product from **Part D** (90mg, 0.403mmol) and CH_2Cl_2 (2.0ml) and added triethylamine (0.062ml, 0.444mmol) and methanesulfonyl chloride (0.035ml, 0.444mmol). Stirred at room temperature 16h. Added triethylamine (0.062ml, 0.444mmol) and methanesulfonyl chloride (0.035ml, 0.444mmol) and stirred at room temperature for 1h. Diluted with EtOAc, washed with 10% citric acid, 10% $NaHCO_3$ and brine. Dried over Na_2SO_4, filtered and concentrated under vacuum. Dissolved in EtOAc and poured into excess hexane. Solid collected by filtration to give the title compound (94mg, 61%).

Part F. Preparation of N-(methylsulfonyl)-N-(6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) quinolin-2-yl)methanesulfonamide.

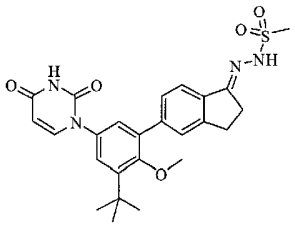
[0438] Combined the product from **Part E** (94mg, 0.248mmol), bis(pinacolato)diboron (94mg, 0.372mmol), potassium acetate (73.0mg, 0.744mmol), Combi-Phos®PD6 (6.22mg, 0.012mmol) and toluene (1.5ml) and refluxed 18h. Cooled to room temperature, diluted with EtOAc and water, filtered through Celite, separated the phases, washed the organic phase with brine. Dried over Na_2SO_4, filtered and concentrated under vacuum. Purification by silica gel column chromatography eluting with EtOAc/hexanes gave title compound (67mg, 63%).

Part G. Preparation of N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)quinolin-2-yl)methanesulfonamide.

[0439] Combined in a microwave tube the product from **Example 2B, Part E** (27mg, 0.067mmol), the product from **Part F** (37.4mg, 0.088mmol), ethanol (1.0ml), toluene (1.0ml) and 1M sodium carbonate (0.067ml, 0.067mmol) and the solution was degassed using N_2 gas for 20min. Tetrakis- (triphenylphosphine)palladium(0) (1.559mg, 1.349µmol) was added and the solution was degassed an additional 5min. The tube was sealed and heated in the microwave at 100°C for 45min. Cooled solution diluted with 1:1 EtOAc:water and filtered through Celite. Aqueous layer was extracted twice more with EtOAc, combined organic extracts and washed with brine. Dried over Na_2SO_4, filtered and concentrated under vacuum. Purification by silica gel column chromatography eluting with MeOH/$CHCl_3$ gave title compound (13.7mg, 41%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.45 (s, 9 H) 3.18 (s, 3 H) 3.30 (s, 3 H) 5.83 (dd, *J*=7.91, 2.02 Hz, 1 H) 6.99 (d, *J*= 8.82 Hz, 1 H) 7.21 (d, *J*=2.57 Hz, 1 H) 7.36 (d, *J*=7.72 Hz, 1 H) 7.52 (d, *J*=8.46 Hz, 1 H) 7.82 - 7.91 (m, 2 H) 7.98 (d, *J*=9.19 Hz, 1 H) 8.29 (s, 1 H); MS (ESI+) *m/z* 495 $(M+H)^+$; (ESI-) *m/z* 493 $(M-H)^-$.

Example 4. Preparation of (E)-N'-(5-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)-2,3-dihydro-1H-inden-1-ylidene)methanesulfonohydrazide (compound IB-L0-2.4).

[0440]



Part A. Preparation of 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-one.

[0441] A mixture of 5-bromo-2,3-dihydro-1H-inden-1-one (2.50g, 11.85mmol), bis(pinacolato) diboron (3.61g, 14.21mmol), potassium acetate (3.49g, 35.5mmol) and Combiphos Pd6 (178mg, 0.36mmol) in toluene (60mL) was heated at reflux for 8h. Cooled, diluted with EtOAc and extracted with water (2 x) and washed with brine. Dried over Na_2SO_4 and stirred for 1h with (3-mercaptopropyl) silica gel. Filtered and concentrated under vacuum to afford a yellow solid. Purification by silica gel column

chromatography eluting with EtOAc/hexanes gave a yellow solid. Triturated with cold hexanes, filtered and dried under vacuum to give the title compound as a fine nearly white solid (1.99g, 65%). A second crop of crystals (140mg) was obtained from the mother liquors, bringing the yield to 70%.

Part B. Preparation of 1-(3-tert-butyl-4-methoxy-5-(1-oxo-2,3-dihydro-1H-inden-5-yl)phenyl) pyrimidine-2,4(1H,3H)-dione.

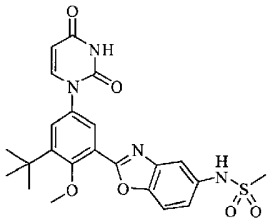
[0442] In a microwave tube, a suspension of the product from **Example 2B, Part E** (130mg, 0.33mmol), the product from **Part A** (101mg, 0.39mmol), and 1.0M sodium carbonate solution (390µL, 0.39mmol) in 1:1 ethanol-toluene (1.20mL) was degassed by nitrogen sparge for 15min. The mixture was treated with 1,1'-bis(diphenylphosphino)ferrocene palladium (II) chloride dichloromethane complex (13mg, 0.016mmol) and degassing was continued for another 5min and heated at 100°C in the microwave for 1h. Cooled, diluted with EtOAc and extracted with 1M citric acid solution and brine. The organic layer was then stirred with (3-mercaptopropyl) silica gel for 1h. Filtered and concentrated under vacuum. Purification by silica gel column chromatography eluting with EtOAc/hexanes gave the title compound as a white solid (80mg, 61 %).

Part C. Preparation of (E)-N'-(5-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)-2,3-dihydro-1H-inden-1-ylidene)methanesulfonohydrazide.

[0443] A suspension of the product from **Part B** (77mg, 0.19mmol) and methanesulfonylhydrazide (22mg, 0.20mmol) in 3:1 THF:MeOH (1.9mL) was warmed at 60°C for 24h. The mixture was concentrated under vacuum and the residue was purified by silica gel column chromatography eluting with EtOAc/hexanes to give the title compound as a white solid (62mg, 66 %). ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.40 (d, J=1.84 Hz, 1 H) 9.94 (s, 1 H) 7.76 (dd, J=13.97, 8.09 Hz, 2 H) 7.52 - 7.59 (m, 1 H) 7.51 (d, J=8.46 Hz, 1 H) 7.11 - 7.40 (m, 2 H) 3.28 (s, 3 H) 2.96 - 3.19 (m, 5 H), 2.85 (m, 2 H), 1.40 (s, 9 H). MS (+ESI) m/z (rel abundance): 497 (100, M+H), 1015 (5, 2M+Na).

Example 5. Preparation of N-(2-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)benzo[d]oxazol-5-yl)methanesulfonamide (compound IB-L0-2.6).

[0444]



Part A. Preparation of methyl 3-tert-butyl-2-hydroxy-5-nitrobenzoate.

[0445] Methyl 3,5-di-tert-butyl-2-hydroxybenzoate (28.66g, 108.4mmol) was dissolved with stirring in 430mL glacial acetic acid and the resulting mixture was treated drop wise with fuming nitric acid (90%, 179.26mL). When the addition was complete, the resulting mixture was stirred for 2.5h. The reaction mixture was poured into a 2.0L of crushed ice and allowed to stand 30min. Afterwards, 1.0L of water was added and the ice water mixture was allowed to melt. The mixture was then filtered, washed with water and dried to provide the title compound (24.57g, 89%).

Part B. Preparation of methyl 3-tert-butyl-2-methoxy-5-nitrobenzoate.

[0446] Methyl 3-tert-butyl-2-hydroxy-5-nitrobenzoate (11.41g, 45.0mmol), potassium carbonate(9.34g, 67.6mmol), acetone (200mL), and dimethyl sulfate (6.46g, 67.6mmol) were added together. The resultant mixture was then heated to reflux for 16h. The mixture was then filtered and the solid was washed with ethyl acetate. The resulting organic liquid was then concentrated

under vacuum to an oil and redissolved in ethyl acetate (600mL). The organic solution was then washed with water, dried, filtered and concentrated under vacuum to an oil that was then subjected to purification via column chromatography (gradient of 5% to 40% EtOAc/Hexanes) to yield the title compound as an oil (10.42, 87%).

Part C. Preparation of methyl 5-amino-3-tert-butyl-2-methoxybenzoate.

[0447] Methyl 3-tert-butyl-2-methoxy-5-nitrobenzoate (10.42g, 39.0mmol), iron powder (325mesh, 10.89g, 195mmol), ammonium chloride (3.13g, 58.5mmol), water (30mL), and methanol (150mL) were added together. The resultant mixture was then refluxed for 1h. The mixture was then cooled to room temperature, filtered through celite, and the celite washed with methanol. The filtrate was then concentrated under vacuum and dissolved in ethyl acetate (600mL). The resultant solution was then washed with water and brine. The organic extract was then dried, filtered and concentrated under vacuum to yield the title compound as an oil (9.25g, 100%).

Part D. Preparation of (E)-methyl 3-tert-butyl-2-methoxy-5-(3-(3-methoxyacryloyl)ureido) benzoate.

[0448] The product obtained as described in **Part C** (2.0g, 8.43mmol) was dissolved in 30mL of N,N-dimethylacetamide and cooled to -25°C. A 0.5Molar solution of E-3-methoxyacryloyl isocyanate in benzene (21.9mL, 10.96mmol) was added drop wise and the resulting solution was stirred at ambient temperature for 4h, and then poured into water. The product was extracted into dichloromethane, washed with brine, dried over sodium sulfate, filtered and evaporated under vacuum to give 100% yield.

Part E. Preparation of methyl 3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxybenzoate.

[0449] The product from **Part D** (3.1g, 8.51mmol) was dissolved in ethanol (60mL). Sulfuric acid (6mL) was added to water (60mL) then this solution was added in one portion to the ethanol. The heterogeneous mixture was heated at 100°C for 3h. The ethanol was removed under vacuum, and then the aqueous solution was extracted with dichloromethane and evaporated to dryness. This residue was purified by flash chromatography, eluting with 1% methanol/dichloromethane to yield 1.23g (44%).

Part F. Preparation of 3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxybenzoic acid.

[0450] The product from **Part E** (1.23g, 3.7mmol) was taken up in ethanol (5mL) and 1Molar sodium hydroxide solution (10mL) and stirred at ambient temperature for 18h. The solution was diluted with 1M HCl and the resulting solid was filtered and dried to give 0.945 g (80%).

Part G. Preparation of 3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxy benzaldehyde.

[0451] The product from **Part F** (0.945g, 2.97mmol) was taken up in thionyl chloride (4.5mL) and the mixture was heated at 80°C for 40min. After evaporation to dryness, the acid chloride was dissolved in dry THF (8mL) and cooled to -78°C. A 1Molar solution of lithium tri-tert-butoxyaluminum hydride in THF (3.0mL, 3.0mmol) was added drop wise. After 45min the cold reaction was quenched with 1M HCl (5mL), extracted into ethyl acetate, and purified by flash column, eluting with dichloromethane followed by 1% methanol/dichloromethane to give 0.635 g (71%).

Part H. Preparation of 1-(3-tert-butyl-4-methoxy-5-(5-nitrobenzo[d]oxazol-2-yl)phenyl) pyrimidine-2,4(1 H,3 H)-dione.

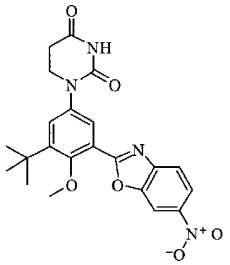
[0452] The product from **Part G** (400mg, 1.323mmol), 2-amino-4-nitrophenol (204mg, 1.323mmol), Charcoal (Darco KB, 191mg, 15.88mmol) and toluene (50mL) were added to a flask and the mixture was heated to 120°C, and stirred open to the air for 48h. Filtered through Celite and concentrated under vacuum. Purification by silica gel column chromatography eluting with CH_2Cl_2/MeOH gave the title compound (300mg, 52%).

Part I. Preparation of N-(2-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)benzo[d]oxazol-5-yl)methanesulfonamide.

[0453] To the product from **Part H** (300mg, 0.687mmol), iron (192mg, 3.44mmol), and ammonium chloride (55mg, 1.031mmol) was added to a mixture of THF (155mL), EtOH (155mL) and water (4.5mL). The resultant solution was heated to 90°C for 45min, and cooled. Filtered through Celit, washed with ethanol, and concentrated under vacuum. The solid was dissolved in ethyl acetate, and washed with water. Dried over Na_2SO_4, filtered and concentrated under vacuum. Purification by silica gel column chromatography eluting with CH_2Cl_2/MeOH provided the aniline. The solid (75mg, 0.185mmol) was dissolved in CH_2Cl_2 (5mL), and pyridine (0.045mL, 0.554mmol) and methanesulfonyl chloride (0.025mL, 0.323mmol) were added and stirred at room temperature for 16h. CH_2Cl_2 was added followed by washing with a 1N HCl. Dried over Na_2SO_4, filtered and concentrated under vacuum. Purification by silica gel column chromatography eluting with CH_2Cl_2/MeOH provided the title compound as a solid (9.8mg, 3%, two steps). 1H NMR (300MHz, DMSO-d6): δ 11.46 (s,1H), 9.85 (s,1H), 7.91 (d, J=2.2Hz, 1H), 7.81 (dd, J=9.9,8.8Hz, 2H), 7.68 (d, J=2.2Hz, 1H), 7.56 (d, J=2.6Hz, 1H), 7.33 (dd, J=8.8,1.8Hz, 1H), 5.68 (d, J=7.7Hz, 1H), 3.64 (s, 3H), 3.00 (s, 3H), 1.42 (s, 9H). MS: m/z 485 (M+H)+.

Example 6. Preparation of 1-(3-tert-butyl-4-methoxy-5-(6-nitrobenzo[d]oxazol-2-yl)phenyl) dihydropyrimidine-2,4(1H,3H)-dione (compound IA-L0-2.6).

[0454]



Part A. Preparation of 3-(3-tert-butyl-4-methoxy-5-(methoxycarbonyl)phenylamino) propanoic acid.

[0455] The product from **Example 5, Part C** (16.44g, 69.3mmol) was dissolved in toluene (200mL). This mixture was heated to reflux and acrylic acid added over time (1mL of acrylic acid added every 3h, 5.23mL total, 76.2mmol). The mixture was then refluxed for 24h. The mixture was then cooled and concentrated under vacuum to dryness to yield an oil as the crude title compound that was used directly in the next reaction.

Part B. Preparation of methyl 3-tert-butyl-5-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-2-methoxybenzoate.

[0456] The product from **Part A** (21.43g, 69.3mmol), urea (10.4g, 173mmol) and acetic acid (glacial, 200mL) were added together. The mixture was then heated to 120°C for 18.5h followed by concentration under vacuum to dryness to an oil. To this oil was added methanol (13mL), and ethyl acetate (350mL). The resultant mixture was allowed to stand for 24-48h whereby a precipitate formed. The resulting solid was filtered off and washed with a small amount of methanol (10mL) and then air dried to yield the title compound as a solid (15.26g, 66%).

Part C. Preparation of 3-tert-butyl-5-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-2-methoxy benzoic acid.

[0457] The product from **Part B** (4.52g, 13.52mmol), methanol (70mL), and tetrahydrofuran (70mL) were added together. The mixture was then stirred vigorously until a homogenous solution resulted. Once homogenous, a solution of aqueous sodium hydroxide (1.0M, 68mL) was added. The mixture was then stirred for 12h, the mixture was then concentrated under vacuum to remove the organic solvent, followed by the addition of aqueous hydrochloric acid (1.0M, 80mL) that resulted in solid formation. The mixture was then concentrated under vacuum. To this material was added hydrochloric acid (12M, 100mL) and the resultant material heated to 100°C for 1.5h. The reaction was then cooled and water added. The resulting solid was filtered, washed with

water, and dried to yield the title compound as a solid (3.55g, 82%).

Part D. Preparation of 3-tert-butyl-5-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-2-methoxy benzaldehyde.

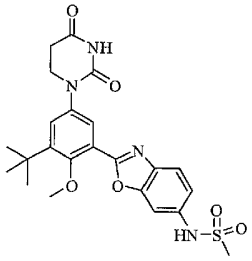
[0458] The product obtained in **Part C** (4.07g, 12.71mmol) and thionyl chloride (40.82mL, 559mmol) were combined and the mixture was refluxed for 2h, followed by concentration under vacuum to provide a light yellow colored solid product. The solid was dissolved in tetrahydrofuran (125mL), the solution cooled to -78°C and $LiAl(OtBu)_3$ (1M, 14mL) was added slowly over 10min while maintaining the temperature at -78°C. The mixture was stirred at 78°C for 2h. The reaction was quenched with hydrochloric acid (aq., 1M, 25mL) at -78°C. The mixture was warmed to room temperature and ethyl acetate was added. The layers were separated and the aqueous layer was washed with ethyl acetate. The organic extracts were combined and washed with half saturated sodium bicarbonate solution. The organic layer was dried, filtered and concentrated under vacuum to yield a solid as the title compound (3.73g, 96%).

Part E. Preparation of 1-(3-tert-butyl-4-methoxy-5-(6-nitrobenzo[d]oxazol-2-yl)phenyl)dihydro pyrimidine-2,4(1H,3H)-dione.

[0459] A mixture of the product from **Part D** (75mg, 0.246mmol), 2-amino-5-nitrophenol (38mg, 0.0246mmol) and Darco KB charcoal (excess) was refluxed in toluene (10mL) for 24h under exposure to atmospheric of oxygen. Cooled, filtered and purified by reverse phase HPLC chromatography eluting with a 40-100% gradient of acetonitrile in water (0.1% TFA) to provide the title compound as a solid (96mg, 64%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.42 (s, 9 H) 2.74 (t, J=6.80 Hz, 2 H) 3.66 (s, 3 H) 3.82 - 3.88 (m, 2 H) 7.56 (d, J=2.57 Hz, 1 H) 7.91 (d, J=2.57 Hz, 1 H) 8.09 (d, J=8.82 Hz, 1 H) 8.37 (dd, J=8.82, 2.21 Hz, 1 H) 8.84 (d, J=2.21 Hz, 1 H) 10.44 (s, 1 H). MS ESI+ (439) (M+H)+.

Example 7. Preparation of N-(2-(3-tert-butyl-5-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-2-methoxyphenyl)benzo[d]oxazol-6-yl)methanesulfonamide (compound IA-L0-2.5).

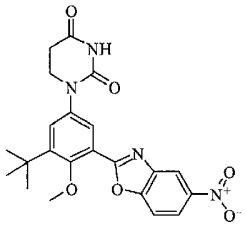
[0460]



[0461] The product from **Example 6** (96mg. 0.219mmol) was reacted a iron (0.614g, 1.10mmol), and ammonium chloride (0.176g, 0.329mmol) in the presence of a mixture of tetrahydrofuran (5mL), ethanol (5mL) and water (3mL). The slurry was heated to 90°C for 45min, cooled to ambient temperature. Filtered through a pad of celite (10g), washed with ethanol (20mL), and the filtrate was concentrated under vacuum to a solid. The resulting solid was dissolved in ethyl acetate and washed with water. Dried over Na_2SO_4, filtered and concentrated under vacuum to a yellow solid, providing the corresponding aniline. The solid was dissolved in dichloromethane (10mL), pyridine (0.670mL, 0.657mmol) and methanesulfonyl chloride (0.221mL, 0.329mmol) were added and the solution stirred at room temperature 16h. CH_2Cl_2 was added followed by washing with a 1N aq. HCl solution. Dried over Na_2SO_4, filtered and concentrated under vacuum. Purification by silica gel column chromatography eluting with 98:2 CH_2Cl_2:MeOH gave the title compound as a solid (25mg, 21%, two steps). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.41 (s, 9 H) 2.73 (t, J=6.62 Hz, 2 H) 3.06 (s, 3 H) 3.61 (s, 3 H) 3.83 (t, J=6.62 Hz, 2 H) 7.28 (dd, J=8.46, 1.84 Hz, 1 H) 7.48 (d, J=2.57 Hz, 1 H) 7.65 (d, J=1.84 Hz, 1 H) 7.80 (d, J=1.47 Hz, 1 H) 7.82 (d, J=4.04 Hz, 1 H) 10.03 (s, 1 H) 10.41 (s, 1 H). MS ESI+ (487) (M+H)+.

Example 8. Preparation of 1-(3-tert-butyl-4-methoxy-5-(5-nitrobenzo[d]oxazol-2-yl)phenyl) dihydropyrimidine-2,4(1H,3H)-dione (compound IA-L0-2.7).

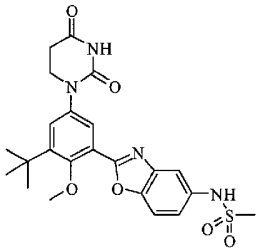
[0462]



[0463] The product from **Example 6, Part D** (150mg, 0.493mmol) was reacted with 2-amino-4-nitrophenol (76mg, 0.493mmol) according to the procedures from **Example 6, Part E** to provide the title compound as a solid (70mg, 32%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.42 (s, 9 H) 2.74 (t, J=6.80 Hz, 2 H) 3.65 (s, 3 H) 3.85 (t, J=6.62 Hz, 2 H) 7.55 (d, J=2.57 Hz, 1 H) 7.89 (d, J=2.94 Hz, 1 H) 8.12 (d, J=8.82 Hz, 1 H) 8.40 (dd, J=9.01, 2.39 Hz, 1 H) 8.76 (d, J=2.21 Hz, 1 H) 10.43 (s, 1 H). MS ESI+ (439) (M+H)+.

Example 9. Preparation of N-(2-(3-tert-butyl-5-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-2-methoxyphenyl)benzo[d]oxazol-5-yl)methanesulfonamide (compound IA-L0-2.8).

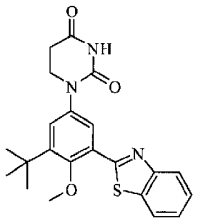
[0464]



[0465] The product from **Example 8** (65mg, 0.148mmol) was reacted according to the procedures from **Example 7** to provide the title compound as a solid (42mg, 44%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.41 (s, 9 H) 2.73 (t, J=6.43 Hz, 2 H) 3.01 (s, 3 H) 3.60 (s, 3 H) 3.83 (t, J=6.43 Hz, 2 H) 7.31 (dd, J=8.64, 2.02 Hz, 1 H) 7.49 (d, J=2.94 Hz, 1 H) 7.56 (d, J=2.21 Hz, 1 H) 7.67 (d, J=2.21 Hz, 1 H) 7.81 (s, 1 H) 9.82 (s, 1 H) 10.41 (s, 1 H). MS ESI+ (487) (M+H)+.

Example 10. Preparation of 1-(3-(benzo[d]thiazol-2-yl)-5-tert-butyl-4-methoxyphenyl)dihydro pyrimidine-2,4(1H,3H)-dione (compound IA-L0-2.3).

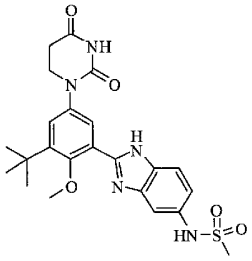
[0466]



[0467] The product from **Example 6, Part D** (75mg, 0.246mmol) was reacted with 2-aminobenzene thiol (0.026mL, 0.246mmol) according to the procedures from **Example 6, Part E** to provide the title compound as a solid (25mg, 25%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.44 (s, 9 H) 2.73 (t, J=6.43 Hz, 2 H) 3.62 (s, 3 H) 3.84 (t, J=6.62 Hz, 2 H) 7.46 (d, J=2.57 Hz, 1 H) 7.48 - 7.60 (m, 2 H) 7.86 (d, J=2.57 Hz, 1 H) 8.13 (dd, J=17.28, 7.72 Hz, 2 H) 10.40 (s, 1 H). MS ESI+ (410) (M+H)+.

Example 11. Preparation of N-(2-(3-tert-butyl-5-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-2-methoxyphenyl)-1H-benzo[d]imidazol-5-yl)methanesulfonamide (compound IA-L0-2.1).

[0468]



Part A. Preparation of N-(3,4-dinitrophenyl)methanesulfonamide.

[0469] A mixture of 3,4-dinitroaniline (5.27g, 28.8mmol), methanesulfonyl chloride (3.36mL, 43.1mmol) and pyridine (5.82mL, 71.9mmol) in CH_2Cl_2 (100mL) was stirred for 24h. Mixture was concentrated under vacuum to provide a crude semi-solid title compound that was used without further purification.

Part B. Preparation of N-(3,4-diaminophenyl)methanesulfonamide.

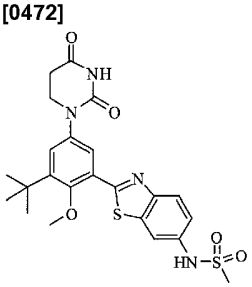
[0470] The product from **Part A** (7.51g, 28.8mmol) was reacted with iron (16g, 288mmol) and NH_4Cl (3.84g, 71.9mmol) in refluxing CH_3OH (100mL) and water (20mL) for 2 h. Filtered through celite and concentrated under vacuum. Purification by silica gel column chromatography eluting with MeOH/CH_2Cl_2 provided the title compound as a dark semi-solid (0.5g, 8%).

Part C. Preparation of N-(2-(3-tert-butyl-5-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-2-methoxy phenyl)-1H-benzo[d]imidazol-5-yl)methanesulfonamide.

[0471] A mixture of the product from **Example 6, Part D** (200mg, 0.657mmol) was reacted with the product from **Part B** (132mg, 0.657mmol) according to the procedures from **Example 6, Part E** to provide the title compound as a solid (112mg, 34%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.43 (s, 9 H) 2.72 (t, J=6.62 Hz, 2 H) 2.93 (s, 3 H) 3.44 (s, 3 H) 3.82 (t, J=6.43 Hz, 2 H) 7.07 - 7.14 (m, 1 H) 7.38 (d, J=2.57 Hz, 1 H) 7.48 - 7.64 (m, 2 H) 7.72 (d, J=2.57 Hz, 1 H) 9.57 (s, 1 H) 10.38 (s, 1 H) 12.55 (s, 1 H). MS ESI+ (486) (M+H)+.

Example 12. Preparation of N-(2-(3-tert-butyl-5-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-2-methoxyphenyl)benzo[d]thiazol-6-yl)methanesulfonamide (compound IA-L0-2.2).

[0472]



Part A. Preparation of N-(3-chloro-4-nitrophenyl)methanesulfonamide.

[0473] A mixture of 3-chloro-4-nitroaniline (4.85g, 28.1mmol), methanesulfonyl chloride (3.29mL, 42.2mmol) and pyridine (6.82mL, 84mmol) in THF (100mL) was stirred for 24h. Poured in 1M HCl (500mL). The resulting precipitate was filtered and air-dried to provide the title compound as a solid (7.03g, 100%).

Part B. Preparation of N-(3-(4-methoxybenzylthio)-4-nitrophenyl)methanesulfonamide.

[0474] A mixture of the product from **Part A** (7.0g, 27.9mmol), (4-methoxyphenyl)methanethiol (3.89mL, 27.9mmol) and K_2CO_3 (11.58g, 84mmol) in DMF was heated at 100°C for 12h. Cooled and poured into 1M HCl (800mL). The resulting precipitate was filtered and air-dried to provide the title compound as a yellow solid (6.98g, 68%).

Part C. Preparation of N-(4-amino-3-(4-methoxybenzylthio)phenyl)methanesulfonamide.

[0475] The product from **Part B** (6.98g, 19.0mmol) was reacted according to the procedures from **Example 11, Part B** to provide the title compound as a yellow semi-solid (4.44 g, 69%).

Part D. Preparation of N,N'-(3,3'-disulfanediylbis(4-amino-3,1-phenylene))dimethane-sulfonamide.

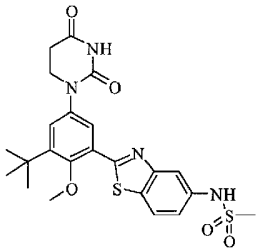
[0476] The product from **Part C** (708mg, 2.09mmol) was reacted with mercuric (II) acetate (667mg, 2.09mmol), anisole (0.457mL, 4.18mmol) and TFA (10mL) at 0°C for 45min. Concentrated under vacuum and dissolved in MeOH. Hydrogen sulfide gas was bubbled into solution for 1h followed by filtration and concentration under vacuum. Purification by silica gel chromatography eluting with EtOAc/hexane gave the title compound as a yellowish solid (340mg, 75%).

Part E. Preparation of N-(2-(3-tert-butyl-5-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-2-methoxyphenyl)benzo[d]thiazol-6-yl)methanesulfonamide.

[0477] The product from **Part D** (100mg, 0.23mmol) was reacted with the product from **Example 6, Part D** (140mg, 0.46mmol), triphenylphosphine (60.4mg, 0.23mmol) and 4-methylbenzene- sulfonic acid (0.0054mL, 0.046mmol) in refluxing toluene for 3h. Concentrated under vacuum and purified by reverse phase HPLC chromatography eluting a 40-100% gradient of acetonitrile in water (0.1% TFA) to give the title compound as a solid (99mg, 43%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.43 (s, 9 H) 2.73 (t, J=6.62 Hz, 2 H) 3.07 (s, 3 H) 3.63 (s, 3 H) 3.83 (t, J=6.62 Hz, 2 H) 7.39 (dd, J=8.82, 2.21 Hz, 1 H) 7.45 (d, J=2.57 Hz, 1 H) 7.83 (d, J=2.57 Hz, 1 H) 7.95 (d, J=2.21 Hz, 1 H) 8.05 (d, J=8.82 Hz, 1 H) 10.03 (s, 1 H) 10.39 (s, 1 H). MS ESI+ (503) (M+H)+.

Example 13. Preparation of N-(2-(3-tert-butyl-5-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-2-methoxyphenyl)benzo[d]thiazol-5-yl)methanesulfonamide (compound IA-L0-2.4).

[0478]



Part A. Preparation of N-(4-chloro-3-nitrophenyl)methanesulfonamide.

[0479] A mixture of 4-chloro-3-nitroaniline (5.0g, 29mmol), methanesulfonyl chloride (2.37mL, 30.4mmol) and pyridine (5.9mL, 72.4mmol) in THF (100mL) was stirred for 24h. Poured in 1M HCl (500mL). The resulting precipitate was filtered and air-dried to provide the title compound as a solid (6.7g, 92%).

Part B. Preparation of N-(4-(4-methoxybenzylthio)-3-nitrophenyl)methanesulfonamide.

[0480] A mixture of the product from **Part A** (3.0g, 12mmol), (4-methoxyphenyl)methanethiol (1.67mL, 12mmol) and K_2CO_3 (4.96g, 36mmol) in DMF was heated at 100°C for 12h. Cooled and poured into 1M HCl (800mL). The resulting precipitate was filtered and air-dried to provide the title compound as a yellow solid (1.95g, 44.2%).

Part C. Preparation of N-(3-amino-4-(4-methoxybenzylthio)phenyl)methanesulfonamide.

[0481] The product from **Part B** (1.43g, 3.88mmol) was reacted according to the procedures from **Example 11, Part B** to provide the title compound as a white solid (1.31g, 100%).

Part D. Preparation of N,N'-(4,4'-disulfanediylbis(3-amino-4,1-phenylene))dimethane-sulfonamide.

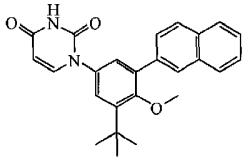
[0482] The product from **Part C** (75mg, 0.222mmol) was reacted with mercuric (II) acetate (70.6mg, 0.222mmol), anisole (0.048mL, 0.443mmol) and TFA (10mL) at 0°C for 45min. Concentrated under vacuum and dissolved in MeOH. Hydrogen sulfide gas was bubbled into solution for 1h followed by filtration and concentration under vacuum. Purification by silica gel column chromatography eluting with EtOAc/Hexane gave the title compound as a yellowish solid (34mg, 71%).

Part E. Preparation of N-(2-(3-tert-butyl-5-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-2-methoxy phenyl)benzo[d]thiazol-5-yl)methanesulfonamide.

[0483] The product from **Part D** (50mg, 0.115mmol) was reacted with the product from **Example 6, Part D** (70mg, 0.230mmol), triphenylphosphine (30.2mg, 0.115mmol) and 4-methylbenzenesulfonic acid (0.00267mL, 0.023mmol) in refluxing toluene for 3h. Concentrated under vacuum and purified by reverse phase HPLC chromatography eluting with a 40-100% gradient of acetonitrile in water (0.1% TFA) to give the title compound as a solid (40mg, 33%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.43 (s, 9 H) 2.73 (t, J=6.80 Hz, 2 H) 3.05 (s, 3 H) 3.63 (s, 3 H) 3.84 (t, J=6.62 Hz, 2 H) 7.35 (dd, J=8.64, 2.02 Hz, 1 H) 7.46 (d, J=2.94 Hz, 1 H) 7.86 (d, J=2.94 Hz, 1 H) 7.92 (d, J=1.84 Hz, 1 H) 8.10 (d, J=8.46 Hz, 1 H) 9.98 (s, 1 H) 10.40 (s, 1 H). MS ESI+ (503) (M+H)+.

Example 14. Preparation of 1-(3-tert-butyl-4-methoxy-5-(naphthalen-2-yl)phenyl) pyrimidine-2,4(1H,3H)-dione (compound IB-L0-2.1).

[0484]



Part A. Preparation of tert-butyl 3-tert-butyl-4-methoxy-5-(naphthalen-2-yl)phenyl carbamate.

[0485] In a resealable Schlenk tube, a solution of the product from **Example 1, Part H** (200mg, 0.56mmol), naphthalene-2-boronic acid (144mg, 0.84mmol), and 1.0M sodium carbonate solution (558µL, 0. 56mmol) in toluene (2.8mL) was degassed by nitrogen sparge for 10min. The mixture was treated with 1,1'-bis(diphenylphosphino)ferrocene palladium (II) chloride dichloromethane complex (14mg, 0.017mmol) and degassing was continued for another 5min. The Schlenk tube was sealed and

warmed at 95°C for 18h. Cooled and diluted with ethyl acetate and water. Treated with Darco G-60 and filtered through celite. Filtrate was extracted with water (2 x) and with brine. Dried over Na_2SO_4, filtered and concentrated. Purification by silica gel column chromatography eluting with 10-75 % EtOAc in hexanes gave the title compound as an oil (210mg, 93 %).

Part B. Preparation of 3-tert-butyl-4-methoxy-5-(naphthalen-2-yl)aniline.

[0486] The product from **Part A** (210mg, 0.52mmol) was dissolved in 4N HCl in dioxane (4.0mL) and stirred at room temperature for 1h. Concentration under vacuum afforded a solid, which was suspended in ethyl acetate and stirred with saturated sodium bicarbonate solution. The organic layer was dried over Na_2SO_4, filtered and concentrated under vacuum to give the title compound, as a brown oil (11 1mg, 70 %).

Part C. Preparation of (E)-N-(3-tert-butyl-4-methoxy-5-(naphthalen-2-yl)phenylcarbamoyl)-3-methoxyacrylamide.

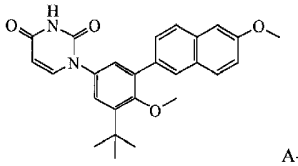
[0487] A solution of the product from **Part B** (11 1mg, 0.36mmol) in dry DMF (2.9mL) at -20°C was treated with (E)-3-methoxyacryloyl isocyanate solution (0.66mL, of 0.55M in benzene, 0.36mmol) followed by gradual warming to room temperature. After stirring for 30min, the mixture was cooled again to -20°C and more (E)-3-methoxyacryloyl isocyanate solution (1.0mL, 0.55mmol) was added. After warming again to room temperature for 30min, the reaction was complete. Diluted with EtOAc and extracted with water and brine. Dried over Na_2SO_4, filtered and concentrated under vacuum. Purification by silica gel column chromatography eluting with 10-100 % EtOAc in hexane gave the title compound as a light yellow oil (144mg, 92%).

Part D. Preparation of 1-(3-tert-butyl-4-methoxy-5-(naphthalen-2-yl)phenyl)pyrimidine-2,4(1H,3H)-dione.

[0488] A suspension of the product from **Part C** (144mg, 0.33mmol) in 2:2:1 ethanol-water-THF (15mL) was treated with 1N sulfuric acid solution (3.0mL) followed by warming at 100°C for 24h. Cooled and diluted with EtOAc and extracted with water and brine. Dried over Na_2SO_4, filtered and concentrated under vacuum. Purification by silica gel column chromatography eluting with 10-100% EtOAc in hexane gave the title compound as a white solid (62mg, 47 %). ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.42 (s, 1 H), 8.08 (s, 1 H), 7.90 - 8.04 (m, 3 H), 7.81 (d, J=7.72 Hz, 1 H), 7.72 (d, J=8.46 Hz, 1 H), 7.56 (dd, J=6.25, 3.31 Hz, 2 H), 7.39 (d, J=2.57 Hz, 1 H), 7.33 (d, J=2.57 Hz, 1 H), 5.65 (d, J=7.72 Hz, 1 H), 3.24 (s, 3 H), 1.43 (s, 9 H). MS +ESI m/z (rel abundance): 401 (100, M+H), 418 (30, M+NH4).

Example 15. Preparation of 1-(3-tert-butyl-4-methoxy-5-(6-methoxynaphthalen-2-yl)phenyl) pyrimidine-2,4(1H,3H)-dione (compound IB-L0-2.2).

[0489]



A-998288.0

Part A. Preparation of tert-butyl 3-tert-butyl-4-methoxy-5-(6-methoxynaphthalen-2-yl)phenyl carbamate.

[0490] The product from **Example 1, Part H** (158mg, 0.44mmol) was reacted with 6-methoxy-naphthalen-2-ylboronic acid (107mg, 0.52mmol) according to the procedures from **Example 14, Part A** to provide the title compound as a white solid (92mg, 47 %).

Part B. Preparation of 3-tert-butyl-4-methoxy-5-(6-methoxynaphthalen-2-yl)aniline.

[0491] The product from **Part A** (92mg, 0.21mmol) was reacted according to the procedures from **Example 14, Part B** to provide the title compound as a pink solid (71mg, 99%).

Part C. Preparation of (E)-N-(3-tert-butyl-4-methoxy-5-(6-methoxynaphthalen-2-yl)phenyl carbamoyl)-3-methoxyacrylamide.

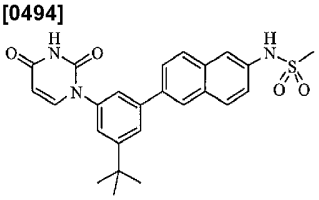
[0492] The product from **Part B** (71mg, 0.21mmol) was reacted according to the procedures from **Example 14, Part C** to provide the title compound as a buff-colored solid (58mg, 59 %).

Part D. Preparation of 1-(3-tert-butyl-4-methoxy-5-(6-methoxynaphthalen-2-yl)phenyl) pyrimidine-2,4(1 H,3 H)-dione.

[0493] A solution of the product from **Part C** (58mg, 0.13mmol) in 2:1:1 ethanol-THF-water (4.0mL) was treated with 1.0M sulfuric acid solution (3.0mL) followed by warming at 95°C for 24h. Cooled and diluted with EtOAc. Extracted with water and brine. Dried over Na_2SO_4, filtered and concentrated under vacuum. Purification by silica gel column chromatography eluting with 10-100 % EtOAc in hexanes gave the product as a faint pink solid (28mg, 52%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.41 (s, 1 H), 8.00 (s, 1 H), 7.91 (dd, J=8.64, 4.60 Hz, 2 H), 7.80 (d, J=7.72 Hz, 1 H), 7.67 (d, J=8.82 Hz, 1 H), 7.34 - 7.47 (m, 2 H), 7.21 - 7.32 (m, 1 H), 7.20 (dd, J=9.01, 2.39 Hz, 1 H), 5.65 (d, J=7.72 Hz, 1 H), 3.90 (s, 3 H), 3.24 (s, 3 H), 1.42 (s, 9 H). MS +ESI m/z (rel abundance): 431 (100, M+H), 448 (45, M+NH4).

Example 16. Preparation of N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl) phenyl)naphthalen-2-yl)methanesulfonamide (compound IB-L0-2.8).

[0494]



Part A. Preparation of 2-bromo-4-tert-butyl-6-nitroaniline.

[0495] A suspension of 4-tert-butyl-2-nitroaniline (1.033g, 5.32mmol) in glacial acetic acid (7.8mL) was warmed with a heat gun until all solids had dissolved. The solution was then cooled and treated portion wise with pyridinium hydrobromide perbromide (1.96g, 6.12mmol). After addition, the solution was stirred at room temperature for 1h. The mixture was added to water (50mL) and treated with a small amount of sodium sulfite. After stirring for 30min, the precipitate was collected by filtration. The solid obtained was washed with water and dissolved in EtOAc. Washed with water and brine. Dried over Na_2SO_4, filtered and concentrated under vacuum to provide the title compound as a yellow-orange solid (1.36g, 94 %).

Part B. Preparation of 1-bromo-3-tert-butyl-5-nitrobenzene.

[0496] **A** solution of tert-butyl nitrite (300µL of 90%, 261mg, 2.27mmol) in dry DMF (4mL) was warmed at 50°C and was treated with a solution of the product from **Part A** (414mg, 1.52mmol) in DMF (3.5mL). After a few minutes stirring, the solution began to bubble vigorously. After warming at 50°C for 1h, additional (300µL) tert-butyl nitrite was added followed by warming at 50°C for 1h. After 18h at room temperature, tert-butyl nitrite (1.2mL) was added and the mixture warmed at 50°C for 2h. Cooled and diluted with EtOAc. Washed with water and brine. Dried over Na_2SO_4, filtered and concentrated under vacuum. Purification by silica gel column chromatography eluting with 5-40 % ethyl acetate in hexanes gave the title compound as a light yellow oil (159mg, 41 %).

Part C. Preparation of 3-bromo-5-tert-butylaniline.

[0497] A solution of the product from **Part B** (770mg, 2.98mmol) in 3:3:1 methanol-water-THF (14.9mL) was treated with ammonium chloride (239mg, 4.47mmol) and iron powder (833mg, 14.92mmol) followed by warming at reflux for 8h. Diluted with EtOAc and water and filtered through celite. The filtrate was extracted with water and brine. Dried over Na_2SO_4, filtered and concentrated under vacuum to give the title compound as a yellow oil.

Part D. Preparation of (E)-N-(3-bromo-5-tert-butylphenylcarbamoyl)-3-methoxy acrylamide.

[0498] A solution of the product from **Part C** (681mg, 2.99mmol) in dry DMF (23mL) at -30°C was treated drop wise with a 0.4M solution of (E)-3-methoxyacryloyl isocyanate in benzene (14.9mL, 5.96mmol). The solution was stirred at -30°C for 30min followed by warming gradually to room temperature, and then stirred for 18h. Diluted with EtOAc and washed with water and brine. Dried over Na_2SO_4, filtered and concentrated under vacuum to afford a yellow solid, which was triturated with ether-hexanes and collected by filtration. Dried under vacuum to give the title compound as a light brown powder. (951mg, 90 %).

Part E. Preparation of 1-(3-bromo-5-tert-butylphenyl)pyrimidine-2,4(1H,3H)-dione.

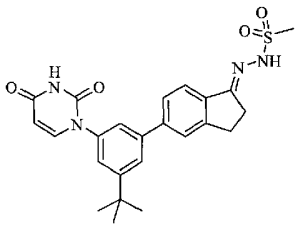
[0499] A suspension of the product from **Part D** (951mg, 2.68mmol) in ethanol (25mL) was treated with a solution of concentrated sulfuric acid (2.60mL, 4.78g, 18.22mmol) in water (13.4mL) followed by warming at 100°C for 1h. Cooled and concentrated to remove ethanol. Cooled to 0°C and the precipitate was collected by filtration and washed with water. Dried under vacuum to give the title compound as an orange solid (619mg, 72 %).

Part F. Preparation of N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)phenyl) naphthalen-2-yl)methanesulfonamide.

[0500] In a microwave tube, a suspension of the product from **Part E** (104mg, 0.32mmol), the product from **Example 2A, Part** B (134mg, 0.39mmol), and 1.0M sodium carbonate solution (386µL, 0.39mmol) in 1:1 ethanol-toluene (2.1mL) was degassed by nitrogen sparge for 10min. The solution was treated with 1,1'-bis(di-tert-butylphosphino)ferrocene-palladium (II) dichloride (20mg, 0.031mmol) and degassing was continued for another 5min. The mixture was heated at 100°C in the microwave for 30min. Diluted with EtOAc and washed with water and brine. Dried over Na_2SO_4 and treated with (3-mercapto propyl) silica gel for 30min. Filtered and concentrated under vacuum to afford an amber solid, which was triturated with ether-hexanes. Collected the solid by filtration and dried under vacuum to provide the title compound (81mg, 54 %). ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.46 (s, 1 H) 10.05 (s, 1 H), 8.25 (s, 1 H) 7.98 (dd, J=11.58, 9.01 Hz, 1 H) 7.86 - 7.93 (m, 1 H) 7.78 - 7.85 (m, 2 H) 7.72 (s, 1 H) 7.67 (s, 1 H) 7.31 - 7.51 (m, 2 H) 5.70 (dd, J=7.72, 2.21 Hz, 1 H) 3.08 (s, 3 H) 1.39 (s, 9 H).

Example 17. Preparation of (E)-N'-(5-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)phenyl)-2,3-dihydro-1H-inden-1-ylidene)methanesulfonohydrazide (compound IB-L0-2.7).

[0501]



Part A. Preparation of 1-(3-tert-butyl-5-(1-oxo-2,3-dihydro-1H-inden-5-yl)phenyl) pyrimidine-2,4(1H,3H)-dione.

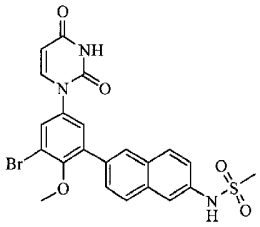
[0502] In a microwave tube, a suspension of the product from **Example 16, Part E,** the product from **Example 4, Part A** (144mg, 0.56mmol), 1.0M sodium carbonate solution (557µL, 0.56mmol) in 1:1 ethanol-toluene (3.0mL) was degassed by nitrogen sparge for 15min. 1,1'-Bis(di-t-butylphosphino) ferrocene palladium (II) chloride complex (15mg, 0.023mmol) was added and degassing was continued for an additional 5 min. The tube was sealed and the mixture was heated at 100°C in the microwave for 30 min. Diluted with EtOAc and water. Washed with 1M citric acid solution, water, and brine. The organic was stirred with (3-mercaptopropyl) silica gel for 1h. Dried over Na_2SO_4, filtered and concentrated under vacuum. Purification by silica gel column chromatography eluting with 10-100 % EtOAc in hexanes gave the title compound as an off-white solid (86mg, 50 %).

Part B. Preparation of (E)-N'-(5-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl) phenyl)-2,3-dihydro-1 H-inden-1-ylidene)methanesulfonohydrazide.

[0503] The product from **Part A** (80mg, 0.21 mmol) was reacted according to the procedures from **Example 4, Part C** to provide the title compound as a white solid (73mg, 73 %). ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.44 (s, 1 H) 9.92 (s, 1 H) 7.64 - 7.98 (m, 5 H) 7.57 (s, 1 H) 7.45 (s, 1 H) 5.68 (d, J=7.72 Hz, 1 H) 3.00 - 3.20 (m, 5 H) 2.85 (d, J=12.50 Hz, 2 H) 1.36 (s, 9 H). MS +ESI m/z (rel abundance): 467 (100, M+H).

Example 18. Preparation of N-(6-(3-bromo-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methanesulfonamide (compound IB-L0-2.69).

[0504]



Part A. Preparation of 2-bromo-4,6-diiodophenol.

[0505] A 1L round-bottom flask was charged with 2-bromophenol (Aldrich, 8.65g, 50mmol) and methanol (100ml) to give a colorless solution. Sodium hydroxide (2.40g, 60.0mmol) was added and stirred until the hydroxide pellets had dissolved. The solution was cooled in an ice water bath and sodium iodide (5.6g, 37.4mmol) was added followed by drop-wise addition of sodium hypochlorite (17mL, 27.5mmol) to give a transparent brown/red solution and gradual precipitation of a thick, white solid. The addition of sodium iodide and bleach was repeated 3 times to give an orange mixture that was stirred for 2h, treated with a solution of sodium thiosulfate in water (20g in 100mL), stirred for 15min and treated drop-wise with concentrated HCl to a constant pH of 1. The mixture was stirred for 15min and filtered to collect a white solid that was washed repeatedly with water and dried to constant mass (14.7g, 69%).

Part B. Preparation of 1-bromo-3,5-diiodo-2-methoxybenzene.

[0506] **A** 500mL round-bottom flask was charged with the product from **Part A** (14.7g, 34.6mmol), iodomethane (2.70ml, 43.3mmol), and sodium hydroxide (2.101ml, 39.8mmol) in acetone (96ml) to give a tan solution. The mixture was stirred for 24h and concentrated. The residue was dissolved in ethyl acetate, washed with water and saturated sodium chloride, dried over sodium sulfate, filtered and concentrated to give a white solid. The solid was recrystallized from hot hexane to give a white solid that was collected by filtration (12.3g, 81%).

Part C. Preparation of 1-(3-bromo-5-iodo-4-methoxyphenyl)pyrimidine-2,4(1H,3H)-dione.

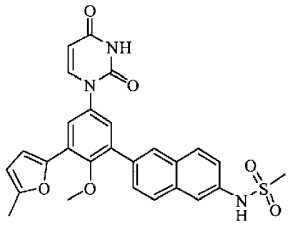
[0507] A 250mL round-bottom flask was charged with the product from **Part B** (8.09g, 18.44mmol), pyrimidine-2,4(1H,3H)-dione (2.273g, 20.28mmol), N-(2-cyanophenyl)picolinamide (0.823g, 3.69mmol), copper (I) iodide (0.351g, 1.844mmol) and potassium phosphate (8.22g, 38.7mmol) in DMSO (70ml). The mixture was sealed, sparged with nitrogen for 15min and heated at 60°C for 16h. The mixture was partitioned with ethyl acetate and water. The organic layer was washed with 1M HCl, water, brine, dried with sodium sulfate, and filtered. The filtrate was treated with 3-mercaptopropyl functionalized silica gel (Aldrich catalog # 538086), filtered through celite and evaporated to give an off-white solid (3.92g, 50%).

Part D. Preparation of N-(6-(3-bromo-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methanesulfonamide.

[0508] To a 5mL microwave tube was added the product from **Part C** (212mg, 0.50mmol), the product from **Example 2A, Part B** (174mg, 0.50mmol), potassium phosphate (223mg, 1.05mmol), PA-Ph (CAS 97739-46-3, 4.38mg, 0.015mmol) and tris(dibenzylideneacetone)dipalladium(0) (4.58mg, 5.00µmol) in tetrahydrofuran (3.0ml) and water (1.0ml). The tube was sealed and the mixture was sparged with nitrogen for 5min and then stirred for 24h. The reaction mixture was partitioned with ethyl acetate and 1M HCl. The organic layer was washed with saturated sodium bicarbonate, brine, dried with sodium sulfate and filtered. The filtrate was treated with 3-mercaptopropyl functionalized silica gel (Aldrich catalog # 538086), filtered through celite and evaporated. The residue was triturated with methanol/ CH_2Cl_2 to give the title compound as a white solid (256mg, 51%). ^{1}H NMR (300 MHz, DMSO-D6) δ ppm 3.08 (s, 3 H) 3.43 (s, 3 H) 5.68 (d, J=8.09 Hz, 1 H) 7.43 (dd, J=8.82, 2.21 Hz, 1 H) 7.60 (d, J=2.57 Hz, 1 H) 7.72 (m, 2 H) 7.82 (d, J=3.31 Hz, 1 H) 7.84 (d, J=1.84 Hz, 1 H) 7.96 (m, 2 H) 8.09 (s, 1 H) 10.07 (s, 1 H) 11.49 (s, 1 H). MS (ESI-) *m/z* 513.9, 515.9 $(M-H)^+$.

Example 19. Preparation of N-(6-(5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxy-3-(5-methylfuran-2-yl)phenyl)naphthalen-2-yl)methanesulfonamide (compound IB-L0-2.58).

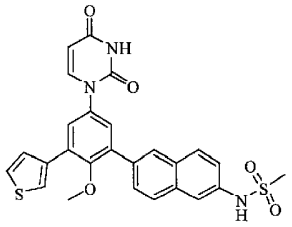
[0509]



[0510] To a 5mL microwave tube was added the product of Example 18 (52mg, 0.101mmol), 4,4,5,5-tetramethyl-2-(5-methylfuran-2-yl)-1,3,2-dioxaborolane (0.025ml, 0.121mmol), 1,1'-bis(di-tert-butylphosphino)ferrocene palladium dichloride (3.28mg, 5.04µmol) and potassium phosphate (42.8mg, 0.201mmol) in THF (3.0ml) and water (1.0ml). The tube was sealed and the mixture was sparged with nitrogen for 5min and then heated at 50°C for 3h. The cooled mixture was partitioned with ethyl acetate and 1M HCl. The organic layer was washed with saturated sodium bicarbonate, brine, dried with sodium sulfate, filtered and concentrated. The filtrate was treated with 3-mercaptopropyl functionalized silica gel, filtered and evaporated. The residue was purified by reverse phase chromatography to give the desired product as a white solid (23mg, 44%, m.p.174-178°C.) ^{1}H NMR (300 MHz, DMSO-D6) δ ppm 2.38 (s, 3 H) 3.09 (s, 3 H) 3.33 (s, 3 H) 5.69 (dd, J=7.72, 2.21 Hz, 1 H) 6.30 (d, J=3.31 Hz, 1 H) 7.00 (d, J=3.31 Hz, 1 H) 7.43 (m, 2 H) 7.74 (d, J=2.57 Hz, 2 H) 7.78 (dd, J=8.46, 1.84 Hz, 1 H) 7.85 (d, J=8.09 Hz, 1 H) 7.97 (t, J=8.82 Hz, 2 H) 8.12 (s, 1 H) 10.05 (s, 1 H) 11.46 (d, J=2.21 Hz, 1 H). MS (ESI+) *m/z* 518 $(M+H)^+$.

Example 20. Preparation of N-(6-(5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxy-3-(thiophen-3-yl)phenyl)naphthalen-2-yl)methanesulfonamide (compound IB-L0-2.53).

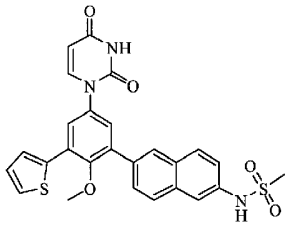
[0511]



[0512] The title compound was prepared according to the procedure of **Example 19** substituting thiophen-3-ylboronic acid for 4,4,5,5-tetramethyl-2-(5-methylfuran-2-yl)-1,3,2-dioxaborolane to give a white solid (12mg, 23%). ^{1}H NMR (300 MHz, DMSO-D6) δ ppm 3.07 (s, 3 H) 3.22 (s, 3 H) 5.69 (d, J=7.72 Hz, 1 H) 7.41 (dd, J=8.64, 2.02 Hz, 1 H) 7.50 (d, J=2.94 Hz, 1 H) 7.59 (dd, J=5.13, 1.08 Hz, 1 H) 7.69 (m, 3 H) 7.76 (dd, J=8.64, 1.65 Hz, 1 H) 7.89 (d, J=7.72 Hz, 1 H) 7.95 (m, 3 H) 8.09 (s, 1 H) 10.05 (s, 1 H) 11.47 (s, 1 H). MS (ESI+) *m/z* 520 $(M+H)^+$.

Example 21. Preparation of N-(6-(5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxy-3-(thiophen-2-yl)phenyl)naphthalen-2-yl)methanesulfonamide (compound IB-L0-2.61).

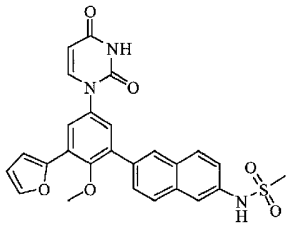
[0513]



[0514] The title compound was prepared according to the procedure of **Example 19** substituting thiophen-2-ylboronic acid for 4,4,5,5-tetramethyl-2-(5-methylfuran-2-yl)-1,3,2-dioxaborolane to give a white solid (8mg, 15%). ^{1}H NMR (300 MHz, DMSO-D6) δ ppm 3.08 (s, 3 H) 3.30 (s, 3 H) 5.70 (d, J=8.09 Hz, 1 H) 7.19 (dd, J=5.33, 3.86 Hz, 1 H) 7.42 (dd, J=8.82, 2.21 Hz, 1 H) 7.49 (d, J=2.57 Hz, 1 H) 7.69 (dd, J=5.15, 1.20 Hz, 1 H) 7.80 (m, 3 H) 7.88 (d, J=7.72 Hz, 1 H) 7.92 (d, J=2.57 Hz, 1 H) 7.98 (m, 2 H) 8.12 (s, 1 H) 10.06 (s, 1 H) 11.48 (s, 1 H). MS (ESI+) *m/z* 520 $(M+H)^+$.

Example 22. Preparation of N-(6-(5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-3-(furan-2-yl)-2-methoxyphenyl)naphthalen-2-yl)methanesulfonamide (compound IB-L0-2.59).

[0515]

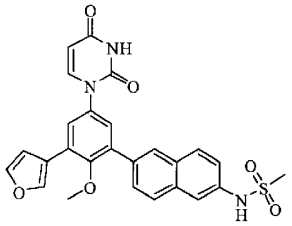


[0516] The title compound was prepared according to the procedure of **Example 19** substituting furan-2-ylboronic acid for 4,4,5,5-tetramethyl-2-(5-methylfuran-2-yl)-1,3,2-dioxaborolane to give a white solid (16mg, 32%). ^{1}H NMR (300 MHz, DMSO-D6) δ ppm 3.09 (s, 3 H) 3.35 (s, 3 H) 5.69 (d, J=7.72 Hz, 1 H) 6.69 (dd, J=3.31, 1.84 Hz, 1 H) 7.11 (d, J=3.31 Hz, 1 H) 7.43 (dd, J=8.82, 2.21 Hz, 1 H) 7.49 (d, J=2.94 Hz, 1 H) 7.80 (m, 5 H) 7.96 (m, 2 H) 8.13 (s, 1 H) 10.06 (s, 1 H) 11.47 (s, 1 H). MS (ESI-) *m/z* 502.1 $(M-H)^+$.

Example 23. Preparation of N-(6-(5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-3-(furan-3-yl)-2-

methoxyphenyl)naphthalen-2-yl)methanesulfonamide (compound IB-L0-2.64).

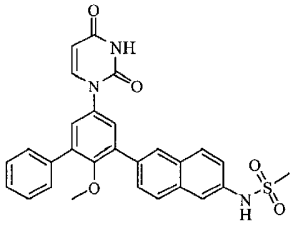
[0517]



[0518] The title compound was prepared according to the procedure of **Example 19** substituting furan-3-ylboronic acid for 4,4,5,5-tetramethyl-2-(5-methylfuran-2-yl)-1,3,2-dioxaborolane to give a white solid (6mg, 12%). ^{1}H NMR (300 MHz, DMSO-D6) δ ppm 3.09 (s, 3 H) 3.30 (s, 3 H) 5.69 (dd, J=7.71, 1.83 Hz, 1 H) 7.10 (dd, J=1.74, 0.78 Hz, 1 H) 7.42 (dd, J=8.82, 2.21 Hz, 1 H) 7.46 (d, J=2.57 Hz, 1 H) 7.73 (d, J=2.21 Hz, 1 H) 7.76 (d, J=2.57 Hz, 1 H) 7.78 (d, J=1.84 Hz, 1 H) 7.81 (t, J=1.84 Hz, 1 H) 7.86 (d, J=7.72 Hz, 1 H) 7.96 (t, J=8.82 Hz, 2 H) 8.10 (s, 1 H) 8.28 (s, 1 H) 10.05 (s, 1 H) 11.48 (s, 1 H). MS (ESI-) *m/z* 502.1 $(M-H)^+$.

Example 24. Preparation of N-(6-(5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxy-biphenyl-3-yl)naphthalen-2-yl)methanesulfonamide (compound IB-L0-2.71).

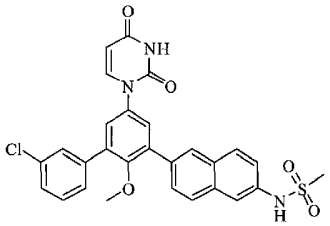
[0519]



[0520] The title compound was prepared according to the procedure of **Example 19** substituting phenylboronic acid for 4,4,5,5-tetramethyl-2-(5-methylfuran-2-yl)-1,3,2-dioxaborolane. The crude product was purified by silica gel chromatography eluting with 3% methanol/ CH_2Cl_2 to give a white solid (10mg, 8%). ^{1}H NMR (300 MHz, DMSO-D6) δ ppm 3.08 (s, 3 H) 3.12 (s, 3 H) 5.69 (dd, J=7.81, 1.47 Hz, 1 H) 7.36 (m, 5 H) 7.56 (d, J=2.57 Hz, 1 H) 7.64 (m, 2 H) 7.74 (d, J=2.21 Hz, 1 H) 7.78 (dd, J=8.46, 1.84 Hz, 1 H) 7.94 (m, 3 H) 8.11 (s, 1 H) 10.04 (s, 1 H) 11.47 (s, 1 H). MS (ESI-) *m/z* 512 $(M-H)^+$.

Example 25. Preparation of N-(6-(3'-chloro-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxybiphenyl-3-yl)naphthalen-2-yl)methanesulfonamide (compound IB-L0-2.74).

[0521]

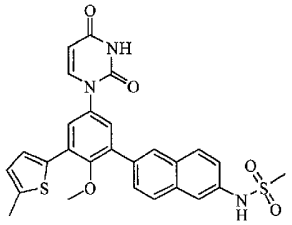


[0522] The title compound was prepared according to the procedure of **Example 19** substituting 3-chlorophenylboronic acid for 4,4,5,5-tetramethyl-2-(5-methylfuran-2-yl)-1,3,2-dioxaborolane to give a white solid (38mg, 68%). ^{1}H NMR (300 MHz, DMSO-D6) δ

ppm 3.09 (s, 3 H) 3.13 (s, 3 H) 5.70 (dd, J=8.09, 2.21 Hz, 1 H) 7.43 (dd, J=8.82, 2.21 Hz, 1 H) 7.52 (m, 3 H) 7.62 (m, 2 H) 7.72 (m, 2 H) 7.79 (dd, J=8.46, 1.47 Hz, 1 H) 7.95 (m, 3 H) 8.12 (s, 1 H) 10.05 (s, 1 H) 11.47 (d, J=2.21 Hz, 1 H). MS (ESI-) *m/z* 546 $(M-H)^+$.

Example 26. Preparation of N-(6-(5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxy-3-(5-methylthiophen-2-yl)phenyl)naphthalen-2-yl)methanesulfonamide (compound IB-L0-2.73).

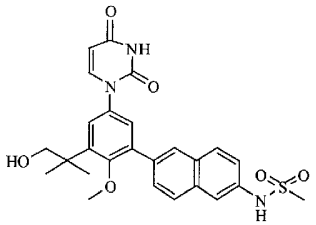
[0523]



[0524] The title compound was prepared according to the procedure of **Example 19** substituting 4,4,5,5-tetramethyl-2-(5-methylthiophen-2-yl)-1,3,2-dioxaborolane for 4,4,5,5-tetramethyl-2-(5-methyl-furan-2-yl)-1,3,2-dioxaborolane to give a white solid (22mg, 41%). ^{1}H NMR (300 MHz, DMSO-D6) δ ppm 2.49 (s, 3 H) 3.09 (s, 3 H) 3.29 (s, 3 H) 5.69 (dd, J=8.09, 2.21 Hz, 1 H) 6.87 (d, J=2.57 Hz, 1 H) 7.43 (m, 2 H) 7.54 (d, J=3.68 Hz, 1 H) 7.76 (m, 2 H) 7.85 (s, 1 H) 7.87 (d, J=5.15 Hz, 1 H) 7.98 (t, J=9.01 Hz, 2 H) 8.11 (s, 1 H) 10.06 (s, 1 H) 11.47 (d, J=2.21 Hz, 1 H). MS (ESI+) *m/z* 534 $(M+H)^+$.

Example 27. Preparation of N-(6-(5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-3-(1-hydroxy-2-methylpropan-2-yl)-2-methoxyphenyl)naphthalen-2-yl)methanesulfonamide (compound IB-L0-2.54).

[0525]



Part A. Preparation of 2-(2-hydroxy-3,5-diiodophenyl)acetic acid.

[0526] To a 250mL round bottom flask was added 2-(2-hydroxyphenyl)acetic acid (Aldrich, 3.04g, 20mmol) in acetonitrile (50ml) to give a colorless solution. N-iodosuccimide (9.00g, 40.0mmol) was added portionwise over 15min to give a red/brown transparent solution that was stirred for 16h. The mixture was concentrated and the resulting solid was triturated in 75mL of water and filtered to collect an orange solid that was dried under vacuum. The crude solid was recrystallized from toluene to give a light orange powder (6.0g, 74%).

Part B. Preparation of methyl 2-(3,5-diiodo-2-methoxyphenyl)acetate.

[0527] To a 250mL round-bottom flask was added the product from **Part A** (6g, 14.85mmol), potassium carbonate (6.16g, 44.6mmol), and dimethyl sulfate (4.12g, 32.7mmol) in acetone (49.5ml) to give a brown suspension. Heated at reflux for 16h, cooled, concentrated and the residue was partitioned between EtOAc and water. The EtOAc layer was washed with brine, dried (Na_2SO_4) and concentrated to a brown oil that was chromatographed on a 40g silica cartridge eluting with 3:1 hexane/EtOAc to give a yellow oil (6.0g, 94%).

Part C. Preparation of methyl 2-(3,5-diiodo-2-methoxyphenyl)-2-methylpropanoate.

[0528] To a 100mL round-bottom flask under nitrogen was added the product from **Part B** (1.728g, 4mmol) in anhydrous THF (20ml) and HMPA (2ml) to give a colorless solution. Methyl iodide (1.251ml, 20.00mmol) was added and the solution was cooled to -40°C. Potassium t-butoxide(12.00ml, 12.00mmol) was added dropwise and the mixture was stirred at -40 to -20°C for 30min and quenched with 1M HCl to a pH of 1. The mixture was extracted 3 X 40ml with EtOAc. The extracts were combined, washed with brine, dried (Na_2SO_4) and concentrated. The crude product was flash chromatographed on a 40g ISCO silica cartridge eluting with 9:1 hexane/EtOAc to give the bis-methylated product as a yellow oil (1.63g, 89%).

Part D. Preparation of 2-(3,5-diiodo-2-methoxyphenyl)-2-methylpropanoic acid.

[0529] A suspension of the product from **Part C** (2.63g, 5.72mmol) in MeOH (40ml) and THF (40ml) was treated with 4.0M sodium hydroxide (28ml, 112mmol) and heated at 80°C for 48 h. The organic solvent was evaporated and the remaining aqueous solution was acidified with 1M HCl producing a solid that was collected by filtration, washed with water and dried to give the desired carboxylic acid (2.46g, 96%).

Part E. Preparation of 2-(3,5-diiodo-2-methoxyphenyl)-2-methylpropan-1-ol.

[0530] A solution of the product from **Part D** (1.00g, 2.242mmol) in THF (40ml) was treated dropwise with borane THF complex 1.0M (20ml, 20mmol) and then heated at 50°C for 24 h. The mixture was treated with methanol (20mL), refluxed for 30 min and concentrated. The resulting residue was washed with water, brine, dried with sodium sulfate, filtered and evaporated. The residue was chromatographed on silica gel eluting with hexane/EtOAc (4:1) to give the desired product (810mg, 84%).

Part F. Preparation of tert-butyl(2-(3,5-diiodo-2-methoxyphenyl)-2-methylpropoxy)-dimethylsilane.

[0531] A solution of the product from **Part E** (432mg, 1.000mmol) in DMF (5ml) was treated with tert-butyldimethylchlorosilane (301mg, 2.000mmol), and imidazole (204mg, 3.00mmol) and stirred for 2h. The mixture was partitioned between 1M HCl and ethyl acetate. The organic layer was washed with saturated sodium bicarbonate, brine, dried with sodium sulfate, filtered and evaporated. The residue was chromatographed on silica gel eluting with hexane/EtOAc (9:1) to give the desired product (522mg, 96%).

Part G. Preparation of 1-(3-(1-(tert-butyldimethylsilyloxy)-2-methylpropan-2-yl)-5-iodo-4-methoxyphenyl)pyrimidine-2,4(1 H,3H)-dione.

[0532] To a 50mL round-bottom flask was added the product from **Part F** (520mg, 0.952mmol), pyrimidine-2,4(1H,3H)-dione (117mg, 1.047mmol), N-(2-cyanophenyl)picolinamide (42.5mg, 0.190mmol), copper(I) iodide (18.13mg, 0.095mmol) and potassium phosphate (424mg, 1.999mmol) in DMSO (5ml). The vessel was sealed, sparged with nitrogen and then heated at 60°C for 24h. The mixture was partitioned between 1M HCl and ethyl acetate. The organic layer was washed with saturated sodium bicarbonate, brine, dried with sodium sulfate, and filtered. The filtrate was treated with 3-mercaptopropyl functionalized silica gel, filtered and evaporated. The residue was chromatographed on silica gel eluting with hexane/EtOAc (3:2) to give the product as a solid (285mg, 65%).

Part H. Preparation of N-(6-(3-(1-(tert-butyldimethylsilyloxy)-2-methylpropan-2-yl)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methanesulfonamide.

[0533] To a 5mL microwave tube was added the product from **Part G** (50mg, 0.094mmol), the product from **Example 2A, Part B** (32.7mg, 0.094mmol), potassium phosphate (42.0mg, 0.198mmol), PA-Ph (CAS 97739-46-3) (0.827mg, 2.83 µmol) and tris(dibenzylideneacetone)palladium(0) (0.863mg, 0.943 µmol) in THF (3.0ml) and water (1.0ml). The vessel was sealed and the mixture was sparged with nitrogen for 5min and then heated at 50°C for 2h. The mixture was partitioned between 1M HCl and ethyl acetate. The organic layer was washed with saturated sodium bicarbonate, brine, dried with sodium sulfate and filtered. The filtrate was treated with 3-mercaptopropyl functionalized silica gel, filtered and evaporated. The residue was chromatographed on

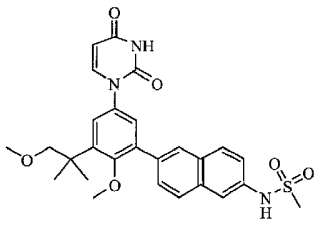
silica gel eluting with hexane/EtOAc (3:7) to give a solid (32mg, 54%).

Part I. Preparation of N-(6-(5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-3-(1-hydroxy-2-methylpropan-2-yl)-2-methoxyphenyl)naphthalen-2-yl)methanesulfonamide.

[0534] The product from **Part H** (31mg, 0.050mmol) in THF (2.0ml) was treated with 1M TBAF (0.3ml, 0.3mmol) in THF and stirred overnight. The mixture was partitioned with water and ethyl acetate. The organic layer was washed with brine three times, dried with sodium sulfate, filtered and evaporated. The residue was chromatographed on silica gel eluting with 2% to 8% methanol in CH_2Cl_2 to give a solid (21mg, 83%). Melting point: 256-257°C. ^{1}H NMR (300 MHz, DMSO-D6) δ ppm 1.35 (s, 6 H) 3.08 (s, 3 H) 3.23 (s, 3 H) 3.67 (d, J=4.78 Hz, 2 H) 4.72 (t, J=4.78 Hz, 1 H) 5.65 (d, J=8.09 Hz, 1 H) 7.36 (m, 3 H) 7.74 (m, 3 H) 7.98 (m, 3 H) 10.04 (s, 1 H) 11.41 (s, 1 H). MS (ESI+) *m/z* 527 $(M+ NH4)^+$.

Example 28. Preparation of N-(6-(5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxy-3-(1-methoxy-2-methylpropan-2-yl)phenyl)naphthalen-2-yl)methanesulfonamide (compound IB-L0-2.66).

[0535]



Part A. Preparation of 1,5-diiodo-2-methoxy-3-(1-methoxy-2-methylpropan-2-yl)benzene.

[0536] To a 25mL round-bottom flask was added the product from **Example 27, Part E.** (259mg, 0.6mmol) and sodium hydride (28.8mg, 1.200mmol) in THF (5ml). The mixture was stirred for 30min and iodomethane (0.045 1, 0.720mmol) was added. The mixture was stirred for 16h and partitioned between ethyl acetate and 1M HCl. The organic layer was washed with saturated sodium bicarbonate, brine, dried with sodium sulfate, filtered and evaporated to give an oil (235mg, 88%).

Part B. Preparation of 1-(3-iodo-4-methoxy-5-(1-methoxy-2-methylpropan-2-yl)phenyl)pyrimidine-2,4(1H,3H)-dione.

[0537] In a 25mL round-bottom flask was added the product from **Part A** (230mg, 0.516mmol), pyrimidine-2,4(1H,3H)-dione (63.6mg, 0.567mmol), N-(2-cyanophenyl)picolinamide (23.02mg, 0.103mmol), copper(I) iodide (9.82mg, 0.052mmol) and potassium phosphate (230mg, 1.083mmol) in DMSO (5ml). The vessel was sealed, sparged with nitrogen and heated at 60°C for 16h. The mixture was cooled and partitioned between ethyl acetate and 1M HCl. The organic layer was washed with saturated sodium bicarbonate, brine, dried with sodium sulfate, filtered and evaporated. The residue was chromatographed on silica gel eluting with 2% to 5% methanol in CH_2Cl_2 to give a solid (140mg, 63%).

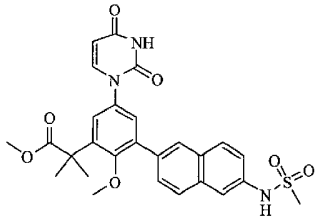
Part C. Preparation of N-(6-(5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxy-3-(1-methoxy-2-methylpropan-2-yl)phenyl)naphthalen-2-yl)methanesulfonamide.

[0538] In a 5ml microwave tube was added the product from **Part B** (43mg, 0.100mmol), the product from **Example 2A, Part B** (34.7mg, 0.100mmol), potassium phosphate (44.6mg, 0.210mmol), PA-Ph (CAS 97739-46-3) (0.876mg, 3.00µmol) and tris(dibenzylideneacetone)palladium(0) (0.915mg, 0.999µmol) in THF (3.0ml) and water (1.0ml). The vessel was sealed, sparged with nitrogen for 5min and heated at 50°C for 2h. The mixture was partitioned with ethyl acetate and 1M HCl. The organic layer was washed with saturated sodium bicarbonate, brine, dried with sodium sulfate, filtered. The filtrate was treated with 3-mercaptopropyl functionalized silica gel, filtered and evaporated. The residue was triturated with methanol/ CH_2Cl_2 (1:1) to give a

solid (28mg, 54%). ^{1}H NMR (300 MHz, DMSO-D6) δ ppm 1.39 (s, 6 H) 3.08 (s, 3 H) 3.23 (s, 3 H) 3.25 (s, 3 H) 3.61 (s, 2 H) 5.65 (d, J=7.72 Hz, 1 H) 7.27 (d, J=2.57 Hz, 1 H) 7.37 (d, J=2.57 Hz, 1 H) 7.42 (dd, J=8.64, 2.02 Hz, 1 H) 7.69 (dd, J=8.46, 1.84 Hz, 1 H) 7.73 (d, J=2.21 Hz, 1 H) 7.78 (d, J=7.72 Hz, 1 H) 7.95 (t, J=8.27 Hz, 2 H) 8.02 (s, 1 H) 10.04 (s, 1 H) 11.41 (s, 1 H). MS (ESI+) *m/z* 541 $(M+ NH4)^+$.

Example 29. Preparation of methyl 2-(5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxy-3-(6-(methylsulfonamido)naphthalen-2-yl)phenyl)-2-methylpropanoate (compound IB-L0-2.70).

[0539]



Part A. Preparation of methyl 2-(5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-3-iodo-2-methoxyphenyl)-2-methylpropanoate.

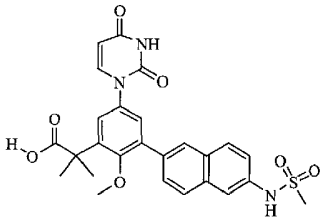
[0540] To a 100mL round-bottom flask under N_2 was added the product from **Example 27, Part C** (410mg, 0.891mmol), 1H-pyrimidine-2,4-dione (120mg, 1.069mmol), and potassium phosphate tribasic (397mg, 1.872mmol) in DMSO (5ml) to give a colorless suspension. N-(2-cyanophenyl) picolinamide (39.8mg, 0.178mmol) was added and the mix was sparged with N_2 for 5min. Copper(I) iodide (16.97mg, 0.089mmol) was added and the mix was sparged once again for 10min, placed under N_2 and heated at 60°C for 18h. The mixture was cooled and partitioned between EtOAc and water adjusting the pH to 1 with HCl. The aqueous layer was extracted 2X with EtOAc. The organics were combined, washed with water, saturated $NaHCO_3$, and saturated NaCl. The organic layer was dried (Na_2SO_4), treated with 3-mercaptopropyl functionalized silica, filtered and concentrated. The crude product was purified by chromatography on an ISCO 40 g silica cartridge eluting with 3% MeOH in CH_2Cl_2 to give a white foam (269mg, 68%).

Part B. Preparation of methyl 2-(5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxy-3-(6-(methylsulfonamido)naphthalen-2-yl)phenyl)-2-methylpropanoate.

[0541] To a 20mL microwave tube was added the product from **Part A** (0.444g, 1.0mmol), the product from **Example 2A, Part B** (0.365g, 1.050mmol), and potassium phosphate tribasic (0.446g, 2.100mmol) in 3:1 tetrahydrofuran-water (12ml) and degassed by nitrogen sparge for 20min. The solution was then treated with PA-Ph (CAS 97739-46-3) (8.77mg, 0.030mmol) and tris(dibenzylidene-acetone)palladium(0) (9.16mg, 10.00µmol) followed by degassing for another 5min. The microwave tube was then sealed and warmed at 50°C for 18h, cooled and partitioned between EtOAc and water adjusting the pH to 1 with 1M HCl. The EtOAc layer was washed with water, saturated $NaHCO_3$, and saturated NaCl. The organic layer was dried over sodium sulfate, stirred for 1h with 3-mercaptopropyl functionalized silica, filtered and concentrated. The crude product was purified by chromatography on an ISCO 12g silica cartridge eluting with 1-3% MeOH in CH_2Cl_2 to give light tan crystals (480mg, 98%). ^{1}H NMR (300 MHz, DMSO-D6) δ ppm 1.52 (s, 6 H) 3.08 (s, 3 H) 3.14 (s, 3 H) 3.64 (s, 3 H) 5.67 (dd, J=8.09, 1.84 Hz, 1 H) 7.37 - 7.48 (m, 3 H) 7.65 (dd, J=8.46, 1.84 Hz, 1 H) 7.73 (d, J=2.21 Hz, 1 H) 7.83 (d, J=8.09 Hz, 1 H) 7.96 (dd, J=8.64, 5.70 Hz, 2 H) 8.01 (s, 1 H) 10.05 (s, 1 H) 11.45 (s, 1 H). MS (ESI-) *m/z* 536 $(M-H)^+$.

Example 30. Preparation of 2-(5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxy-3-(6-(methylsulfonamido)naphthalen-2-yl)phenyl)-2-methylpropanoic acid (compound IB-L0-2.77).

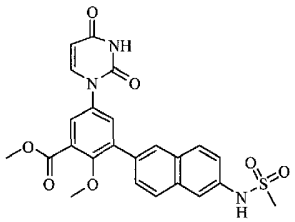
[0542]



[0543] A mixture of the product from **Example 29** (108mg, 0.2mmol) and sodium hydroxide (1mL, 4.00mmol) in methanol, THF, water (3:3:1, 10mL) was heated at 80°C for 18h, cooled and carefully acidified to pH 1 with concentrated HCl resulting in the formation of a white precipitate. The solid was collected by filtration, washed with water and dried. The crude material was triturated in 1mL of 1:1 EtOAc/MeOH, sonicated for 5min and the solid was collected by filtration as a bright white solid (58mg, 54% yield), mp >300°C. ^{1}H NMR (300 MHz, DMSO-D6) δ ppm 1.50 (s, 6 H) 3.08 (s, 3 H) 3.18 (s, 3 H) 5.66 (d, J=7.72 Hz, 1 H) 7.34 - 7.45 (m, 3 H) 7.67 (dd, J=8.64, 1.65 Hz, 1 H) 7.73 (d, J=1.84 Hz, 1 H) 7.82 (d, J=7.72 Hz, 1 H) 7.96 (dd, J=9.01, 4.60 Hz, 2 H) 8.02 (s, 1 H) 10.04 (s, 1 H) 11.43 (s, 1 H) 12.15 (s, 1 H). MS (ESI-) *m/z* 522 $(M-H)^+$.

Example 31. Preparation of methyl 5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxy-3-(6-(methylsulfonamido)naphthalen-2-yl)benzoate (compound IB-L0-2.72).

[0544]



Part A. Preparation of methyl 3,5-diiodo-2-methoxybenzoate.

[0545] A mixture of 2-hydroxy-3,5-diiodobenzoic acid (3.9g, 10.0mmol) potassium carbonate (4.15g, 30.0mmol) and dimethyl sulfate (2.77g, 22.0mmol) in acetone (33ml) was heated at reflux for 16h, cooled and concentrated. The residue was dissolved in EtOAc and washed with water, brine, dried (Na_2SO_4), filtered and concentrated to give an off-white solid (4.2g, quantitative yield).

Part B. Preparation of methyl 5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-3-iodo-2-methoxybenzoate.

[0546] To a 100mL round-bottom flask under N_2 was added the product from **Part A** (2.09g, 5.0mmol), 1H-pyrimidine-2,4-dione (0.67g, 6.0mmol), and potassium phosphate tribasic (2.2g, 10.5mmol) in DMSO (20ml) to give a colorless suspension. N-(2-cyanophenyl)picolinamide (220mg, 1.0mmol) was added and the mix was sparged with N_2 for 5min. Copper(I) iodide (95mg, 0.5mmol) was added and the mix was sparged once again for 10min, placed under N_2 and heated at 60°C for 18h. The mixture was cooled and partitioned between EtOAc and water adjusting the pH to 1 with HCl. The aqueous layer was extracted 2X with EtOAc. The organics were combined, washed with water, saturated $NaHCO_3$, and saturated NaCl. The organic layer was dried (Na_2SO_4), treated with 3-mercaptopropyl functionalized silica, filtered and concentrated. The crude product was purified by chromatography on an ISCO 40g silica cartridge eluting with 3% MeOH in CH_2Cl_2 to give a white foam (1.0g, 50 %).

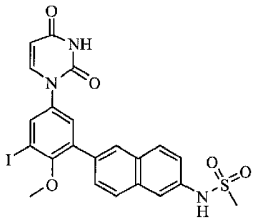
Part C. Preparation of methyl 5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxy-3-(6-(methylsulfonamido)naphthalen-2-yl)benzoate.

[0547] A mixture of the product from **Part B** (101mg, 0.25mmol), the product from **Example 2A, Part** B (91mg, 0.263mmol), and

potassium phosphate tribasic (11 1mg, 0.525mmol) in 3:1 tetrahydro-furan-water (12mL) was degassed by nitrogen sparge for 20min. The solution was then treated with PA-Ph (CAS 97739-46-3) (2.192mg, 7.50µmol) and tris(dibenzylideneacetone)palladium(0) (2.289mg, 2.500µmol) followed by degassing for another 5min. The microwave tube was then sealed, warmed at 50°C for 18h, cooled and partitioned between EtOAc and water adjusting the pH to 1 with 1M HCl. The EtOAc layer was washed with water, saturated NaHCO3, and saturated NaCl. The organic layer was dried Na_2SO_4, stirred for 1h with 3-mercaptopropyl functionalized silica, filtered and concentrated. The crude product was purified by chromatography on an ISCO 12g silica cartridge eluting with 3% MeOH in CH_2Cl_2 to give an off-white foam (80mg, 63 %). ^{1}H NMR (300 MHz, DMSO-D6) δ ppm 3.09 (s, 3 H) 3.45 (s, 3 H) 3.89 (s, 3 H) 5.69 (d, J=7.72 Hz, 1 H) 7.43 (dd, J=8.82, 2.21 Hz, 1 H) 7.68 - 7.79 (m, 4 H) 7.84 (d, J=7.72 Hz, 1 H) 7.89 - 8.01 (m, 2 H) 8.09 (s, 1 H) 10.06 (s, 1 H) 11.49 (s, 1 H). MS (ESI-) *m/z* 494 $(M-H)^+$.

Example 32. Preparation of N-(6-(5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-3-iodo-2-methoxyphenyl)naphthalen-2-yl)methanesulfonamide (compound IB-L0-2.57).

[0548]



Part A. Preparation of 1,3,5-triiodo-2-methoxybenzene.

[0549] In a 250mL pressure vessel was added 2,4,6-triiodophenol (5g, 10.60mmol) in MTBE (60ml) to give a yellow solution. The solution was cooled in an ice bath and 2.0M trimethylsilyldiazomethane (7.95ml, 15.90mmol) was added at a fast drip followed by dropwise addition of methanol (6mL) resulting in calm bubbling. The vessel was sealed and stirred at room temperature for 4h. The reaction solution was partitioned between EtOAc and water and the organic layer was washed with 1M HCl, saturated $NaHCO_3$, and saturated NaCl. The EtOAc was dried ($MgSO_4$), filtered and concentrated to give a tan solid that was used without purification (4.8g, 94 %).

Part B. Preparation of 1-(3,5-diiodo-4-methoxyphenyl)pyrimidine-2,4(1H,3H)-dione.

[0550] To a 100mL round-bottom flask under N_2 was added the product from **Part A** (3.5g, 7.2mmol), 1H-pyrimidine-2,4-dione (0.97g, 8.64mmol), and potassium phosphate tribasic (3.2g, 15.0mmol) in DMSO (50ml) to give a colorless suspension. N-(2-cyanophenyl)picolinamide (320mg, 1.44mmol) was added and the mix was sparged with N_2 for 5min. Copper(I) iodide (137mg, 0.72mmol) was added and the mix was sparged once again for 10min, placed under N_2 and heated at 60°C for 18h. The mixture was cooled and partitioned between EtOAc and water adjusting the pH to 1 with HCl. The aqueous layer was extracted 2X with EtOAc. The organics were combined, washed with water, saturated $NaHCO_3$, and saturated NaCl, dried (Na_2SO_4), treated with 3-mercaptopropyl functionalized silica, filtered and concentrated. The resulting solid was triturated in 2:1 hexane/EtOAc to give an off white powder (2.2g, 62 %).

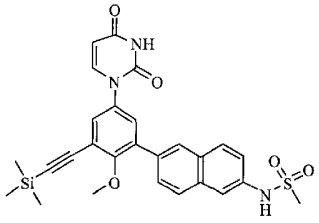
Part C. Preparation of N-(6-(5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-3-iodo-2-methoxyphenyl)naphthalen-2-yl)methanesulfonamide.

[0551] A mixture of the product from **Part B** 1-(3,5-diiodo-4-methoxyphenyl)pyrimidine-2,4(1H,3H)-dione (118mg, 0.25mmol), the product from **Example 2A, Part B** (87mg, 0.25mmol), 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride CH_2Cl_2 complex (10.21mg, 0.013mmol) and sodium carbonate (0.250ml, 0.25mmol) in toluene (1.0ml) and ethanol (1.0ml) was sparged with nitrogen for 5min and microwaved at 100°C for 30min. The mixture was cooled and partitioned with ethyl acetate and 1M HCl. The organic layer was washed with saturated sodium bicarbonate, brine, dried with sodium sulfate, filtered and evaporated. The

residue was chromatographed on silica eluting with ethyl acetate/hexane (2:3 to 4:1) to give the title compound (16mg, 11%). ^{1}H NMR (300 MHz, DMSO-D6) δ ppm 3.08 (s, 3 H) 3.35 (s, 3 H) 5.67 (d, J=8.09 Hz, 1 H) 7.42 (dd, J=8.82, 2.21 Hz, 1 H) 7.59 (d, J=2.57 Hz, 1 H) 7.73 (m, 2 H) 7.81 (d, J=8.09 Hz, 1 H) 7.95 (m, 3 H) 8.09 (s, 1 H) 10.06 (s, 1 H) 11.47 (s, 1 H). MS (ESI-) *m/z* 562 $(M-H)^+$.

Example 33. Preparation of N-(6-(5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxy-3-((trimethylsilyl)ethynyl)phenyl)naphthalen-2-yl)methanesulfonamide (compound IB-L0-2.78).

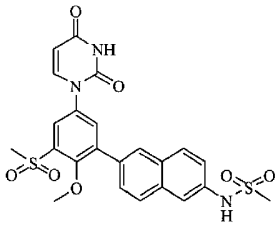
[0552]



[0553] In a 5mL microwave tube were combined ethynyltrimethylsilane (0.044ml, 0.32mmol), the product from **Example 32** (45.1mg, 0.08mmol), copper(I) iodide (0.762mg, 4.0µmol), bis(triphenylphosphine)palladium(II) chloride (2.81mg, 4.0µmol) and triethylamine (0.056ml, 0.40mmol) in acetonitrile (2ml). The mixture was sparged with nitrogen for 5min, sealed and microwaved at 80°C for 20min. The reaction mixture was cooled and partitioned with ethyl acetate and water. The organic layer was washed with brine, dried with sodium sulfate, filtered and evaporated. The residue was chromatographed on silica eluting with 1-4% methanol in CH_2Cl_2 to give a solid, (18mg, 42%) m.p.175-178°C. ^{1}H NMR (300 MHz, DMSO-D6) δ ppm 0.25 (s, 9 H) 3.07 (s, 3 H) 3.65 (s, 3 H) 5.66 (dd, J=7.91, 2.02 Hz, 1 H) 7.41 (dd, J=8.82, 2.21 Hz, 1 H) 7.58 (m, 2 H) 7.69 (dd, J=8.46, 1.84 Hz, 1 H) 7.72 (d, J=2.21 Hz, 1 H) 7.81 (d, J=7.72 Hz, 1 H) 7.93 (m, 2 H) 8.05 (d, J=1.32 Hz, 1 H) 10.04 (s, 1 H) 11.45 (d, J=2.21 Hz, 1 H). MS (ESI+) *m/z* 534 $(M+H)^+$.

Example 34. Preparation of N-(6-(5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxy-3-(methylsulfonyl)phenyl)naphthalen-2-yl)methanesulfonamide (compound IB-L0-2.68).

[0554]



Part A. Preparation of 4-nitrobenzene-2-diazo-1-oxide.

[0555] To a 250mL round-bottom flask was added 2-amino-4-nitrophenol (6.165g, 40.0mmol) in 48% tetrafluoroboric acid (15ml). Sodium nitrite (2.76g, 40.0mmol) in water (6ml) was added dropwise at 0°C and the mixture was stirred at room temperature for 30min. The solid was collected by filtration, washed with tetrafluoroboric acid and water. The solid was suspended in acetone (50ml), filtered and dried to give a solid (3.31g, 50%).

Part B. Preparation of 2-(methylthio)-4-nitrophenol.

[0556] To a 1L beaker was added the product from **Part A** (2.70g, 16.35mmol) in ice water (250g) to give a brown suspension.

Copper (0.520g, 8.18mmol) was added, followed by addition of sodium thiomethoxide (2.292g, 32.7mmol) in water (50ml) slowly. The mixture was stirred at room temperature for 24h. The mixture was filtered and the filtrate was acidified with 1M HCl producing a solid that was collected by filtration and dried (2.53g, 84%).

Part C. Preparation of 2-(methylsulfonyl)-4-nitrophenol.

[0557] To a 250mL round-bottom flask was added the product from **Part B** (1.111 g, 6.00mmol) in MeOH (20ml) to give a brown suspension. Oxone (7.746g, 12.60mmol) in water (20ml) was added slowly at 0°C. The mixture was warmed to room temperature, stirred for 1h and partitioned with ethyl acetate and 1M HCl. The organic layer was washed with brine, dried with sodium sulfate, filtered and evaporated. The residue was chromatographed on silica gel eluting with 1% to 5% methanol in CH_2Cl_2 to give a solid (0.472g, 36%).

Part D. Preparation of 2-iodo-6-(methylsulfonyl)-4-nitrophenol.

[0558] To a 50mL round-bottom flask was added the product from **Part C** (470mg, 2.164mmol) in MeOH (10ml) and water (2.5ml). Iodine monochloride (0.130ml, 2.60mmol) in CH_2Cl_2 (2.0mL) was added dropwise and the mixture was stirred at room temperature, poured into water (200mL) and stirred for 10min. The resulting solid was collected by filtration and dried (636mg, 86%).

Part E. Preparation of 1-iodo-2-methoxy-3-(methylsulfonyl)-5-nitrobenzene.

[0559] To a 50mL pressure vessel was added the product from **Part D** (630mg, 1.836mmol) in MTBE (6ml) to give a yellow solution. The mixture was cooled in an ice bath and 2M trimethylsilyldiazomethane (1.377ml, 2.75mmol) was added at a fast drip followed by dropwise addition of MeOH (0.4ml) resulting in calm bubbling. The vessel was sealed and stirred at room temperature for 1h. The mixture was partitioned with ethyl acetate and 1M HCl. The organic layer was washed with saturated sodium bicarbonate, brine, dried with sodium sulfate, filtered and evaporated to give an off-white solid (655mg, 100%).

Part F. Preparation of 3-iodo-4-methoxy-5-(methylsulfonyl)aniline.

[0560] To a 250mL round-bottom flask was added the product from **Part E** (0.650g, 1.820mmol), ammonium chloride (0.146g, 2.73mmol), and iron (0.508g, 9.10mmol) in THF/MeOH/water (50ml, 2/2/1). The mixture was refluxed for 2h, cooled and filtered. The filtrate was evaporated and the residue was partitioned with ethyl acetate and water. The organic layer was washed with brine, dried with sodium sulfate, filtered and evaporated to give a solid (590mg, 99%).

Part G. Preparation of (E)-N-(3-iodo-4-methoxy-5-(methylsulfonyl)phenylcarbamoyl)-3-methoxyacrylamide.

[0561] To a 100mL round-bottom flask was added the product from **Part F** (500mg, 1.528mmol) in DMF (15.0ml). The solution was cooled under nitrogen to -20°C and (E)-3-methoxyacryloyl isocyanate (15.28ml, 6.11mmol; prepared as described by Santana, L.; et al. J. Heterocyclic Chem. 1999, 36, 293-295) was added dropwise. The mixture was stirred at this temperature for 15min, then warmed to room temperature and stirred for 45min. The mixture was diluted with ethyl acetate and washed by water (3 x 50ml), brine (3 x 50ml), dried with sodium sulfate, filtered and evaporated. The residue was triturated with ethyl acetate/hexane to give a solid (425mg, 61%).

Part H. Preparation of 1-(3-iodo-4-methoxy-5-(methylsulfonyl)phenyl)pyrimidine-2,4(1H,3H)-dione.

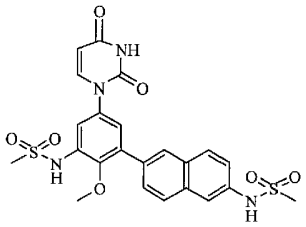
[0562] To a 100mL round-bottom flask was added the product from **Part G** (420mg, 0.925mmol) in ethanol (10ml) to give a suspension. Concentrated sulfuric acid (1mL, 18.76mmol) in water (10ml) was added and the mixture was heated at 110°C for 2h. The reaction mix was cooled, diluted with water (50ml) and stirred for 10min The solid material was collected by filtration, washed with water and dried to give a white solid (325mg, 83%).

Part I. Preparation of N-(6-(5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxy-3-(methylsulfonyl)phenyl)naphthalen-2-yl)methanesulfonamide.

[0563] To a 5mL microwave tube was added the product from **Part H** (63.3mg, 0.15mmol), the product from **Example 2A, Part B** (52.1mg, 0.150mmol), 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride complex (6.12mg, 7.50µmol) and 1M sodium carbonate (0.150ml, 0.150mmol) in the solvents of toluene (1.0ml) and ethanol (1.0ml). The vessel was sealed and the mixture was sparged with nitrogen for 5min and microwaved at 100°C for 30min. The mixture was partitioned with ethyl acetate and 1M HCl. The organic layer was washed with saturated sodium bicarbonate, brine, dried with sodium sulfate, filtered and evaporated. The residue was purified on silica gel eluting with 1% to 8% methanol in CH_2Cl_2 to give crude product. A final trituration in 1:1 methanol/ethyl acetate afforded pure solid (26mg, 34%). ^{1}H NMR (300 MHz, DMSO-D6) δ ppm 3.10 (s, 3 H) 3.44 (s, 3 H) 3.45 (s, 3 H) 5.71 (d, J=8.09 Hz, 1 H) 7.44 (dd, J=8.82, 2.21 Hz, 1 H) 7.75 (d, J=1.84 Hz, 1 H) 7.80 (dd, J=8.46, 1.84 Hz, 1 H) 7.86 (d, J=8.09 Hz, 1 H) 7.91 (d, J=2.57 Hz, 1 H) 7.96 (d, J=2.57 Hz, 1 H) 8.00 (m, 2 H) 8.16 (d, J=1.47 Hz, 1 H) 10.10 (s, 1 H) 11.51 (s, 1 H). MS (ESI+) *m/z* 533 $(M+NH4)^+$.

Example 35. Preparation of N-(5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxy-3-(6-(methylsulfonamido)naphthalen-2-yl)phenyl)methanesulfonamide (compound IB-L0-2.75).

[0564]



Part A. Preparation of 2,4-diiodo-6-nitrophenol.

[0565] To a solution of 2-nitrophenol (2.78g, 20mmol) in MeOH (120ml) and water (30mL) was added dropwise a solution of iodine monochloride (2.105ml, 42.0mmol) in 10mL CH_2Cl_2. The mixture was stirred for 2h, poured into 600mL water, stirred and sonicated for 30min. The mixture was filtered to collect a yellow solid that was washed 3x with water (50mL each wash) and dried to constant mass (7.3g, 93%). m

Part B. Preparation of 1,5-diiodo-2-methoxy-3-nitrobenzene.

[0566] A 50mL pressure vessel was charged with the product from **Part A** and MTBE (10ml) to give a yellow solution. The solution was cooled in an ice bath and 2M trimethylsilyldiazomethane (2.251ml, 4.50mmol) was added at a fast drop followed by dropwise addition of MeOH (0.6ml) resulting in calm bubbling. The vessel was sealed and stirred allowing warm to room temperature over 4h. The mixture was partitioned with ethyl acetate and 1M HCl. The organic layer was washed with saturated sodium bicarbonate, brine, dried with sodium sulfate, filtered and evaporated to give a yellow solid (1.22g, 100%).

Part C. Preparation of 3,5-diiodo-2-methoxyaniline.

[0567] In a 250 round-bottom flask was added the product from **Part B** (0.98g, 2.420mmol), ammonium chloride (0.194g, 3.63mmol), and iron (0.676g, 12.10mmol) in THF/methanol/water (20ml/20ml/10ml). The mixture was refluxed for 16ho, cooled and filtered. The filtrate was evaporated and the residue was partitioned with water and ethyl acetate. The organic layer was dried with sodium sulfate, filtered and evaporated to give an oil (780mg, 86%).

Part D. Preparation of 1-(3-amino-5-iodo-4-methoxyphenyl)pyrimidine-2,4(1H,3H)-dione.

[0568] In a 25mL round-bottom flask was added the product from **Part C** (650mg, 1.734mmol), pyrimidine-2,4(1H,3H)-dione (214mg, 1.907mmol), N-(2-cyanophenyl)picolinamide (77mg, 0.347mmol), copper(I) iodide (33.0mg, 0.173mmol) and potassium phosphate (773mg, 3.64mmol) in DMSO (5ml). The vessel was sealed and the mixture was sparged with nitrogen for 15min and heated at 60°C for 16h. The mixture was partitioned with ethyl acetate and 1M HCl. The organic layer was washed with saturated sodium bicarbonate, brine, dried with sodium sulfate and filtered. The filtrate was treated with 3-mercaptopropyl functionalized silica gel, filtered and evaporated. The residue was chromatographed on silica eluting with 5:95 methanol/D CH_2Cl_2CM to give a solid (125mg, 20%).

Part E. Preparation of N-(5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-3-iodo-2-methoxyphenyl)methanesulfonamide.

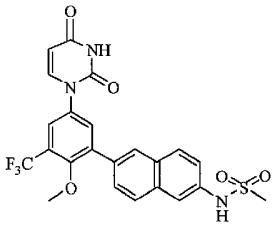
[0569] A solution of the product from **Part D** (110mg, 0.306mmol) in pyridine (2ml) was treated with methanesulfonyl chloride (0.048ml, 0.612mmol) and stirred for 24h. The solvent was evaporated and the residue was partitioned with ethyl acetate and 1M HCl. The organic layer was washed with brine, dried with sodium sulfate, filtered and evaporated. The residue was purified on silica gel eluting with 2% to 5% methanol in CH_2Cl_2 to give a solid (20mg, 15%).

Part F. Preparation of N-(5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxy-3-(6-(methylsulfonamido)naphthalen-2-yl)phenyl)methanesulfonamide.

[0570] To a 5mL microwave tube was added the product from **Part E** (18mg, 0.041mmol), **Example 2A, Part B** (14.30mg, 0.041mmol), potassium phosphate (18.35mg, 0.086mmol), PA-Ph (CAS 97739-46-3) (0.361mg, 1.235µmol) and tris(dibenzylideneacetone)dipalladium(0) (0.377mg, 0.412µmol) in THF (3.0ml) and water (1.0ml). The vessel was sealed and the mixture was sparged with nitrogen for 5min and heated at 50°C for 2h. The mixture was partitioned with ethyl acetate and 1M HCl. The organic layer was washed with saturated sodium bicarbonate, brine, dried with sodium sulfate, filtered and evaporated. The residue was purified on silica gel eluting with 2% to 5% methanol in CH_2Cl_2 to give a solid. A final trituration in 1:1 methanol/ CH_2Cl_2 gave the desired product (7mg, 32%). ^{1}H NMR (300 MHz, DMSO-D6) δ ppm 3.09 (s, 3 H) 3.17 (s, 3 H) 3.37 (s, 3 H) 5.69 (dd, J=7.91, 2.02 Hz, 1 H) 7.34 (d, J=2.57 Hz, 1 H) 7.43 (dd, J=8.82, 2.21 Hz, 1 H) 7.47 (d, J=2.57 Hz, 1 H) 7.73 (m, 2 H) 7.81 (d, J=8.09 Hz, 1 H) 7.94 (d, J=6.25 Hz, 1 H) 7.97 (d, J=6.62 Hz, 1 H) 8.07 (s, 1 H) 9.45 (s, 1 H) 10.05 (s, 1 H) 11.45 (d, J=1.84 Hz, 1 H). MS (ESI-) *m/z* 529 (M-H).

Example 36. Preparation of N-(6-(5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxy-3-(trifluoromethyl)phenyl)naphthalen-2-yl)methanesulfonamide (compound IB-L0-2.56).

[0571]



Part A. Preparation of 4-iodo-2-(trifluoromethyl)phenol.

[0572] To a solution of 2-(trifluoromethyl) phenol (3.24g, 20mmol) in MeOH (40ml) was added sodium hydroxide (0.960g, 24.0mmol) and stirred until the hydroxide was dissolved. The mixture was cooled to 0°C and sodium iodide was added (3.0g, 20mmol) followed by dropwise addition of 10% aqueous sodium hypochlorite (9.0ml, 14.6mmol). The addition of sodium iodide followed by sodium hypochlorite was repeated twice more. The mixture was stirred at ambient temperature for 2h and treated dropwise with concentrated HCl to pH 1. The mixture was extracted 3 X with EtOAc. The extracts were combined, washed with

brine, dried with sodium sulfate, filtered and evaporated. The residue was purified on silica gel eluting with EtOAc/hexane (1:9) to give the mono-iodo product (5.0 g, 87%).

Part B. Preparation of 2-bromo-4-iodo-6-(trifluoromethyl)phenol.

[0573] In a 250mL round-bottom flask was added the product from **Part A** (5.00g, 17.36mmol) and 1,3-dibromo-5,-dimethylhydantoin (2.73g, 9.55mmol) in $CHCl_3$ (80ml) to give an orange solution. The mixture was stirred for 2h, washed with water, brine, dried with sodium sulfate, filtered and evaporated. The crude product was purified on silica gel eluting with ethyl acetate/hexane (5:95) to give a solid (3.5g, 54%).

Part C. Preparation of 1-bromo-5-iodo-2-methoxy-3-(trifluoromethyl)benzene.

[0574] A mixture of the product from **Part B** (3.2g, 8.72mmol), iodomethane (1.36ml, 21.8mmol), and 50% sodium hydroxide (0.507ml, 9.59mmol) in acetone (20ml) was stirred for 24h. The solvent was evaporated and the residue was partitioned with ethyl acetate and water. The organic layer was washed with brine, dried with sodium sulfate, filtered and evaporated. The crude material was purified on silica gel eluting with ethyl acetate/hexane (5:95) to give a solid (2.67g, 80%).

Part D. Preparation of 1-(3-bromo-4-methoxy-5-(trifluoromethyl)phenyl)pyrimidine-2,4 (1H,3H)-dione.

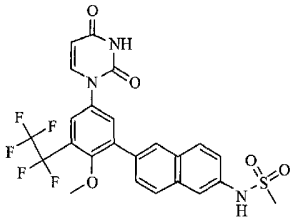
[0575] In a 20mL microwave tube was added the product from **Part C** (762mg, 2.0mmol), pyrimidine-2,4(1H,3H)-dione (247mg, 2.2mmol), N-(2-cyanophenyl)picolinamide (89mg, 0.4mmol), copper(I) iodide (38.1mg, 0.2mmol) and potassium phosphate (892mg, 4.2mmol) in DMSO (10ml). The vessel was sealed and the mixture was sparged with nitrogen for 15min and heated at 60°C for 16h. The mixture was partitioned with ethyl acetate and 1M HCl. The organic layer was washed with saturated sodium bicarbonate, brine, dried with sodium sulfate and filtered. The filtrate was treated with 3-mercaptopropyl functionalized silica gel, filtered and evaporated. The residue was purified on silica gel eluting with ethyl acetate/hexane (2:3) to give the desired product (63mg, 9%).

Part E. Preparation of N-(6-(5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxy-3-(trifluoromethyl)phenyl)naphthalen-2-yl)methanesulfonamide.

[0576] In a 5mL microwave tube was added the product from **Part D** (60mg, 0.164mmol), the product from **Example 2A, Part B** (62.8mg, 0.181mmol), 1,1'-bis(di-tert-butylphosphino)ferrocene palladium dichloride (5.36mg, 8.22µmol) and potassium phosphate (69.8mg, 0.329mmol) in THF/water (3ml/1ml). The vessel was sealed and the mixture was sparged with nitrogen for 5min and heated at 60°C for 2h. The mixture was partitioned with ethyl acetate and 1M HCl. The organic layer was washed with saturated sodium bicarbonate, brine, dried with sodium sulfate and filtered. The filtrate was treated with 3-mercaptopropyl functionalized silica gel, filtered and evaporated. The residue was purified by reverse phase chromatography to give the title compound as a solid (26mg, 31%). ^{1}H NMR (300 MHz, DMSO-D6) δ ppm 3.10 (s, 3 H) 3.37 (s, 3 H) 5.71 (dd, J=7.72, 2.21 Hz, 1 H) 7.44 (dd, J=8.82, 2.21 Hz, 1 H) 7.75 (s, 1 H) 7.78 (d, J=1.84 Hz, 1 H) 7.88 (m, 3 H) 7.98 (d, J=3.31 Hz, 1 H) 8.01 (d, J=3.68 Hz, 1 H) 8.15 (s, 1 H) 10.09 (s, 1 H) 11.51 (d, J=2.21 Hz, 1 H). MS (ESI-) *m/z* 504.1 $(M-H)^+$.

Example 37. Preparation of N-(6-(5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxy-3-(perfluoroethyl)phenyl)naphthalen-2-yl)methanesulfonamide (compound IB-L0-2.60).

[0577]



Part A. Preparation of 1-methoxy-4-nitro-2-(perfluoroethyl)benzene.

[0578] To a 250mL round-bottom flask was added 2-bromo-1-methoxy-4-nitrobenzene (3.5g, 15.08mmol), copper(I) iodide (5.75g, 30.2mmol), and sodium 2,2,3,3,3-pentafluoropropanoate (5.25g, 28.2mmol) in DMF (75ml) and toluene (25ml) to give a tan suspension. The mixture was heated at 150°C and toluene was removed by a Dean-Stark trap. The mixture was heated at 155°C for 6h under nitrogen, cooled and poured into 100mL of water and 100mL of ether, filtered through a 1-inch plug of Celite and the plug was rinsed with ether. The filtrate layers were separated. The organic layer was washed with brine, dried (Na_2SO_4) filtered and concentrated. The dark oil was flash chromatographed on an Isco 40g silica cartridge eluting with 4:1 hexane/EtOAc to give a yellow oil that was a (3:1) mix of desired material and starting material (1.5g, 37%).

Part B. Preparation of 4-nitro-2-(perfluoroethyl)phenol.

[0579] In a 100mL round-bottom flask was added the product from **Part A** (1.4g, 5.16mmol) and pyridine hydrochloride (4g, 34.6mmol) neat. The mixture was heated at 210°C for 20min, cooled, and partitioned between EtOAc and water. The organic layer was washed with brine, dried (Na_2SO_4) and concentrated. The crude product was flash chromatographed on an Isco 12g silica cartridge eluting with 3:2 hecxane/EtOAc to give a yellow oil (1.3g, 98%).

Part C. Preparation of 2-iodo-4-nitro-6-(perfluoroethyl)phenol.

[0580] In a 100mL round-bottom flask was added the product from **Part B** (1.3g, 5.06mmol) and N-iodosuccinimide (1.251 g, 5.56mmol) in acetonitrile (16.85ml) to give a yellow solution. The solution was stirred for 16h, diluted with 100mL EtOAc and washed 2 x 50ml with 10% sodium thiosulfate, brine, dried (Na_2SO_4) and concentrated to an orange semisolid. The semisolid was flash chromatographed on an Isco 40g silica cartridge eluting with 3:1 hexane EtOAc to give a deep yellow/orange oil (1.3g, 67%).

Part D. Preparation of 1-iodo-2-methoxy-5-nitro-3-(perfluoroethyl)benzene.

[0581] In a 100mL round-bottom flask was added the product from **Part C** (1.04g, 2.72mmol) potassium carbonate (0.563g, 4.07mmol) and dimethyl sulfate (0.411g, 3.26mmol) in acetone (20ml) to give a brown suspension. The mixture was heated at gentle reflux for 16h, cooled, diluted into EtOAc, washed with water and brine. The organic layer was dried Na2SO4, filtered and concentrated to a yellow oil that was purified by flash chromatography on an Isco 40g silica cartridge eluting with 9:1 hexane/EtOAc (600mg, 56%).

Part E. Preparation of 3-iodo-4-methoxy-5-(perfluoroethyl)aniline.

[0582] In a 250mL round-bottom flask was added the product from **Part D** (0.6g, 1.511mmol), iron (0.422g, 7.56mmol), and ammonium chloride (0.121g, 2.267mmol) in a solvent mix of EtOH (9ml), THF (9ml) and water (3ml) to give a brown suspension that was heated at 95-100°C for 2h. The reaction mix was filtered through a plug of Celite and the Celite was rinsed repeatedly with EtOH. The filtrate was concentrated and the residue was dissolved in EtOAc, washed with water, brine, dried (Na_2SO_4), filtered and concentrated to give an oil (560mg, 99%).

Part F. Preparation of 1,5-diiodo-2-methoxy-3-(perfluoroethyl)benzene.

[0583] In a 25mL round-bottom flask under nitrogen was added the product from **Part E** (0.565g, 1.539mmol), tert-butyl nitrite (0.293ml, 2.463mmol), copper(I) iodide (0.293g, 1.539mmol), sodium iodide (0.231g, 1.539mmol) and iodine (0.195g, 0.770mmol) in DME (15.39ml) to give a brown suspension. The mixture was heated at 60°C for 3h, cooled and filtered through Celite washing the Celite pad well with EtOAc. The EtOAc filtrate was treated with 10% sodium thiosulfate, brine, dried (Na_2SO_4), filtered and concentrated to a dark oil. The crude material was purified by flash chromatography on an Isco 40g silica cartridge eluting with 95:5 hexane/EtOAc to give a yellow oil (360mg, 49%).

Part G. Preparation of 1-(3-iodo-4-methoxy-5-(perfluoroethyl)phenyl)pyrimidine-2,4(1H,3H)-dione.

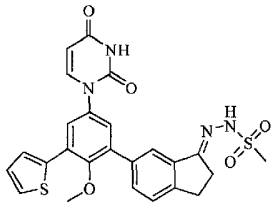
[0584] In a 20mL microwave tube was added the product from **Part F** (0.36g, 0.753mmol), 1H-pyrimidine-2,4-dione (0.101g, 0.904mmol), potassium phosphate tribasic (0.336g, 1.582mmol) N-(2-cyanophenyl)picolinamide (0.034g, 0.151mmol) and copper(I) iodide (0.014g, 0.075mmol in DMSO (7ml). The vessel was sealed and the mixture was sparged with N_2 for 30min, heated at 60°C for 24h, cooled and diluted into EtOAc. The EtOAc layer was washed with 1M HCl, saturated NaHCO3, and saturated NaCl, dried (Na_2SO_4), filtered and concentrated. The residue was flash chromatographed on an Isco 40g silica cartridge eluting with hexane --> 1:1 hexane/EtOAc to give a yellow foam (100mg, 29%).

Part H. Preparation of N-(6-(5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxy-3-(perfluoroethyl)phenyl)naphthalen-2-yl)methanesulfonamide.

[0585] In a 5mL microwave tube were combined the product from **Part G** (0.10g, 0.216mmol), **Example 2A, Part B** (0.075g, 0.216mmol), and potassium phosphate tribasic (0.096g, 0.454mmol) in 3:1 tetrahydrofuran-water (5mL) and degassed by nitrogen sparge for 10min. The mixture was then treated with PA-Ph (CAS 97739-46-3) (1.898mg, 6.49µmol) and tris(dibenzylideneacetone)dipalladium(0) (1.982mg, 2.164µmol) followed by degassing for another 5min. The flask was then sealed and stirred at 50°C for 16h and partitioned between EtOAc and water. The EtOAc layer was washed with 0.1M HCl, saturated $NaHCO_3$, and saturated NaCl. The organic was dried Na_2SO_4, stirred for 0.5h with 3-mercapto-propyl functionalized silica to remove metals, filtered and concentrated. The crude product was purified by chromatography on an Isco 12g silica cartridge eluting with CH_2Cl_2 --> 3% MeOH in CH_2Cl_2 to give a light yellow foam (84mg, 99%) m.p. 162-165°C. ^{1}HNMR (300 MHz, DMSO-D6) δ ppm 3.10 (s, 3 H) 3.33 (s, 3 H) 5.70 (d, J=7.72 Hz, 1 H) 7.44 (dd, J=8.82, 2.21 Hz, 1 H) 7.70 - 7.76 (m, 2 H) 7.80 (d, J=2.57 Hz, 1 H) 7.86 (d, J=8.09 Hz, 1 H) 7.91 (d, J=2.57 Hz, 1 H) 8.00 (dd, J=8.82, 2.94 Hz, 2 H) 8.12 (s, 1 H) 10.10 (s, 1 H) 11.50 (s, 1 H). MS (ESI-) *m/z* 554 $(M-H)^+$.

Example 38. Preparation of (E)-N'-(6-(5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxy-3-(thiophen-2-yl)phenyl)-2,3-dihydro-1H-inden-1-ylidene)methanesulfonohydrazide (compound IB-L0-2.51).

[0586]



Part A. Preparation of 1-(3-bromo-4-methoxy-5-(1-oxo-2,3-dihydro-1H-inden-5-yl)phenyl)-pyrimidine-2,4(1H,3H)-dione.

[0587] In a 100mL round-bottom flask was added the product from **Example 18, Part C** (846mg, 2.00mmol), **Example 4, Part A** (516mg, 2.000mmol), potassium phosphate (892mg, 4.20mmol), PA-Ph (CAS 97739-46-3) (17.54mg, 0.060mmol) and tris(dibenzylideneacetone)-dipalladium(0) (18.31mg, 0.020mmol) in THF (12.0ml) and water (4.0ml). The vessel was sealed and the mixture was sparged with nitrogen for 5min and stirred at ambient temperature for 72h. The mixture was partitioned with ethyl

acetate and 1M HCl. The organic layer was washed with saturated sodium bicarbonate, brine, dried with sodium sulfate and filtered. The filtrate was treated with 3-mercaptopropyl functionalized silica gel, filtered through celite and evaporated. The residue was purified with silica gel eluting with 1 to 4% methanol in CH_2Cl_2 to give a solid (690mg, 81%).

Part B. Preparation of (E)-N'-(5-(3-bromo-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)-2,3-dihydro-1H-inden-1-ylidene)methanesulfonohydrazide.

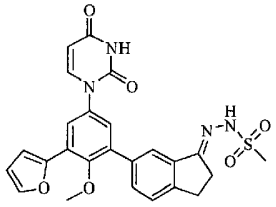
[0588] In a 50mL round-bottom flask was added the product from **Part A** (685mg, 1.603mmol) and methanesulfonohydrazide (194mg, 1.764mmol) in MeOH (20ml). The mixture was warmed to 40°C and stirred for 24h. The mixture was cooled, filtered and washed with methanol to give a solid (569mg, 68%).

Part C. Preparation of (E)-N'-(6-(5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxy-3-(thiophen-2-yl)phenyl)-2,3 -dihydro-1 H-inden-1-ylidene)methanesulfonohydrazide.

[0589] In a 5mL microwave tube was added the product from **Part B** (52mg, 0.100mmol), thiophen-2-ylboronic acid (12.81mg, 0.100mmol), 1,1'-bis(di-tert-butylphosphino)ferrocene palladium dichloride (3.26mg, 5.01µmol) and potassium phosphate (42.5mg, 0.200mmol) in THF (3.0ml) and water (1.0ml). The mixture was sparged by nitrogen for 5min and heated at 50°C for 3h. The mixture was partitioned with ethyl acetate and 1M HCl. The organic layer was washed with saturated sodium bicarbonate, brine, dried with sodium sulfate and filtered. The filtrate was treated with 3-mercaptopropyl functionalized silica gel, filtered through celite and evaporated. The residue was purified by reverse phase chromatography AA method to give a white solid (27mg, 52%). ^{1}H NMR (300 MHz, DMSO-D6) δ ppm 2.86 (m, 2 H) 3.09 (s, 3 H) 3.14 (m, 2 H) 3.32 (s, 3 H) 5.69 (d, J=7.72 Hz, 1 H) 7.18 (dd, J=5.15, 3.68 Hz, 1 H) 7.41 (d, J=2.57 Hz, 1 H) 7.63 (m, 3 H) 7.75 (m, 2 H) 7.86 (d, J=8.09 Hz, 1 H) 7.91 (d, J=2.94 Hz, 1 H) 9.96 (s, 1 H) 11.48 (s, 1 H). MS (ESI+) *m/z* 523 $(M+H)^+$.

Example 39. Preparation of (E)-N'-(6-(5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-3-(furan-2-yl)-2-methoxyphenyl)-2,3-dihydro-1H-inden-1-ylidene)methanesulfonohydrazide (compound IB-L0-2.55).

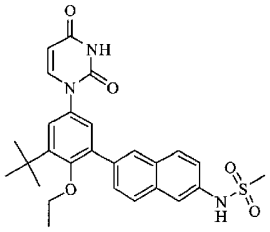
[0590]



[0591] In a 5ml microwave tube was added the product from **Example 38, Part B** (52mg, 0.100mmol), furan-2-ylboronic acid (11.20mg, 0.100mmol), 1,1'-bis(di-tert-butylphosphino)ferrocene palladium dichloride (3.26mg, 5.01µmol) and potassium phosphate (42.5mg, 0.200mmol) in THF (3.0ml) and water (1.0ml). The mixture was sparged by nitrogen for 5min and heated at 50°C for 3h. The mixture was partitioned with ethyl acetate and 1M HCl. The organic layer was washed with saturated sodium bicarbonate, brine, dried with sodium sulfate and filtered. The filtrate was treated with 3-mercaptopropyl functionalized silica gel, filtered through celite and evaporated. The residue was purified by reverse phase chromatography AA method to give a solid (24mg, 47%). ^{1}H NMR (300 MHz, DMSO-D6) δ ppm 2.86 (m, 2 H) 3.09 (s, 3 H) 3.14 (m, 2 H) 3.36 (s, 3 H) 5.68 (d, J=8.09 Hz, 1 H) 6.69 (dd, J=3.31, 1.84 Hz, 1 H) 7.09 (d, J=3.31 Hz, 1 H) 7.41 (d, J=2.57 Hz, 1 H) 7.62 (m, 2 H) 7.75 (d, J=8.09 Hz, 1 H) 7.80 (d, J=2.57 Hz, 1 H) 7.86 (m, 2 H) 9.97 (s, 1 H) 11.46 (s, 1 H). MS (ESI+) *m/z* 507 $(M+H)^+$.

Example 40. Preparation of N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-ethoxyphenyl)naphthalen-2-yl)methanesulfonamide (compound IB-L0-2.23).

[0592]



Part A. Preparation of 2-tert-butyl-4-iodophenol.

[0593] To a 250mL round-bottom flask was added 2-tert-butylphenol (3.76g, 25mmol) in MeOH (50.0ml) to give a colorless solution. Sodium hydroxide (1.200g, 30.0mmol) was added and the mix was stirred until the hydroxide was completely dissolved. The solution was cooled to 0°C and treated with sodium iodide (1.75g, 11.6mmol) followed by dropwise addition of 10% sodium hypochlorite solution (7.2ml, 11.6mmol). The addition of sodium iodide followed by sodium hypochlorite was repeated twice and the mixture was stirred at 0°C for 30min. The mixture was treated with 10% w/w solution of sodium thiosulfate, stirred for 30min and treated with concentrated HCl dropwise to a constant pH of 1. The mixture was extracted 3X with EtOAc. The extracts were combined, washed with brine, dried (MgS04), filtered and concentrated. The crude oil was flash chromatographed on an ISCO 80g silica cartridge eluting with hexane --> 4:1 hexane/EtOAc to give a yellow oil (5.2g , 75%).

Part B. Preparation of 2-bromo-6-tert-butyl-4-iodophenol.

[0594] To a 250mL round-bottom flask was added the product from **Part A** (4.8g, 17.38mmol) and 1,3-dibromo-5,5-dimethylhydantoin (2.61g, 9.13mmol) in chloroform (87ml) to give an orange solution. The reaction mixture was stirred for 2h resulting in a black solution that was washed with water, brine, dried (Na_2SO_4) and concentrated. The black oil was flash chromatographed on a 120g Isco silica cartridge eluting with hexane to give a pinkish solid (4.84g, 78%).

Part C. Preparation of 1-bromo-3-tert-butyl-2-ethoxy-5-iodobenzene.

[0595] To a 50mL round-bottom flask was added the product from **Part B** (888mg, 2.5mmol), ethyl iodide (409mg, 2.63mmol), and potassium carbonate (415mg, 3.00mmol) in acetone (12ml) to give a green suspension. The mixture was heated at reflux for 16h, cooled and concentrated. The residue was partitioned between water and EtOAc. The organic layer was washed twice with brine, dried over Na_2SO_4, filtered and concentrated to a red oil. The oil was flash chromatographed on an Isco 40g silica cartridge eluting with hexane to give a clear oil (820mg, 86%).

Part D. Preparation of 1-(3-bromo-5-tert-butyl-4-ethoxyphenyl)pyrimidine-2,4(1H,3H)-dione.

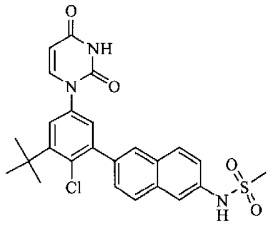
[0596] In a 20mL microwave tube under nitrogen flush was added the product from **Part C** (0.4g, 1.044mmol), 1H-Pyrimidine-2,4-dione (0.140g, 1.253mmol), and potassium phosphate tribasic (0.465g, 2.193mmol) in DMSO (5ml) to give a colorless suspension. N-(2-cyanophenyl)picolinamide (0.047g, 0.209mmol) was added and the mix was sparged with nitrogen for 10min. Copper(I) iodide (0.020g, 0.104mmol) was added and the mix was sparged once again for 10min, placed under nitrogen and heated at 60°C for 18h. The mixture was cooled and partitioned between EtOAc and water adjusting the pH to 1 with HCl. The aqueous layer was extracted 2X with EtOAc. The organics were combined, washed with water, saturated $NaHCO_3$, and saturated NaCl. The organic layer was dried (Na_2SO_4), stirred with 3-mercaptopropyl functionalized silica for 1h, filtered and concentrated. The crude product was purified by chromatography on an ISCO 12g silica cartridge eluting with 2% MeOH in CH_2Cl_2 to give a white powder (266mg, 69%).

Part E. Preparation of N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-ethoxyphenyl)naphthalen-2-yl)methanesulfonamide.

[0597] In a 5mL microwave tube was added the product from **Part D** (55.1mg, 0.15mmol), the product from **Example 2A, Part B** (52.1mg, 0.150mmol), potassium phosphate tribasic (63.7mg, 0.300mmol) and 1,1'-bis(di-tert-butylphosphino)ferrocene palladium dichloride (4.89mg, 7.50µmol) in THF (3ml) water (1ml). The mixture was sparged for 10min with nitrogen, heated sealed at 50°C for 4h, cooled and diluted into EtOAc. The EtOAc layer was washed with 1M HCl, saturated $NaHCO_3$, saturated NaCl, dried (Na_2SO_4) and treated simultaneously with mercaptopropyl silica gel, filtered and concentrated. The residue was flash chromatographed on a 12g Isco silica cartridge eluting with 2% MeOH in CH_2Cl_2 to give a solid, (16mg, 21%) m.p. 196-202°C. ^1H NMR (300 MHz, DMSO-D6) δ ppm 1.00 (t, J=6.99 Hz, 3 H) 1.44 (s, 9 H) 3.09 (s, 3 H) 3.43 (q, J=7.11 Hz, 2 H) 5.64 (dd, J=7.91, 1.29 Hz, 1 H) 7.32 (d, J=2.94 Hz, 1 H) 7.36 (d, J=2.94 Hz, 1 H) 7.41 (dd, J=8.82, 2.21 Hz, 1 H) 7.72 (s, 1 H) 7.74 (d, J=1.47 Hz, 1 H) 7.80 (d, J=7.72 Hz, 1 H) 7.90 - 8.00 (m, 2 H) 8.05 (s, 1 H) 10.04 (s, 1 H) 11.41 (s, 1 H). MS (ESI-) *m/z* 506 $(M-H)^+$.

Example 41. Preparation of N-(6-(3-tert-butyl-2-chloro-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)phenyl)naphthalen-2-yl)methanesulfonamide (compound IB-L0-2.14).

[0598]



Part A. Preparation of 2-bromo-6-tert-butyl-4-iodoaniline.

[0599] In a 50mL round-bottom flask was added 2-bromo-6-tert-butylaniline [prepared by the method of Onitsuka, et.al. Organometallics, 25(5), 2006, pp 1270-1278] (1.18g, 5.17mmol) and sodium bicarbonate (0.782g, 9.31mmol) in water (5ml). The mixture was cooled in an ice bath and iodine (1.444g, 5.69mmol) was added in several portions. The mixture was warmed to ambient temperature and stirred for 16h. The mixture was treated with aqueous sodium thiosulfate, extracted by ethyl acetate, dried with sodium sulfate, filtered and evaporated. The residue was purified on silica gel eluting with 5% ethyl acetate in hexane to give an oil (1.2g, 65%).

Part B. Preparation of 1-bromo-3-tert-butyl-2-chloro-5-iodobenzene.

[0600] To a mixture oftert-butyl nitrite (0.198ml, 1.5mmol) and copper(II) chloride (161mg, 1.2mmol) in acetonitrile (5mL) was added the product from **Part A** (354mg, 1.0mmol) as a solution in acetonitrile (5mL). The mixture was heated at 60°C for 30min, cooled, partitioned with ethyl acetate and 1M HCl. The organic layer was washed with brine, dried with sodium sulfate, filtered and evaporated. The residue was purified on silica gel eluting with 5% ethyl acetate in hexane to give the product (300mg, 81%).

Part C. Preparation of 1-(3-bromo-5-tert-butyl-4-chlorophenyl)pyrimidine-2,4(1H,3H)-dione.

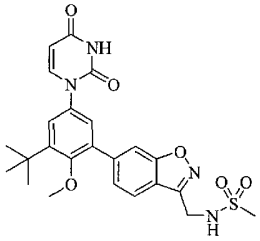
[0601] In a 20mL microwave tube was added the product from **Part B** (300mg, 0.803mmol), pyrimidine-2,4(1H,3H)-dione (99mg, 0.884mmol), N-(2-cyanophenyl)picolinamide (35.9mg, 0.161mmol), copper(I) iodide (15.30mg, 0.080mmol) and potassium phosphate (358mg, 1.687mmol) in DMSO (5ml). The mixture was sealed, purged with nitrogen and heated at 60°C for 4h. The mixture was partitioned with ethyl acetate and 1M HCl. The organic layer was washed with saturated sodium bicarbonate, brine, dried with sodium sulfate and filtered. The filtrate was treated with 3-mercaptopropyl functionalized silica gel, filtered and evaporated. The residue was purified on silica gel eluting with 10% to 40% ethyl acetate in hexane to give a solid (175mg, 61%).

Part D. Preparation of N-(6-(3-tert-butyl-2-chloro-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)phenyl)naphthalen-2-yl)methanesulfonamide.

[0602] In a 5mL microwave tube was added the product from **Part C** (35.8mg, 0.10mmol), the product from **Example 2A, Part B** (38.2mg, 0.110mmol), 1,1'-bis(di-tert-butylphosphino)ferrocene palladium dichloride (3.26mg, 5.00µmol) and potassium phosphate (42.5mg, 0.200mmol) in THF/Water (3ml:1ml). The mixture was purged with nitrogen for 5min and heated at 60°C for 2h. The mixture was partitioned with ethyl acetate and 1M HCl. The organic layer was washed with saturated sodium bicarbonate, brine, dried with sodium sulfate and filtered. The filtrate was treated with 3-mercaptopropyl functionalized silica gel, filtered and evaporated. The residue was purified on silica gel eluting with 1:1 ethyl acetate/hexane to give a solid that was triturated with 1% methanol in CH_2Cl_2 to give a white solid (29mg, 55%), melting point: > 280°C. ^{1}H NMR (300 MHz, DMSO-D6) δ ppm 1.53 (s, 9 H) 3.08 (s, 3 H) 5.69 (d, J=7.72 Hz, 1 H) 7.42 (m, 2 H) 7.52 (dd, J=8.46, 1.84 Hz, 1 H) 7.56 (d, J=2.57 Hz, 1 H) 7.74 (d, J=1.84 Hz, 1 H) 7.84 (d, J=7.72 Hz, 1 H) 7.88 (s, 1 H) 7.91 (d, J=8.82 Hz, 1 H) 7.95 (d, J=9.19 Hz, 1 H) 10.04 (s, 1 H) 11.46 (s, 1 H). MS (ESI-) *m/z* 496 $(M-H)^+$.

Example 42. Preparation of *N*-((6-(3-*tert*-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxyphenyl)benzo[*d*]isoxazol-3-yl)methyl)methanesulfonamide (compound IB-L0-2.45).

[0603]



Part A. Preparation of *N*-((6-bromobenzo[*d*]isoxazol-3-yl)methyl)-*N*-(4-methoxybenzyl)-methanesulfonamide.

[0604] To a refluxing solution of 6-bromo-3-methylbenzo[d]isoxazole (1.0g, 4.72mmol) in CCl_4 (25ml) was added 1-bromopyrrolidine-2,5-dione (0.923g, 5.19mmol) and benzoic peroxyanhydride (0.114g, 0.472mmol). The mixture was refluxed for 6h, and then cooled to room temperature, filtered thru celite, and concentrated in vacuo. The crude product was purified by column chromatography on silica gel using CH_2Cl_2 as the eluent to give the dibromide as a solid (0.84g, 43%). To a solution of the dibromide (0.20g, 0.687mmol) and *N*-(4-methoxybenzyl)methanesulfonamide (0.148g, 0.687mmol) in EtOH (3ml) was added 1N aq. NaOH (0.722ml, 0.722mmol), and the resulting mixture was stirred at 80°C for 90min. The mixture was partitioned between 0.1N aq. HCL (10mL) and EtOAc (2 x 10mL), and the combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by column chromatography on silica gel using 2:3 EtOAc:hexanes as eluent to give the title compound as an oil (65mg, 22%).

Part B. Preparation of *N*-(4-methoxybenzyl)-*N*-((6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[*d*]isoxazol-3-yl)methyl)methanesulfonamide.

[0605] A solution of the product from **Part A** (56mg, 0.132mmol), bis(pinacolato)diboron (37mg, 0.145mmol), and potassium acetate (39mg, 0.395mmol) in 1,4-dioxane (1.3mL) was degassed by bubbling with N_2 gas for 15min. 1,1'-Bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (3mg, 0.004mmol) was added, and the resulting mixture was stirred at 80°C for 16h, filtered and concentrated in vacuo. The crude product was purified by column chromatography on silica gel using 1:2 EtOAc:hexanes as the eluent to give the title compound as a colorless oil (49mg, 79%).

Part C. Preparation of *N*-((6-(3-*tert*-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxyphenyl)benzo[*d*]isoxazol-3-yl)methyl)-*N*-(4-methoxybenzyl)methanesulfonamide.

[0606] A mixture of the product from **Example C** (31.8mg, 0.079mmol), the product from **Part B** (45mg, 0.095mmol) in EtOH

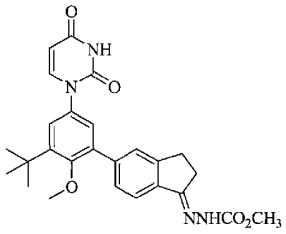
(0.5mL), toluene (0.5mL) 1M aq. Na_2CO_3 (0.095mL, 0.095mmol) was degassed by bubbling with N_2 gas for 10min. 1,1'-Bis(diphenylphosphino)ferrocene-palladium(II) dichloride dichloromethane complex (2mg, 2.4µmol) was added, and degassing with N_2 was continued for 5min. The reaction mixture was sealed and heated at 100°C in a microwave reactor for 1h. The mixture was concentrated in vacuo, and the crude product was purified by column chromatography on silica gel using 1:9 MeOH:$CHCl_3$ as the eluent. The title compound was obtained as a light brown solid (41mg, 83%).

Part D. Preparation of *N*-((6-(3-*tert*-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxyphenyl)benzo[*d*]isoxazol-3-yl)methyl)methanesulfonamide.

[0607] A solution of the product from **Part C** (39mg, 0.063mmol) in TFA (0.5mL) was stirred at 40°C for 6h. TFA was removed in vacuo and the crude product was purified by column chromatography on silica gel using 4% MeOH in $CHCl_3$ as the eluent to give the title compound (13mg, 41%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.39 (s, 1 H) 7.74 - 7.82 (m, 2 H) 7.57 (dd, *J*=8.27, 1.65 Hz, 1 H) 7.36 (d, *J*=7.72 Hz, 1 H) 7.25 (d, *J*=2.57 Hz, 1 H) 7.19 (d, *J*=2.94 Hz, 1 H) 5.82 (dd, *J*=7.72, 2.21 Hz, 1 H) 5.25 - 5.33 (m, 1 H) 4.70 (d, *J*=6.25 Hz, 2 H) 3.29 (s, 3 H) 3.12 (s, 3 H) 1.45 (s, 9 H).

Example 43. Preparation of methyl 2-(5-(3-*tert*-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxyphenyl)-2,3-dihydro-1*H*-inden-1-ylidene)hydrazinecarboxylate (compound IB-L0-2.24).

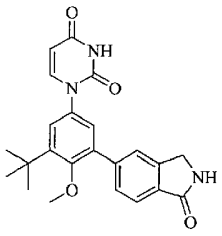
[0608]



[0609] To a solution of the product from **Example 4, Part B** (0.05g, 0.124mmol) in MeOH (1ml) was added methyl carbazate (17mg, 0.185mmol). The mixture was stirred at 60°C for 16h, and then concentrated in vacuo. The crude product was purified by column chromatography on silica gel using 5% MeOH in CH_2Cl_2 as the eluent to give the title compound (44mg, 74%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.40 (s, 1 H) 10.05 (s, 1 H) 7.78 (d, *J*=8.09 Hz, 1 H) 7.69 (d, *J*=7.72 Hz, 1 H) 7.45 - 7.57 (m, 2 H) 7.24 - 7.33 (m, 2 H) 5.64 (d, *J*=8.09 Hz, 1 H) 3.71 (s, 3 H) 3.28 (s, 3 H) 3.06 - 3.16 (m, 2 H) 2.78 - 2.88 (m, 2 H) 1.40 (s, 9 H).

Example 44. Preparation of 1-(3-*tert*-butyl-4-methoxy-5-(1-oxoisoindolin-5-yl)phenyl)-pyrimidine-2,4(1*H*,3*H*)-dione (compound IB-L0-2.30).

[0610]



Part A. Preparation of 5-bromo-2-(2,4-dimethoxybenzyl)isoindolin-1-one.

[0611] To a solution of methyl 4-bromo-2-(bromomethyl)benzoate (1.0g, 3.25mmol) and (2,4-dimethoxyphenyl)methanamine (0.65g, 3.90mmol) in THF (16mL) was added triethylamine (0.91mL, 6.5mmol), and the resulting mixture was stirred at room

temeprature for 16h. The resulting solid was filtered off, and the filtrate was concentrated in vacuo. The crude product was purified by column chromatography on silica gel using 1:4 EtOAc:hexanes as the eluent to give the title compound as a colorless solid (0.52g, 44%).

Part B. Preparation of 2-(2,4-dimethoxybenzyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoindolin-1-one.

[0612] The product from **Part A** (100mg, 0.276mmol) was subjected to the conditions described for **Example 42, Part B** to give the title compound as an oil (107mg, 95%).

Part C. Preparation of 1-(3-*tert*-butyl-5-(2-(2,4-dimethoxybenzyl)-1-oxoisoindolin-5-yl)-4-methoxyphenyl)pyrimidine-2,4(1*H*,3*H*)-dione.

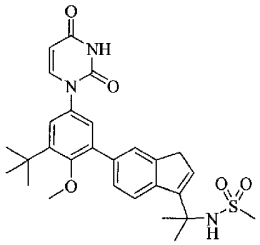
[0613] The product from **Part C** (44mg, 0.111mmol) was subjected to the conditions described for **Example 42, Part C** to give the title compound (50mg, 81%).

Part D. Preparation of 1-(3-*tert*-butyl-4-methoxy-5-(1-oxoisoindolin-5-yl)phenyl) pyrimidine-2,4(1*H*,3*H*)-dione.

[0614] A solution of the product from **Part C** (48mg, 0.086mmol) in CH_2Cl_2 (0.3ml) and TFA (0.6ml, 7.79mmol) was stirred at room temperature for 16h, and then concentrated in vacuo. The crude product was purified by column chromatography on silica gel using 5% MeOH in $CHCl_3$ as the eluent to give the title compound as a colorless solid (22mg, 63%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.41 (d, *J*=1.84 Hz, 1 H) 8.61 (s, 1 H) 7.72 - 7.83 (m, 3 H) 7.62 - 7.69 (m, 1 H) 7.29 - 7.36 (m, 2 H) 5.65 (dd, *J*=8.09, 2.21 Hz, 1 H) 4.44 (s, 2 H) 3.25 (s, 3 H) 1.41 (s, 9 H).

Example 45. Preparation of *N*-(2-(6-(3-*tert*-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*-yl)-2-methoxyphenyl)-1*H*-inden-3-yl)propan-2-yl)methanesulfonamide (compound IB-L0-2.41).

[0615]



Part A. Preparation of 6-bromo-1*H*-indene-3-carbonitrile.

[0616] To a solution of 5-bromo-2,3-dihydro-1H-inden-1-one (1g, 4.74mmol) in anhydrous THF (15ml) at -10°C was added 2M lithium diisopropylamide in THF (0.242ml, 0.483mmol) dropwise. The resulting mixture was stirred at -10°C for 15min before diethylcyanophosphonate (0.791ml, 5.21mmol) was added dropwise. Following the addition, the mixture was allowed to warm to room temperature, and was stirred at room temperature for 3h. The mixture was cooled to -78°C and borontrifluoride diethyl etherate (1.196ml, 9.52mmol) was added dropwise. Following the addition, the mixture was stirred at -78°C for 1h and was then allowed to warm to room temperature and was stirred at room temperature for 16h. The mixture was concentrated in vacuo, and the residue was partitioned between EtOAc (50mL) and H_2O (2 x 50mL). The organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo, and the crude product was purified by column chromatography on silica gel using 9:1 EtOAc:hexanes as the eluent. The title compound was obtained as an tan solid (0.72g, 69%).

Part B. Preparation of *N*-(2-(6-bromo-1*H*-inden-3-yl)propan-2-yl)methanesulfonamide.

[0617] Anhydrous cerium(III) chloride (0.224g, 0.909mmol) was flame dried under vacuum and placed under dry N_2. Anhydrous THF (1.5ml) was added, and the resulting mixture was stirred under N_2 at 45°C for 48h. The mixture was cooled to room temperature, and the product from **Part A** (0.1g, 0.454mmol) was added. The resulting mixture was cooled to -78°C, and a 1.5M solution of methyl-lithium lithium bromide complex (0.757ml, 1.136mmol) in Et_2O was added dropwise over 15min. Following the addition, the mixture was allowed to warm to -20°C and was stirred for 24h. Concentrated aq. NH_4OH (0.3mL) was added dropwise, and the mixture was allowed to warm to room temperature, was stirred for 30min, and was then filtered and washed with THF (2 x 5mL). The filtrate was concentrated in vacuo, and the crude product was purified by column chromatography on silica gel using 5% MeOH in CH_2Cl_2 as the eluent to give a solid (23mg, 20%). To a solution of this solid (23mg, 0.091mmol) in CH_2Cl_2 (1mL) was added methanesulfonyl chloride (0.011mL, 0.137mmol). The mixture was cooled to 0°C and diisopropylethylamine (0.024ml, 0.137mmol) was added dropwise. The resulting mixture was stirred at room temperature for 90min, and was then partitioned between 0.1 N aq. HCl (2mL) and CH_2Cl_2 (3 x 2mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo, and the crude product was purified by column chromatography on silica gel to give the title compound (17mg, 56%).

Part C. Preparation of *N*-(2-(6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-inden-3-yl)propan-2-yl)methanesulfonamide.

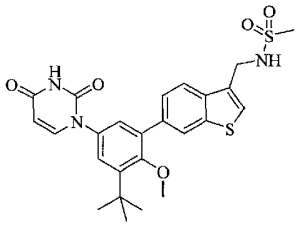
[0618] The product from **Part C** (50mg, 0.151mmol) was subjected to the conditions described for **Example 42, Part B** to give the title compound as a colorless solid (37mg, 65%).

Part D. Preparation of *N*-(2-(6-(3-*tert*-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxyphenyl)-1*H*-inden-3-yl)propan-2-yl)methanesulfonamide.

[0619] The product from **Part C** (35mg, 0.093mmol) was subjected to the conditions described for **Example 42, Part C** to give the title compound as a colorless solid (41mg, 84%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.40 (s, 1 H) 7.94 (d, *J*=8.09 Hz, 1 H) 7.78 (d, *J*=8.09 Hz, 1 H) 7.65 (d, *J*=1.50 Hz, 1 H) 7.56 (s, 1 H) 7.48 (dd, *J*=8.09, 1.47 Hz, 1 H) 7.27 (s, 2 H) 6.48 (s, 1 H) 5.63 (d, *J*=8.09 Hz, 1 H) 3.43 (s, 2 H) 3.25 (s, 3 H) 2.63 (s, 3 H) 1.68 (s, 6 H) 1.41 (s, 9 H).

Example 46. Preparation of *N*-((6-(3-*tert*-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2)-yl)-2-methoxyphenyl)benzo[*b*]thiophen-3-yl)methyl)methanesulfonamide (compound IB-L0-2.11).

[0620]



Part A. Preparation of ethyl 6-bromobenzo[*b*]thiophene-2-carboxylate.

[0621] A solution of ethyl thioglycolate (0.65g, 5.42mmol), 4-bromo-2-fluorobenzaldehyde (1.0g, 4.93mmol) and triethylamine (1.25mL, 12.3mmol) in DMSO (5mL) was heated at 75°C for 2h. The mixture was partitioned between H_2O (50mL) and CH_2Cl_2 (2 x 50mL), and the combined organic layers were dried over Na_2SO_4. The drying agent was filtered off, and the solvent was removed in vacuo to give the title compound as an oil (1.29g, 92%).

Part B. Preparation of 6-bromobenzo[b]thiophene-2-carboxylic acid.

[0622] To a solution of the product from **Part A** (1.21g, 4.24mmol) in THF (10mL) was added a solution of LiOH (0.305g, 12.73mmol) in H_2O (4mL) and the resulting mixture was stirred at 40°C for 2h. The mixture was partitioned between H_2O (50mL) and CH_2Cl_2 (50mL). The aqueous layer was adjusted to pH = 2 using 1N HCl, and extracted with CH_2Cl_2 (2 x 50mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo to give the title compound as an oil (1.04g, 95%).

Part C. Preparation of 6-bromobenzo[*b*]thiophene.

[0623] The product from **Part B** (0.70g, 2.73mmol) and DBU (1.35mL, 8.94mmol) were combined in DMA (6mL) in a sealed tube and heated at 200°C in a microwave reactor for 70min. The resulting dark solution was diluted with 1 M HCl (20mL) and extracted with CH_2Cl_2 (2 x 20mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo, and the crude product was purified by column chromatography on silica gel using CH_2Cl_2 as the eluent to give the title compound as an oil (0.484g 83%).

Part D. Preparation of 6-bromo-3-(chloromethyl)benzo[b]thiophene.

[0624] To a solution of the product from **Part C** (0.484g, 2.27mmol) in benzene (0.20mL) was added 37% aq. formaldehyde solution (1mL) and concentrated HCl (1mL). The resulting mixture was heated at 70°C for 1h. while HCl gas was bubbled through the mixture. The mixture was partitioned between H_2O (20mL) and CH_2Cl_2 (2 x 20mL), and the combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by column chromatography on silica gel using CH_2Cl_2 to give the title compound as a waxy solid (0.49g, 82%).

Part E. Preparation of *N*-((6-bromobenzo[*b*]thiophen-3-yl)methyl)-*N*-(2,4-dimethoxybenzyl) methanesulfonamide.

[0625] To a solution of the product form **Part D** (275mg, 1.05mmol) and *N*-(2.4-dimethoxybenzyl)-methanesulfonamide (284mg, 1.15mmol) in DMA (6mL) was added K_2CO_3 (160mg, 1.15mmol), and the mixture was stirred at room temperature for 3h. The mixture was partitioned between H_2O (20mL) and Et_2O (2 x 20mL), and the combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by column chromatography on silica gel using 2% EtOAc in CH_2Cl_2 as the eluent to give the title compound as a waxy solid (316mg, 64%).

Part F. Preparation of *N*-(2,4-dimethoxybenzyl)-N-((6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[*b*]thiophen-3-yl)methyl)methanesulfonamide.

[0626] The product from **Part E** (300mg, 0.64mmol) was subjected to the conditions described for **Example 42, Part B** to give the title compound as a waxy solid (248mg, 75%).

Part G. Preparation of *N*-((6-(3-*tert*-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxyphenyl)benzo[*b*]thiophen-3-yl)methyl)-*N*-(2,4-dimethoxybenzyl)methanesulfonamide.

[0627] The product from **Part F** (214mg, 0.414mmol) was subjected to the conditions described for **Example 42, Part C** to give the title compound as a light yellow solid (238mg, 87%).

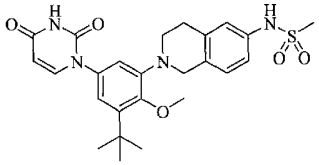
Part H. Preparation of *N*-((6-(3-*tert*-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxyphenyl)benzo[*b*]thiophen-3-yl)methyl)methanesulfonamide.

[0628] To a solution of the product from **Part G** (230mg, 0.34mmol) in CH_2Cl_2 (4mL) was added trifluoroacetic acid (0.5mL), and

the mixture was stirred at room temperature for 30min. The solution was diluted with CH_2Cl_2 (10mL and extracted with saturated aq. $NaHCO_3$ (2 x 10mL The organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo, and the crude product was purified by column chromatography on silica gel eluting with 3% MeOH in CH_2Cl_2 to give the title compound as an off-white solid (149mg, 84%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.41 (s, 1 H) 8.16 (d, *J*=1.10Hz, 1 H) 8.02 (d, *J*=8.46 Hz, 1 H) 7.79 (d, *J*=7.72 Hz, 1 H) 7.71 (s, 1 H) 7.60 - 7.66 (m, 2 H) 7.29 - 7.38 (m, 2 H) 5.65 (d, *J*=7.72 Hz, 1 H) 4.44 (d, *J*=5.88 Hz, 2 H) 3.24 (s, 3 H) 2.95 (s, 3 H) 1.42 (s, 9 H).

Example 47. Preparation of *N*-(2-(3-*tert*-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxyphenyl)-1,2,3,4-tetrahydroisoquinolin-6-yl)methanesulfonamide (compound IB-L0-2.19).

[0629]



Part A. Preparation of 1-(3-amino-5-*tert*-butyl-4-methoxyphenyl)pyrimidine-2,4(1*H*,3*H*)-dione.

[0630] To a solution of the product from **Example 5, Part F** (170mg, 0.534mmol) and triethylamine (223uL, 1.6mmol) in THF (5mL) was added diphenylphosphorylazide (173uL, 0.80mmol). The resulting mixture was stirred at room temperature for 1h, and was then stirred at 45°C for 1h. Water (280uL) was added, and the resulting mixture was stirred at 50°C for 1h, and then stirred at room temperature for 16h. The solution was diluted with H_2O (10mL), and the resulting solid was filtered off. The solid was suspended in 1M aq. HCl and filtered to give the amine product as the HCl salt. This salt was suspended in aq. $NaHCO_3$ (20mL) and extracted with EtOAc (2 x 20mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo to give the title compound as a colorless solid (55mg, 36%).

Part B. Preparation of 1-(3-*tert*-butyl-4-methoxy-5-(6-nitro-3,4-dihydroisoquinolin-2(1*H*)-yl)phenyl)pyrimidine-2,4(1*H*,3*H*)-dione.

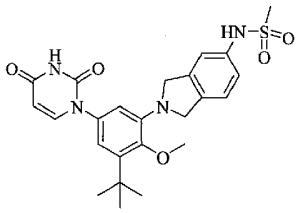
[0631] A solution of the product from **Part A** (100mg, 0.28mmol) and 2-(2-(methylsulfonyloxy)-ethyl)-4-nitrobenzyl methanesulfonate (196mg, 0.68mmol) were in anhydrous DMA (4mL) was stirred at 80°C for 18h. The cooled mixture was partitioned between H_2O (20mL) and EtOAc (2 x 20mL), and the combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was suspended in CH_2Cl_2 and filtered to remove unreacted aniline starting material. The filtrate was concentrated in vacuo, and the crude product was purified by column chromatography on silica gel eluting with 1% MeOH in CH_2Cl_2 to give the title compound as a light yellow solid (39.3mg, 31%).

Part C. Preparation of *N*-(2-(3-*tert*-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxyphenyl)-1,2,3,4-tetrahydroisoquinolin-6-yl)methanesulfonamide.

[0632] To a solution of the product from **Part B** (35mg, 0.078mmol) in THF (0.5mL), MeOH (0.5mL) and H_2O (0.25mL) was added Fe powder (17.4mg, 0.41mmol) and NH_4Cl (6.2mg, 0.12mmol, and the resulting mixture was stirred at 70°C for 1h. The hot mixture was filtered through celite and rinsed with THF and MeOH. The filtrate was concentrated and dried in vacuo to give a solid. To a solution of the solid (32mg, 0.076mmol) and pyridine (26uL, 0.32mmol) in CH_2Cl_2 (1.5mL) was added methanesulfonyl chloride (7.7uL, 0.099mmol). The mixture was stirred at room temperature for 1h then concentrated in vacuo. The crude product was purified by column chromatography on silica gel eluting with 5% MeOH in CH_2Cl_2 to give the title compound as a light yellow solid (7mg, 19%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.71 (d, J=8.09 Hz, 1 H) 7.14 - 7.21 (m, 1 H) 7.05 - 7.12 (m, 3 H) 6.98 (d, J=2.57 Hz, 1 H) 5.65 (d, J=7.72 Hz, 1 H) 4.18 (s, 2 H) 3.86 (s, 3 H) 3.03 (t, J=4.23 Hz, 2 H) 2.99 (s, 3 H) 1.38 (s, 9 H).

Example 48. Preparation of *N*-(2-(3-*tert*-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxyphenyl)isoindolin-5-yl)methanesulfonamide (compound IB-L0-2.79).

[0633]



Part A. Preparation of (4-nitro-1,2-phenylene)bis(methylene)dimethanesulfonate.

[0634] To a solution of 4-nitrophthalic acid (500mg, 2.37mmol) in THF (24mL) at room temperature was added a 1M solution of BH_3•THF complex (9.95mL, 9.95mmol) dropwise. This solution was stirred at 65°C for 1h, and then allowed to cool to room temperature. To the mixture was added MeOH (1mL), and the mixture was stirred for 30min and concentrated in vacuo. The residue was partitioned between 1M aq. HCl (20mL) and EtOAc (2 x 20mL), and the combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by column chromatography on silica gel eluting with 3% MeOH in CH_2Cl_2 to give an oil (253mg, 58%). To a solution of the oil (250mg, 2.37mmol) and triethylamine (438uL, 3.14mmol) in anhydrous CH_2Cl_2 (30mL) at 0°C was added methanesulfonyl chloride (234uL, 3.0mmol) dropwise. The solution was stirred at room temperature for 18h, and was partitioned between 1M aq. HCl (20mL) and CH_2Cl_2 (2 x 20mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by column chromatography on silica gel eluting with CH_2Cl_2 to give the title compound (150mg, 32%).

Part B. Preparation of 1-(3-*tert*-butyl-4-methoxy-5-(5-nitroisoindolin-2-yl)phenyl) pyrimidine-2,4(1*H*,3*H*)-dione.

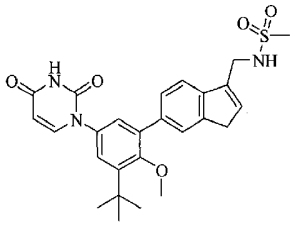
[0635] To a solution of the product of **Part A** (110mg, 0.324mmol) and the product of **Example 47, Part A** (113mg, 0.389mmol) in anhydrous 1,4-dioxane (4mL) was added sodium bicarbonate (60mg, 0.71mmol) and diisopropylethylamine (142uL, 0.81mmol) and the resulting mixture was stirred at 95°C for 16h. The mixture was partitioned between 0.5M aq. HCl (10mL) and CH_2Cl_2 (2 x 10mL), and the combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by column chromatography on silica gel eluting with 1% MeOH in CH_2Cl_2 to give the title compound as a light yellow solid (110mg, 78%).

Part C. Preparation of *N*-(2-(3-*tert*-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxyphenyl)isoindolin-5-yl)methanesulfonamide.

[0636] The product from **Part B** (100mg, 0.25mmol) was subjected to the conditions described for **Example 47, Part C** to give the title compound as an off-white solid (53mg, 45%). ^{1}H NMR (300 MHz, DMSO-d_6) • 11.37 (s, 1 H) 9.70 (s, 1 H) 7.71 (d, J=7.72 Hz, 1 H) 7.34 (d, J=8.09 Hz, 1 H) 7.23 (d, J=1.84 Hz, 1 H) 7.13 (dd, J=8.09, 1.84 Hz, 1 H) 6.98 (d, J=2.57 Hz, 1 H) 6.81 (d, J=2.21 Hz, 1 H) 5.62 (d, J=7.72 Hz, 1 H) 4.52 (s, 2 H) 4.50 (s, 2 H) 3.63 (s, 3 H) 2.98 (s, 3 H) 1.38 (s, 9 H).

Example 49. Preparation of *N*-((6-(3-*tert*-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxyphenyl)-1*H*-inden-3-yl)methyl)methanesulfonamide (compound IB-L0-2.13).

[0637]



Part A. Preparation of 5-bromo-1-(trimethylsilyloxy)-2,3-dihydro-1*H*-indene-1-carbonitrile.

[0638] To a solution of 5-bromo-2,3-dihydro-1*H*-inden-1-one (10.0g, 47.4mmol) and *N*-methyl-morpholine *N*-oxide (1.67g, 14.21mmol) in CH_2Cl_2 (50ml) was added trimethylsilylcyanide (7.05g, 71.1mmol), and the resultant solution was stirred at room temperature for 72h, and then concentrated in vacuo. The crude product was purified by column chromatography on silica gel using 5% EtOAc in hexanes as the eluent to give the title compound as a colorless liquid (12.65g, 86%).

Part B. Preparation of 1-(aminomethyl)-5-bromo-2,3-dihydro-1*H*-inden-1-ol.

[0639] To a solution of the product from **Part A** (18.44g, 59.4mmol) in anhydrous Et_2O (250mL) under N_2 gas at 0°C was added a 1M solution of $LiAlH_4$ in Et_2O (62.4mL, 62.4mmol) dropwise over 1h. Following the addition, the mixture was allowed to warm to rt and was stirred at room temperature for 2h. The mixture was cooled in an ice bath while H_2O (4.3mL) was added dropwise, followed by the addition of 15% aq. NH_4OH (4.3mL), and then H_2O (13mL). The mixture was stirred at room temperature for 15min, and then filtered through celite and rinsed with EtOAc. The filtrate was concentrated in vacuo, and the residue was suspended in Et_2O (40mL) to give a precipitate that was filtered and dried to give the title compound as a colorless solid (10.0g, 70%).

Part C. Preparation of (6-bromo-1H-inden-3-yl)methanamine hydrochloride salt.

[0640] To a solution of the product from **Part B** (10.0g, 41.3mmol) in MeOH (100mL) was added 6N aq. HCl (125mL) and the mixture was stirred at 70°C for 3h and then allowed to cool to room temperature. MeOH was removed in vacuo to give a precipitate that was collected by filtration, washed with H_2O, and dried in vacuo to provide the title compound as a colorless solid (9.89g, 92%).

Part D. Preparation of *N*-((6-bromo-1*H*-inden-3-yl)methyl)methanesulfonamide.

[0641] To a suspension of the product from **Part C** (6.46g, 24.8mmol) in anhydrous CH_2Cl_2 (260mL) was added methanesulfonyl chloride (3.86mL, 49.6mmol) and diisopropylethylamine (13.05mL, 74.4mmol), and the resulting mixture was stirred at room temperature for 10h. The solution was washed with 1N aq. HCl (2 x 300mL), and the organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was suspended in Et_2O (100mL) to give a precipitate that was collected by filtration and dried to give the title compound as a colorless solid (6.25g, 83%).

Part E. Preparation of *N*-((6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-inden-3-yl)methyl)methanesulfonamide.

[0642] A solution of the product from **Part D** (2.0g, 6.62mmol), bis(pinacolato)diboron (1.85g, 7.28mmol), potassium acetate (1.95g, 19.86mmol) and 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (0.27g, 0.331mmol) in anhydrous 1,4-dioxane (80mL) under N_2 was stirred at 95°C for 8h. The cooled mixture was filtered through celite, washed with EtOAc (2 x 20mL) and then concentrated in vacuo. The crude product was purified by column chromatography on silica gel using 1:2 EtOAc:hexanes as the eluent to give the title compound as a colorless oil (2.02g, 87%).

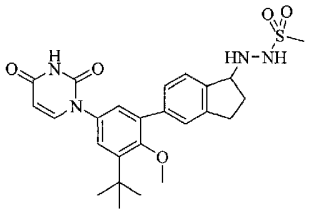
Part F. Preparation of *N*-((6-(3-*tert*-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxyphenyl)-1*H*-inden-3-

yl)methyl)methanesulfonamide.

[0643] A mixture of the product from **Part E** (3.14g, 8.99mmol), the product from **Example C** (3.78g, 9.44mmol), tripotassium phosphate (3.82, 17.98mmol), 1,3,5,7-tetramethyl-2,4,8-trioxa-6-phospha-6-phenyl-adamantane (Cytec [97739-46-3]) (105mg, 0.36mmol), and tris(dibenzylidineacetone)-dipalladium(0) (165mg, 0.18mmol) was placed under N_2 gas. To the mixture was added, via canula, a mixture of THF (45mL) and H_2O (15mL) that had been degassed by bubbling Ar gas for 10min. The resulting mixture was further degassed by bubbling with Ar for an additional 15min. The mixture was stirred at 50°C for 1.5h while Ar was continuously bubbled through the solution. Additional tris(dibenzyl idineacetone)dipalladium(0) (55mg, 0.6mmol) in THF (2mL) was added, and the mixture was stirred at 50°C for 1h. The mixture was allowed to cool to rt, and was partitioned between CH_2Cl_2 (300ml) and 1N aq. HCl (150mL). To the orange organic layer was added 3-mercaptopropyl-functionalized silica gel (10g, Aldrich) and$mgSO_4$, and the mixture was stirred at room temperature for 16h, filtered and concentrated in vacuo. The crude product was purified by column chromatography on silica gel using 3:1 EtOAc:hexanes as the eluent to give the title compound as a colorless solid (2.7g, 61%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.40 (s,1H), 7.78 (d, *J*=7.4Hz,1H), 7.66 (s,1H), 7.60 (d,J=7.7Hz,1H), 7.50 (m,2H), 7.25 (m,2H), 6.56 (m,1H), 5.64 (dd, J=2.2,7.7Hz,1H), 4.18 (d, J=5.1Hz,2H), 3.46 (s,2H), 3.25 (s,3H), 2.96 (s,3H), 1.41 (s,9H).

Example 50. Preparation of *N*'-(5-(3-*tert*-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxyphenyl)-2,3-dihydro-1*H*-inden-1-yl)methanesulfonohydrazide (compound IB-L0-2.31).

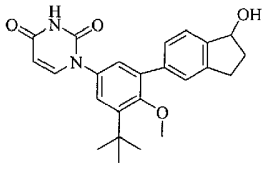
[0644]



[0645] To a solution of the product from **Example 4, Part C** (100mg, 0.201mmol) was in THF (2mL) and MeOH (2mL) was added 2 drops of 10% HCl in MeOH, followed by sodium cyanoborohydride (19mg, 0.302mmol). The mixture was adjusted to pH 4 with the addition of 10% HCl in MeOH, and was then stirred at room temperature for 1h. The resulting mixture was partitioned between saturated aq. sodium bicarbonate (5mL) and CH_2Cl_2 (20mL), and the organic layer was dried over Na_2SO_4, filtered and concentrated. The crude product was purified by column chromatography on silica gel using 3% MeOH in CH_2Cl_2 as the eluent to provide the title compound as a colorless solid (58mg, 58%). ^{1}H NMR (300 MHz, DMSO-d6)
δ
11.39(s,1H), 8.18(d,J=3.7Hz,1H), 7.77(d,J=7.7Hz,1H), 7.51(d,J=8.1Hz,1H), 7.38(m,2H), 7.27(d,J=2.6Hz,1H), 7.21(d,J=2.9Hz,1H), 5.63(d,J=7.7Hz,1H), 5.25(m,1H), 4.39(m,1H), 3.27(s,3H), 2.98(m,1H), 2.83(s,3H), 2.78(m,1H), 2.22(m,1H), 2.07(m,1H), 1.40(s,9H).

Example 51. Preparation of -1-(3-*tert*-butyl-5-(1-hydroxy-2,3-dihydro-1*H*-inden-5-yl)-4 methoxyphenyl)pyrimidine-2,4(1*H*,3*H*)-dione (compound IB-L0-2.36).

[0646]

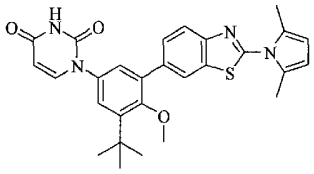


[0647] To a solution of the product from **Example 4, Part B** (150mg, 0.371mmol) in MeOH (3mL) and CH_2Cl_2 (3mL) was added sodium borohydride (28mg, 0.742mmol), and the mixture was stirred at room temperature for 1h. The mixture was partitioned

between 1N aq. HCl (10mL) and CH_2Cl_2 (20mL), and the organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by column chromatography on silica gel using 5% MeOH in CH_2Cl_2 as the eluent to provide the title compound as a colorless solid (90mg, 60%). ^{1}H NMR (300MHz, DMSO-d6):
δ
11.39(s,1H), 7.44(d, J= 4.0Hz, 1H), 7.40 (m, 2H), 7.21 (d, J= 2.6 Hz, 1H), 7.26 (d, J= 2.6 Hz, 1H), 5.63 (d, J= 8.1 Hz, 1H), 5.29 (d, J= 5.9 Hz,1H), 5.09 (m, 1H), 3.26 (s, 3H), 2.97 (m, 1H), 2.79 (m, 1H), 2.38 (m, 1H), 1.83 (m, 1H), 1.40 (s, 9H).

Example 52. Preparation of 1-(3-*tert*-butyl-5-(2-(2,5-dimethyl-1*H*-pyrrol-1-yl)benzo[d]thiazol-6-yl)-4-methoxyphenyl)pyrimidine-2,4(1*H*,3*H*)-dione (compound IB-L0-2.47).

[0648]



Part A. Preparation of 6-bromo-2-(2,5-dimethyl-1H-pyrrol-1-yl)benzo[*d*]thiazole.

[0649] A solution 6-bromobenzo[*d*]thiazol-2-amine (5.75g, 25.1mmol), hexane-2,5-dione (2.95mL, 25.1mmol), and PPTS (0.95g, 3.76mmol) in benzene (100ml) was refluxed for 16h while water was removed with a Dean-Stark trap. The cooled mixture was poured into EtOAc (100mL) and extracted with saturated aq. $NaHCO_3$ (2 x 100mL) and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by column chromatography on silica gel using 9:1 EtOAc:hexanes as the eluent to give the title compound as an orange oil (6.46g, 84%).

Part B. Preparation of 2-(2,5-dimethyl-1H-pyrrol-1-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[d]thiazole.

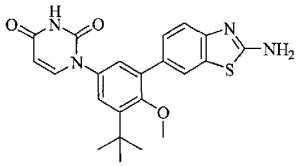
[0650] A mixture of the product from **Part A** (3.24g, 10.54mmol), bis(pinacolato)diboron (4.01 g, 15.81mmol), bis(di-tert-butyl(hydroxy)phosphino)palladium(II) dichloride (0.264g, 0.527mmol), and potassium acetate (3.10g, 31.6mmol) in anhydrous toluene (25mL) was degassed by bubbling with N_2 gas for 15min, and then heated at reflux under N_2 for 72h. The cooled mixture was filtered through celite and washed with EtOAc, and the filtrate was concentrated in vacuo. The crude product was purified by column chromatography on silica gel using 9:1 EtOAc:hexanes as the eluent to give the title compound (2.77g, 74%).

Part C. Preparation of 1-(3-*tert*-butyl-5-(2-(2,5-dimethyl-1H-pyrrol-1-yl)benzo[d]thiazol-6-yl)-4-methoxyphenyl)pyrimidine-2,4(1*H*,3*H*)-dione.

[0651] The product from **Part B** (405mg, 1.14mmol) was subjected to the conditions described for **Example 42, Part C** to give the title compound (430mg, 68%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.43 (d, *J*=2.21 Hz, 1 H) 8.32 (d, *J*=1.47 Hz, 1 H) 8.12 (d, *J*=8.46 Hz, 1 H) 7.80 (d, *J*=7.72 Hz, 1 H) 7.76 (dd, *J*=8.46, 1.84 Hz, 1 H) 7.35 (q, *J*=2.5 Hz, 2 H) 5.97 (s, 2 H) 5.66 (dd, *J*=7.72, 2.21 Hz, 1 H) 3.30 (s, 3 H) 2.30 (s, 6 H) 1.43 (s, 9 H).

Example 53. Preparation of 1-(3-(2-aminobenzo[*d*]thiazol-6-yl)-5-*tert*-butyl-4-methoxy-phenyl)pyrimidine-2,4(1*H*,3*H*)-dione (compound IB-L0-2.27).

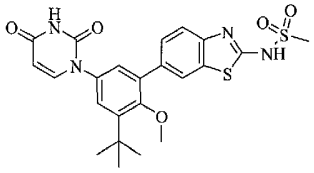
[0652]



[0653] To a solution of the product from **Example 52** (4.0g, 8.0mmol) in trifluoroacetic acid (50mL) was added a few drops of H_2O, and the resulting mixture was stirred at 80°C for 2.5h, and then concentrated in vacuo. A solution of the residue in MeOH was neutralized using conc. NH_4OH, concentrated in vacuo, and the crude product was purified by column chromatography on silica gel using 9:1 CH_2Cl_2:MeOH as the eluent to give the title compound (3.3g, 98%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.40 (s, 1 H) 7.81 (s, 1 H) 7.77 (d, J=8.09 Hz, 1 H) 7.57 (s, 1 H) 7.40 (s, 1 H) 7.33 - 7.38 (m, 1 H) 7.25 (s, 1 H) 5.60 - 5.69 (m, 1 H) 3.26 (s, 3 H) 1.40 (s, 9 H).

Example 54. Preparation of *N*-(6-(3-*tert*-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxyphenyl)benzo[*d*]thiazol-2-yl)methanesulfonamide (compound IB-L0-2.28).

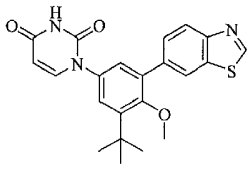
[0654]



[0655] To a solution of the product from **Example 53** (0.35g, 0.83mmol) in anhydrous CH_2Cl_2 (50mL) was added methanesulfonyl chloride (194µL, 2.49mmol) and pyridine (1.34mL, 16.6mmol). The resulting mixture was stirred at room temperature for 16h and concentrated in vacuo. The crude product was purified by C-18 reverse-phase HPLC using an acetonitrile:H_20 (0.1% TFA) gradient to give the title compound (19mg, 4%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 13.09 (s, 1 H) 11.41 (d, *J*=1.84 Hz, 1 H) 7.96 (d, *J*=1.47 Hz, 1 H) 7.77 (d, *J*=8.09 Hz, 1 H) 7.57 (dd, 1 H) 7.42 (d, *J*=8.09 Hz, 1 H) 7.25 - 7.32 (m, 2 H) 5.64 (dd, *J*=8.09, 2.21 Hz, 1 H) 3.25 (s, 3 H) 3.02 (s, 3 H) 1.40 (s, 9 H).

Example 55. Preparation of 1-(3-(benzo[*d*]thiazol-6-yl)-5-*tert*-butyl-4-methoxyphenyl) pyrimidine-2,4(1*H*,3*H*)-dione (compound IB-L0-2.33).

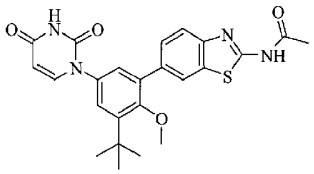
[0656]



[0657] To a solution of the product from **Example 53** (30mg, 0.071mmol) in anhydrous 1,4-dioxane (3mL) under N_2 was added isoamyl nitrite (19µL, 0.142mmol). The resulting mixture was stirred at reflux for 1h, and concentrated in vacuo. The crude product was purified by C-18 reverse-phase HPLC using an acetonitrile:H_2O (0.1% TFA) gradient to give the title compound (14mg, 48%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.42 (d, *J*=1.84 Hz, 1 H) 9.44 (s, 1 H) 8.34 (d, *J*=1.47 Hz, 1 H) 8.19 (d, *J*=8.46 Hz, 1 H) 7.79 (d, *J*=7.72 Hz, 1 H) 7.73 (dd, *J*=8.46, 1.84 Hz, 1 H) 7.32 - 7.37 (m, 2 H) 5.65 (dd, *J*=7.91, 2.39 Hz, 1 H) 3.24 (s, 3 H) 1.42 (s, 9 H).

Example 56. Preparation of *N*-(6-(3-*tert*-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxyphenyl)benzo[d]thiazol-2-yl)acetamide (compound IB-L0-2.49).

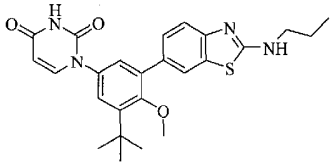
[0658]



[0659] A mixture of the product from **Example 53** (30mg, 0.071mmol) and acetic anhydride (3mL) was stirred at 100°C for 2h, and then allowed to cool to room temperature. The resulting solid was collected by filtration, washed with H_2O, and dried to give the title compound as an off-white solid (29mg, 88%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.42 (s, 1 H) 11.41 (d, J=2.21 Hz, 1 H) 8.12 (d, J=1.47 Hz, 1 H) 7.82 (d, J=8.46 Hz, 1 H) 7.78 (d, J=8.09 Hz, 1 H) 7.61 (dd, J=8.46, 1.84 Hz, 1 H) 7.31 (q, J=2.70 Hz, 2 H) 5.64 (dd, J=8.09, 2.21 Hz, 1 H) 3.24 (s, 3 H) 2.22 (s, 3 H) 1.41 (s, 9 H).

Example 57. Preparation of 1-(3-*tert*-butyl-4-methoxy-5-(2-(propylamino)benzo[*d*]thiazol-6-yl)phenyl)pyrimidine-2,4(1*H*,3*H*)-dione (compound IB-L0-2.46).

[0660]



Part A. Preparation of 1-(3-*tert*-butyl-5-(2-chlorobenzo[*d*]thiazol-6-yl)-4-methoxyphenyl) pyrimidine-2,4(1*H*,3*H*)-dione.

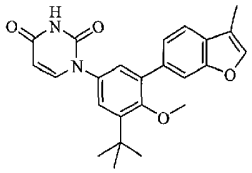
[0661] To a mixture of the product from **Example 53** (50mg, 0.118mmol) and copper(II) chloride (24mg, 0.178mmol) in acetonitrile (3mL) at 0°C was added *tert*-butyl nitrite (21µL, 0.178mmol). The mixture was stirred at 0°C for 1h, and then warmed to 65°C and stirred for 2h. The mixture was concentrated in vacuo and purified by column chromatography on silica gel using 5% MeOH in CH_2Cl_2 to give the title compound as an off-white solid (43mg, 82%).

Part B. Preparation of 1-(3-*tert*-butyl-4-methoxy-5-(2-(propylamino)benzo[*d*]thiazol-6-yl) phenyl)pyrimidine-2,4(1*H*,3*H*)-dione.

[0662] A mixture of the product from **Part A** (50mg, 0.11mmol), 1-aminopropane (9µL, 0.11mol), and K_2CO_3 (15.6mg, 0.11mmol) in anhydrous DMF (5mL) was stirred at 100°C for 24h. The mixture was concentrated in vacuo and purified by column chromatography on silica gel using 2% MeOH in EtOAc as the eluent to give the title compound as an off-white solid (21mg, 40 %). ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.39 (d, *J*=1.84 Hz, 1 H) 8.12 (t, *J*=5.52 Hz, 1 H) 7.82 (d, *J*=1.47 Hz, 1 H) 7.77 (d, *J*=7.72 Hz, 1 H) 7.44 (t, *J*=9.01 Hz, 1 H) 7.37 - 7.41 (m, 1 H) 7.25 (s, 2 H) 5.63 (dd, *J*=7.91, 2.02 Hz, 1 H) 3.33 - 3.38 (m, 2 H) 3.26 (s, 3 H) 1.56 - 1.69 (m, 2 H) 1.40 (s, 9 H) 0.94 (t, *J*=7.35 Hz, 3 H).

Example 58. Preparation of 1-(3-*tert*-butyl-4-methoxy-5-(3-methylbenzofuran-6-yl)phenyl)-pyrimidine-2,4(1*H*,3*H*)-dione (compound IB-L0-2.42).

[0663]



Part A. Preparation of methyl 2-(2-acetyl-5-bromophenoxy)acetate.

[0664] A solution of 1-(4-bromo-2-hydroxyphenyl)ethanone (1.35g, 6.28mmol) in anhydrous DMF (16mL) was treated in several portions with sodium hydride (377mg of 60% in oil, 226mg, 9.42mmol) followed by stirring at room temperature for 30min. The mixture was then treated with methyl bromoacetate (871µL, 1.45g, 9.48mmol) dropwise (solution became warm after addition was complete) followed by stirring at room temperature for 18h. The mixture was diluted with ethyl acetate and extracted with water (4x) and saturated sodium chloride solution. Drying (Na_2SO_4) and concentration in vacuo afforded a nearly colorless solid, which was purified by column chromatography on silica gel, eluting with 20-100% ethyl acetate in hexanes. These procedures afforded the title compound as a colorless solid (1.47g, 82%).

Part B. Preparation of 2-(2-acetyl-5-bromophenoxy)acetic acid.

[0665] A solution of the product from **Part A** (1.47g, 5.12mmol) in tetrahydrofuran (26mL) was treated with 1.0N sodium hydroxide solution (6.7mL, 6.7mmol) followed by stirring at room temperature for 3h, at which point the reaction was complete. The mixture was concentrated in vacuo to remove tetrahydrofuran and then was diluted with water and cooled to 0°C. The mixture was acidified to pH 3 by addition of 1N hydrochloric acid solution, and then the product extracted with ethyl acetate. The organic layer was extracted with saturated sodium chloride solution and dried (Na_2SO_4). Concentration in vacuo afforded the title compound as a colorless solid (1.36g, 97%).

Part C. Preparation of 6-bromo-3-methylbenzofuran.

[0666] A solution of the product from **Part B** (500mg, 1.83mmol) in acetic anhydride (9.2mL) was treated with sodium acetate (300mg, 3.66mmol) followed by warming at reflux for 18h. The mixture was cooled to room temperature and diluted with toluene and concentrated in vacuo to azeotropically remove acetic anhydride. This process was repeated 3x. The mixture was then diluted with ethyl acetate and stirred with saturated sodium bicarbonate solution for 1h. The layers were separated and the organic layer was extracted with saturated sodium chloride solution. Drying (Na_2SO_4) and concentration in vacuo afforded amber oil, which was purified by column chromatography on silica gel, eluting with 8-50 % ethyl acetate in hexanes. These procedures afforded the title compound as a colorless liquid (316mg, 82%).

Part D. Preparation of 4,4,5,5-tetramethyl-2-(3-methylbenzofuran-6-yl)-1,3,2-dioxaborolane.

[0667] In a microwave tube, a mixture of the product from **Part C** (303mg, 1.44mmol), bis(pinacolato)diboron (401mg, 1.58mmol) and potassium acetate (423mg, 4.31mmol) in anhydrous dioxane (5mL) was degassed by nitrogen sparge for 15min. The mixture was treated with 1,1'-bis-(diphenylphosphino)ferrocene palladium (II) chloride dichloromethane complex (24mg, 0.029mmol) followed by degassing for another 5min. The microwave tube was sealed and the mixture was warmed at 90°C for 18h. The mixture was cooled and diluted with ethyl acetate and extracted with water and saturated sodium chloride solution. The organic layer was dried (Na_2SO_4) and stirred with (3-mercapto-propyl) silica gel for 1h. The mixture was filtered and concentrated in vacuo to afford a brown semisolid, which was purified by column chromatography on silica gel, eluting with 8-40% ethyl acetate in hexanes. These procedures afforded the title compound as colorless oil, which slowly solidified upon standing (307mg, 83%).

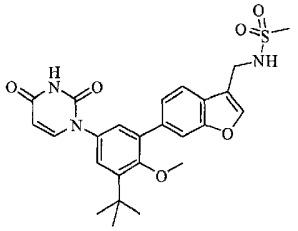
Part E. Preparation of 1-(3-*tert*-butyl-4-methoxy-5-(3-methylbenzofuran-6-yl)phenyl)-pyrimidine-2,4(1H,3*H*)-dione.

[0668] In a microwave tube, a solution of the product from **Part D** (307mg, 1.19mmol), the product from **Example C** (414mg,

1.03mmol), 1,3,5,7-tetramethyl-2,4,8-trioxa-6-phospha-6-phenyl-adamantane (Cytec [97739-46-3]) (15mg, 0.052mmol), and tribasic potassium phosphate (439mg, 2.07mmol) in 3:1 tetrahydrofuran-water (8mL) was degassed by nitrogen sparge for 20min. The mixture was treated with tris(dibenzylideneacetone)dipalladium (0) (12mg, 0.012mmol) followed by degassing for another 10min. During this period, the solution turned from an initially deep maroon color to a greenish brown color. The microwave tube was sealed and the solution warmed at 50°C for 56h. The solution was cooled and diluted with ethyl acetate and acidified with 1M citric acid solution. The organic layer was extracted with saturated sodium chloride solution, dried (Na_2SO_4), and then stirred with (3-mercaptopropyl) silica gel for 1h. After filtration and concentration in vacuo, the residue obtained was purified by column chromatography on silica gel, eluting with 4-20% acetone in dichloromethane, followed by a second column chromatography on silica gel, eluting with 20-100% ethyl acetate in hexanes. These procedures afforded the title compound as a colorless solid (355mg). ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.40 (d, *J*=1.84 Hz, 1 H) 7.74 - 7.92 (m, 2 H) 7.58 - 7.76 (m, 2 H) 7.46 (dd, *J*=8.09, 1.47 Hz, 1 H) 7.30 (q, J=2.82 Hz, 2 H) 5.64 (dd, J=8.09, 2.21 Hz, 1 H) 3.22 (s, 3 H) 2.25 (s, 3 H) 1.41 (s, 9 H).

Example 59. Preparation of *N*-((6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxyphenyl)benzofuran-3-yl)methyl)methanesulfonamide (compound IB-L0-2.18).

[0669]



Part A. Preparation of 6-bromo-3-(bromomethyl)benzofuran.

[0670] A solution of the product from **Example 58, Part C** (1.0g, 4.74mmol) and dibenzoyl peroxide (287mg, 1.19mmol) in chlorobenzene (24mL) at reflux was treated in four portions with N-bromosuccinimide (843mg, 4.74mmol) over 30min. The mixture was then stirred at reflux for 2h. The mixture was cooled, filtered and concentrated and purified by column chromatography on silica gel, eluting with 7-30% chloroform in hexanes. The procedures afforded the title compound as a light yellow oil (438mg, 32%).

Part B. Preparation of *N*-((6-bromobenzofuran-3-yl)methyl)-*N*-(4-methoxybenzyl)methane-sulfonamide.

[0671] A solution of the product from Part A (515mg, 1.78mmol), *N*-(4-methoxybenzyl)methane-sulfonamide (421mg, 1.95mmol), and potassium carbonate (260mg, 1.95mmol) in anhydrous DMF (8.9mL) was stirred at 70°C for 3h. The mixture was cooled and diluted with ethyl acetate and extracted with water (4x). The organic layer was then extracted with saturated sodium chloride solution and dried (Na_2SO_4). Concentration in vacuo afforded a beige solid. This material was purified by column chromatography on silica gel, eluting with 20-100% ethyl acetate in hexanes. These procedures afforded the title compound as a colorless solid (224mg, 35%).

Part C. Preparation of *N*-(4-methoxybenzyl)-*N*-((6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzofuran-3-yl)methyl)methanesulfonamide.

[0672] The product from **Part B** (186mg, 0.44mmol) was subjected to the conditions described for **Example 58, Part D** to afford the title compound as a colorless solid (177mg, 86%).

Part D. Preparation of *N*-((6-(3-*tert*-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxyphenyl)benzofuran-3-yl)methyl)-*N*-(4-methoxybenzyl)methanesulfonamide.

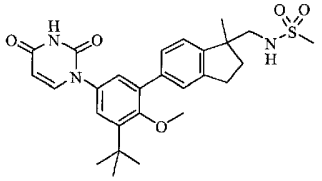
[0673] In a microwave tube, a suspension of the product from **Part C** (169mg, 0.36mmol), the product from **Example C** (143mg, 0.36mmol), and 1.0M sodium carbonate solution (0.5mL, 0.50mmol) in 1:1 ethanol-toluene (3mL) was degassed by nitrogen sparge for 20min. The solution was treated with 1,1-bis(diphenylphosphino)ferrocene-palladium(II) chloride dichloromethane complex (7mg, 9µmol) followed by degassing for another 5min. The microwave tube was sealed and the mixture heated a 100°C in the microwave oven for 1h. The mixture was diluted with ethyl acetate and water, and acidified with 1M citric acid solution. The organic layer was extracted with saturated sodium chloride solution, dried (Na_2SO_4), and allowed to stand overnight over (3-mercaptopropyl) silica gel. Filtration and concentration in vacuo afforded an off-white foam which was purified by column chromatography on silica gel, eluting with 5-30% ethyl acetate in dichloromethane. The procedures afforded the title compound as a colorless solid (96mg, 43%).

Part E. Preparation of *N*-((6-(3-*tert*-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxyphenyl)benzofuran-3-yl)methyl)methanesulfonamide.

[0674] A solution of the product from **Part D** (88mg, 0.14mmo) in dichloromethane (1.4mL) was treated with trifluoroacetic acid (1.4mL) followed by stirring at room temperature for 18h, and then stirring at 40°C for 2h. The mixture was concentrated in vacuo to afford a dark, purple-brown foam, which was subjected to column chromatography on silica gel, eluting with 5-50% ethyl acetate in methylene chloride to afford an impure material, which was purified by reverse phase chromatography on a C-18 column, eluting with 1% water-TFA/acetonitrile. The procedures afforded the title compound as a solid (3.9mg). ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.31 - 11.48 (m, 1 H) 8.01 (s, 1 H) 7.68 - 7.94 (m, 2 H) 7.40 - 7.65 (m, 2 H) 7.10 - 7.38 (m, 2 H) 5.65 (dd, *J*=7.91, 2.02 Hz, 1 H) 4.33 (d, *J*=5.88 Hz, 2 H) 3.23 (s, 3 H) 2.95 (s, 3 H) 1.41 (s, 9 H).

Example 60. Preparation of *N*-((5-(3-*tert*-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxyphenyl)-1-methyl-2,3-dihydro-1*H*-inden-1-yl)methyl)methanesulfonamide (compound IB-L0-2.25).

[0675]



Part A. Preparation of 5-bromo-1-(1,3-dithian-2-yl)-2,3-dihydro-1*H*-inden-1-ol.

[0676] A solution of 1,3-dithiane (11.96g, 99mmol) in anhydrous tetrahydrofuran (100mL) at -30°C was treated dropwise over 10min with n-butyllithium (2.5M in hexanes, 38.4mL, 96mmol) followed by stirring at -15°C for 2h. The solution was then treated with a solution of 5-bromo-2,3-dihydro-1H-inden-1-one (15g, 71.1mmol) in anhydrous tetrahydrofuran (250mL) over 1h, maintaining the temperature between -9°C and 2°C. The mixture was then allowed to set in the refrigerator at 2-8°C for 18h. The solution was concentrated in vacuo to afford a maroon oil, which was treated with 1 N hydrochloric acid solution and extracted with ether. The ether layer was extracted with saturated sodium chloride solution, dried (Na_2SO_4) and concentrated in vacuo to afford an amber oil (23.55g).

Part B. Preparation of 2-(5-bromo-2,3-dihydro-1*H*-inden-1-ylidene)-1,3-dithiane.

[0677] A solution of the product from **Part A** (23.55g, 71.1mmol) in benzene (350mL) was treated with p-toluenesulfonic acid monohydrate (3.0g) followed by stirring at reflux for 1h while removing water by means of a Dean-Stark trap. The mixture was extracted with saturated sodium bicarbonate solution and then with saturated sodium chloride solution. Drying (Na_2SO_4) and concentration in vacuo afforded the product as an amber, oil (22.27g).

Part C. Preparation of 5-bromo-2,3-dihydro-1*H*-indene-1-carboxylic acid.

[0678] A solution of the product from **Part B** (22.27g, 71.1mmol) in glatial acetic acid (375mL) was treated with concentrated hydrochloric acid solution (125mL) followed by stirring at reflux for 3h. The mixture was cooled and concentrated in vacuo by azeotroping off the acetic acid and water with toluene (3x). The brown oil obtained was filtered through a plug of 70-230 mesh silica gel in a 2L sintered glass funnel (volume of silica gel ca. 1800mL) eluting with dichloromethane to remove non-polar impurities (1,3-propanedithiol, *inter alia*) and then with ethyl acetate to elute the title compound, which was obtained as a brown solid (9.85g, 58%).

Part D. Preparation of methyl 5-bromo-2,3-dihydro-1*H*-indene-1-carboxylate.

[0679] A suspension of the product from **Part C** (9.85g, 40.9mmol) in methanol (400mL) was treated with 4 N hydrogen chloride in 1,4-dioxane (125mL) and the mixture was stirred at reflux for 8h. The mixture was concentrated in vacuo to afford brown oil, which was purified by column chromatography on silica gel, eluting with 0-30% methyl t-butyl ether in chloroform. These procedures afforded the title compound as an amber oil (7.99g, 77%).

Part E. Preparation of methyl 5-bromo-1-methyl-2,3-dihydro-1*H*-indene-1-carboxylate.

[0680] A solution of the product from **Part D** (2.03g, 7.96mmol) in anhydrous tetrahydrofuran (40mL) at -78°C under N_2 was treated dropwise with lithium bis(trimethylsilyl)amide (1.0M in tetrahydrofuran, 9.55mL, 9.55mmol) over 10min. The solution was stirred at -78°C for 45min and then treated with methyl iodide (1.5mL, previously dried by passage through a plug of basic alumina). The mixture was then gradually allowed to warm to rt and was stirred for 18h. The mixture was quenched by addition of saturated ammonium chloride solution (2mL). The mixture was concentrated in vacuo to remove tetrahydrofuran and the residue was diluted with ethyl acetate. The mixture was extracted with saturated ammonium chloride solution and with saturated sodium chloride solution. Drying (Na_2SO_4) and concentration in vacuo afforded the title compound as an amber oil (2.06g, 96%).

Part F. Preparation of 5-bromo-1-methyl-2,3-dihydro-1*H*-indene-1-carboxylic acid.

[0681] A solution of the product from **Part E** (2.06g, 7.65mmol) and potassium trimethylsilanoate (5.5g of 90%, 4.91g, 38.3mmol) in tetrahydrofuran (40mL) was stirred at reflux for 3h. The mixture was cooled and concentrated in vacuo to remove tetrahydrofuran. The maroon residue was dissolved in water (ca. 175mL) and extracted with methyl t-butyl ether. The aqueous phase was cooled to 0°C and acidified to pH 3 by addition of concentrated hydrochloric acid solution. The mixture was extracted with ethyl acetate (2x) and then with saturated sodium chloride solution. The solution was dried (Na_2SO_4) and treated with Darco G-60, followed by filtration through celite. The filtrate was concentrated in vacuo to afford the title compound as a light yellow solid (1.93g, 99%).

Part G. Preparation of 5-bromo-1-methyl-2,3-dihydro-1*H*-indene-1-carboxamide.

[0682] A solution of the product from **Part F** (1.56g, 6.12mmol) and DMF (473µL, 447mg, 6.12mmol) in hexanes (100mL) was treated with oxalyl chloride (1.61mL, 2.32g, 18.4mmol) followed by stirring at room temperature for 1h. The mixture was treated with celite and then filtered through celite. The filtrate was concentrated in vacuo and dissolved in acetone (75mL) and cooled to 0°C. The solution was treated with 28% aqueous ammonia solution (75mL) followed by stirring at 0°C for 30min and then warming to room temperature. The mixture was concentrated in vacuo and extracted with ethyl acetate. The organic layer was extracted with saturated sodium chloride solution and dried (Na_2SO_4). Concentration in vacuo afforded the title compound as an oil (1.55g, 100%).

Part H. Preparation of (5-bromo-1-methyl-2,3-dihydro-1*H*-inden-1-yl)methanamine hydrochloride.

[0683] In a flask equipped with a vigreaux column and a short path distillation head, a solution of the product from **Part G** (1.21g, 4.76mmol) in anhydrous tetrahydrofuran (8mL) was warmed to a gentle reflux and treated dropwise with borane-dimethylsulfide

complex (904µL, 723mg, 9.52mmol). The resulting mixture was stirred at reflux for 2h. The solution was cooled to rt and carefully treated with methanol until bubbling ceased, followed by careful treatment with 4N hydrogen chloride in 1,4-dioxane solution (4mL). The mixture was then concentrated in vacuo. The colorless solid obtained was triturated with ether and collected by filtration. After drying in a vacuum oven at 50°C for 2h, the title compound was obtained as a colorless solid (893mg, 68%).

Part I. Preparation of *tert*-butyl (5-bromo-1-methyl-2,3-dihydro-1*H*-inden-1-yl)methylcarbamate.

[0684] A suspension of the product from **Part H** (893mg, 3.23mmo) in tetrahydrofuran (165mL) was treated with di-tert-butyl dicarbonate (846mg, 3.87mmol) and saturated sodium bicarbonate solution (7.2mL, ca. 6.46mmol) followed by stirring at room temperature for 18h. The mixture was diluted with ethyl acetate and extracted with water and saturated sodium chloride solution. The solution was dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash chromatography, eluting with 5-40% ethyl acetate in hexanes. These procedures afforded the title compound as a colorless solid (1.03g, 94%).

Part J. Preparation of *tert-butyl* (1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3é-dihydro-1H-inden-1-yl)methylcarbamate.

[0685] The product from **Part I** (1.03g, 3.03mmol) was subjected to the conditions described for **Example 58, Part D** to afford the title compound as a colorless solid (977mg, 83%).

Part K. Preparation of *tert*-butyl (5-(3-*tert*-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxyphenyl)-1-methyl-2,3-dihydro-1*H*-inden-1-yl)methylcarbamate.

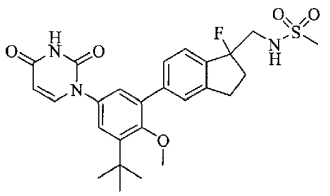
[0686] The product from **Part J** (965mg, 2.49mmol) was subjected to the conditions described for **Example 59, Part D** to afford the title compound as a colorless solid (618mg, 47%).

Part L. Preparation of *N*-((5-(3-*tert*-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxyphenyl)-1-methyl-2,3-dihydro-1*H*-inden-1-yl)methyl)methanesulfonamide.

[0687] The product from **Part K** (446mg, 0.84mmol) was dissolved in 4N hydrogen chloride in dioxane solution (12mL), followed by stirring at room temperature for 18h. The suspension of colorless solid obtained was then concentrated in vacuo. This material was suspended in dichloromethane (5mL) and cooled to 0°C, followed by sequential treatment with triethylamine (280µL, 203mg, 2.01mmol) and methanesulfonyl chloride (81µL, 120mg, 1.05mmol). The mixture was stirred at 0°C for 1h and then warmed to room temperature and diluted with dichloromethane. The mixture was extracted with 1M citric acid solution and then dried (Na_2SO_4) and concentrated in vacuo. The residue was dissolved in 3:1 tetrahydrofuran-water (8mL) and treated with potassium carbonate (231mg, 1.68mmol) followed by stirring at room temperature for 1h. The mixture was concentrated in vacuo and the residue diluted with water and then acidified to ca. pH 2 by addition of 1M citric acid. The product was extracted with ethyl acetate and the organic layer was extracted with saturated sodium chloride solution. Drying (Na_2SO_4) and concentration in vacuo afforded a colorless solid, which was purified by column chromatography on silica gel, eluting with 30-100% ethyl acetate in hexanes. The procedures afforded the title compound as a colorless solid (184mg, 43%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.39 (s, 1 H) 7.77 (d, *J*=7.72 Hz, 1 H) 7.14 - 7.48 (m, 5 H) 7.06 (t, *J*=6.62 Hz, 1 H) 5.63 (d, *J*=7.72 Hz, 1 H) 3.18 - 3.33 (m, 3 H) 2.96 - 3.15 (m, 2 H) 2.85 - 3.00 (m, 2 H) 2.70 - 2.87 (m, 3 H) 2.10 - 2.34 (m, 1 H) 1.63 - 1.90 (m, 1 H) 1.40 (s, 9 H) 1.20 - 1.34 (m, 3 H).

Example 61. Preparation of *N*-((5-(3-*tert*-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxyphenyl)-1-fluoro-2,3-dihydro-1*H*-inden-1-yl)methyl)methanesulfonamide (compound IB-L0-2.12).

[0688]



Part A. Preparation of 5-(5-bromo-2,3-dihydro-1*H*-inden-1-ylidene)-2,2,3,3,7,7,8,8-octamethyl-4,6-dioxa-3,7-disilanonane.

[0689] To a solution of the product from **Example 60, Part C** (1.2g, 4.98mmol) in anhydrous THF (5mL) was added TBSCl (1.726g, 11.45mmol), and the resulting yellow solution was cooled to 0°C in an ice bath. A 1.0M solution of LiHMDS in THF (11.95mL, 11.95mmol) was added dropwise over 5min, and the resulting dark red solution was stirred at 0°C for 90min, and then at room temeprature for 6h. The solvent was removed in vacuo and the oily semi solid residue was treated with pentane (2 x 35mL) to precipitate LiCl. The slurry was filtered and the solvent was removed in vacuo to give the title compound as a brown oil (2.3g).

Part B. Preparation of 5-bromo-1-fluoro-2,3-dihydro-1*H*-indene-1-carboxylic acid.

[0690] To a mixture of 1-chloromethyl-4-fluoro-1,1-diazoniabicyclo[2.2.2.]octane bis(tetrafluoroborate)(Selectfluor, 2.26g, 6.37mmol in CH_3CN (20mL) was added the product from **Part A** (2.3g, 4.90mmol) in CH_3CN (6mL). The resulting yellow-orange solution was stirred at room temperature overnight. The reaction mixture was poured into 50mL 1N HCl (aqueous), extracted with EtOAc (2 x 35mL). The combined organic extracts are washed with 0.5N NaOH (3 x 30mL). The combined aqueous extracts are washed with EtOAc (2 x 25mL), then adjusted mixture to pH 1 with 5N HCl (10mL). The resulting cloudy brown solution was extracted with EtOAc (2 x 50mL), the combined organic layers were washed with 10% NaCl and then treated with decolorizing carbon and stirred for 1h. The mixture was dried over anhydrous Na_2SO_4(s), filtered through Celite and the solvent removed in vacuo to give the title compound as leaving a yellow oil (0.84g).

Part C. Preparation of 5-bromo-1-fluoro-2,3-dihydro-1H-indene-1-carbonyl chloride.

[0691] To a solution of the product from **Part B** (0.95g, 3.67mmol) in CH_2Cl_2 was added oxalyl chloride (0.96mL, 11.00mmol), followed by DMF (0.28mL). The resulting bubbling solution was stirred at room temperature for 2h, filtered through Celite, and the solvent was removed in vacuo to give the title compound as a brown oil (0.99g).

Part D. Preparation of 5-bromo-1-fluoro-2,3-dihydro-1H-indene-1-carboxamide.

[0692] To a solution of the product from **Part C** (0.99g, 3.57mmol) in acetone (20mL) and at 0°C was added aqueous NH_4OH (28%, 0.28mL, 3.57mmol), and the resulting dark brown mixture was stirred at 0°C for 1h. The reaction mixture was concentrated in vacuo, and the residue was partitioned between water and EtOAc (2 x 50mL). The combined organic extracts were washed with 1N H_3PO_4, 10% $NaHCO_3$ (aq), 10% NaCl, and dried over anhydrous Na_2SO_4(s), filtered and concentrated in vacuo. The brown solid was purified by column chromatography on silica gel using a solvent gradient of CH_2Cl_2/MeOH (99/1to96/4). The title compound was obtained as a brown solid (0.205g, 22 %).

Part E. Preparation of *tert*-butyl (5-bromo-1-fluoro-2,3-dihydro-1*H*-inden-1-yl)methylcarbamate.

[0693] To a solution of the product from **Part D** (0.234g, 0.907mmol) in anhydrous THF (5mL) at 80°C was added borane-DMS complex (0.172mL, 1.813mmol) dropwise. The reaction flask was equipped with a short-path condenser, and the mixture was stirred at reflux for 2h, collecting THF and DMS. The mixture was then cooled to room temperature and MeOH (5mL) was added, followed by 4N HCl in 1,4-dioxane (5mL). The solvent was removed in vacuo to give a colorless solid (0.25g, 98%). The solid was

dissolved in THF (5mL), and to the solution was added triethylamine (0.137mL, 0.980mmol), followed by di-*tert*-butyl dicarbonate (0.214g, 0.980mmol). The cloudy mixture was stirred at room temperature for 30min, and 10% aq. $NaHCO_3$ (1mL) was added. The resulting mixture was stirred at room temperature for 18h and then concentrated in vacuo to an oily residue. The residue was dissolved in EtOAc (50mL), washed with water, 1N H_3PO_4, 10% NaCl, and dried over anhydrous Na_2SO_4(s). The drying agent was filtered off, and the solvent was removed in vacuo to give the title compound as an oil (0.27g, 88%).

Part F. Preparation of *tert*-butyl (1-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1*H*-inden-1-yl)methylcarbamate.

[0694] The product from **Part E** (0.27g, 0.784mmol) was subjected to the conditions described for **Example 42, Part B** to give the title compound as a tan solid (0.159g, 52 %).

Part G. Preparation of *tert*-butyl (5-(3-*tert*-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxyphenyl)-1-fluoro-2,3-dihydro-1*H*-inden-1-yl)methylcarbamate.

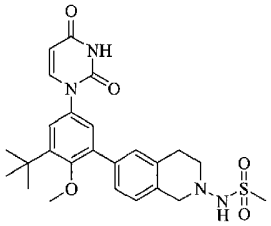
[0695] To a solution of the product from **Part F** (0.159g, 0.405mmol), the product from **Example C** (0.162g, 0.405 mol), 1,3,5,7 tetramethyl-2,4,8-trioxa-6-phospha-6-phenyl adamantane (PA-Ph, CAS 97739-46-3) (3.55 g, 0.012mmol) in THF (3mL) was added K_3PO_4 (0.181g, 0.851mmol) and water (1mL), followed by tris(dibenzylideneacetone)dipalladium(0) catalyst (3.71mg, 0.00405mmol). The resulting mixture was degassed by bubbling with N_2 for 20min, and then stirred at room temperature for 12h. The reaction mixture was diluted with EtOAc (50mL), washed with 1N H_3PO_4, 10% $NaHCO_3$, 10% NaCl, and dried over anhydrous Na_2SO_4(S). The mixture was filtered and solvent was removed in vacuo to give a brown oil, which was purified by column chromatography on silica gel, eluting with 98/2 CH_2Cl_2/MeOH. The title compound was isolated as a colorless solid (0.118g, 54%).

Part H. Preparation of *N*-((5-(3-*tert*-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxyphenyl)-1-fluoro-2,3-dihydro-1*H*-inden-1-yl)methyl)methanesulfonamide.

[0696] The product from **Part G** (0.118g, 0.219mmol) was dissolved in 4N HCl in 1,4-dioxane (2mL) and stirred at room temperature for 1h. The solvent was removed in vacuo and the residue was suspended in CH_2Cl_2 and evaporated (2 x 4mL) to give a colorless solid (0.10g, 96%). This solid was dissolved in CH_2Cl_2 (1mL) and the resulting slurry was stirred in an ice bath. Triethylamine (0.059mL, 0.422mmol) was added to the slurry resulting in a clear solution and to this was added methanesulfonyl chloride (0.02mL, 0.253mmol). The resulting mixture was stirred in the ice bath for 1h. The reaction mixture was diluted with CH_2Cl_2 50mL, washed with 1N H_3PO_4, 10% $NaHCO_3$, 10% NaCl, and dried over anhydrous Na_2SO_4(s). The drying agent was filtered off, and solvent was removed in vacuo leaving a crude product that was purified by column chromatography on silica gel, eluting with a gradient of 1:1 to 3:7 hexane:EtOAc. The title compound was obtained as a colorless solid (64mg, 62 %). ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.39 (s, 1 H) 7.77 (d, *J*=7.72 Hz, 1 H) 7.30 - 7.48 (m, 3 H) 7.12 - 7.32 (m, 3 H) 5.63 (d, *J*=7.72 Hz, 1 H) 3.27 (s, 3 H) 2.94 - 3.08 (m, 4 H) 2.91 (s, 3 H) 2.17 - 2.38 (m, 1 H) 1.76 - 1.97 (m, 1 H) 1.40 (s, 9 H).

Example 62. Preparation of *N*-(6-(3-*tert*-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxyphenyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)methanesulfonamide (compound IB-L0-2.43).

[0697]



Part A. Preparation of *N*-(3-bromophenethyl)-2,2,2-trifluoroacetamide.

[0698] To a solution of 2-(3-bromophenyl)ethanamine (10g, 50.0mmol) in dichloromethane (200ml) at 0°C were added 2,6-lutidine (6.40ml, 55.0mmol) and then trifluoroacetic anhydride (7.77ml, 55.0mmol) dropwise, and the reaction was stirred at room temperature overnight. Water was added at 0°C and the reaction was washed with 1M HCl, H_2O, and sat $NaHCO_3$. The organic was dried over$mgSO_4$, filtered and concentrated to provide the title compound as a tan solid (14.7g, 99%).

Part B. Preparation of 1-(6-bromo-3,4-dihydroisoquinolin-2(1*H*)-yl)-2,2,2-trifluoro-ethanone.

[0699] To the product from **Part A** (14.70g, 49.6mmol) and paraformaldehyde (2.39g, 80mmol) was added a mixture of acetic acid (81ml) and sulfuric acid (53.7ml) at room temperature. The suspension was stirred for 60h during which time it became a solution. The reaction was poured into cold water. The reaction was diluted with ethyl acetate and washed with water, sat $NaHCO_3$, and brine. The organic layer was dried over$mgSO_4$, filtered and concentrated to provide the title compound, contaminated with the 8-bromo isomer, as a colorless oil (10.5 g, 67%).

Part C. Preparation of 6-bromo-1,2,3,4-tetrahydroisoquinoline.

[0700] To a solution of the product from **Part B** (9.5g, 30.8mmol) in methanol (231ml) and water (77ml) at room temperature was added potassium carbonate (8.52g, 61.7mmol) and the reaction was stirred at room temperature for 30min. The reaction was diluted with water and 25% isopropanol in chloroform and the pH was adjusted to 9 with 1N HCl. The mixture was extracted twice with 25% isopropanol in chloroform. The combined organic layers were dried over$mgSO_4$, filtered and concentrated to give the title compound, contaminated with the 8-bromo isomer (6.55g, quantitative).

Part D. Preparation of 6-bromo-2-nitroso-1,2,3,4-tetrahydroisoquinoline.

[0701] To a solution of the product from **Part C** (6.55g, 30.9mmol) in acetic acid (61.8ml) and 3N aq. hydrochloric acid (10.29ml, 30.9mmol) at 0°C was added 1.9M sodium nitrite (20.64ml, 39.2mmol) dropwise, and the reaction was stirred at room temperature overnight. The solvent was evaporated and the reaction was diluted with 25% isopropanol in chloroform and sat $NaHCO_3$. The aqueous layer was extracted twice with 25% isopropanol in chloroform. The combined organic layers were dried over$mgSO_4$, filtered and concentrated to give the title compound, contaminated with the 8-bromo isomer (6.97 g, 94%).

Part E. Preparation of 6-bromo-3,4-dihydroisoquinolin-2(1H)-amine.

[0702] To a solution of the product from **Part D** (0.5g, 2.074mmol) in methanol (4.15ml) was added zinc (0.542g, 8.30mmol) and the reaction was cooled to 0°C, followed by dropwise addition of AcOH (4.15ml). The reaction was warmed to rt and the reaction was stirred for 2.5h. The reaction was filtered and the solid was washed with methanol. The filtrate was evaporated and the residue was diluted with water and 25% isopropanol in chloroform and saturated $NaHCO_3$ was added. A white solid was removed by filtration, and the aqueous layer was extracted twice with 25% isopropanol in chloroform. The combined organic layers were dried over$mgSO_4$, filtered and concentrated to give the title compound, contaminated with the 8-bromo isomer (0.472g, quantitative).

Part F. Preparation of *tert*-butyl 6-bromo-3,4-dihydroisoquinolin-2(1*H*)-ylcarbamate.

[0703] A solution of the product from **Part E** (0.472g, 2.078mmol) in THF (20.78ml) was cooled to 0°C followed by addition of di-*tert*-butyl dicarbonate (0.531ml, 2.286mmol), and the reaction was stirred at room temperature overnight. Solvent was removed in vacuo, and the crude product was purified by column chromatography on silica gel (isolated lower R_f product) using a gradient starting with dichloromethane and ending with 10% ethyl acetate in dichloromethane to give the title compound (49mg, 73%).

Part G. Preparation of *tert*-butyl 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydroisoquinolin-2(*H*)-ylcarbamate.

[0704] A solution of the product from **Part F** (100mg, 0.306mmol), bis(pinacolato)diboron (85mg, 0.336mmol), and potassium acetate (57.3µl, 0.917mmol) in 1,4-dioxane (3.0mL) was degassed by bubbling with N_2 gas for 15min. 1,1'-Bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (11.18mg, 0.015mmol) was added, and the resulting mixture was stirred at 95°C for 16h. The cooled solution was diluted with 25% isopropanol in chloroform and washed with water. The organic layer was dried overmgSO4, filtered and concentrated in vacuo. The product was purified by column chromatography on silica gel eluting with a gradient starting with dichloromethane and ending with 25% ethyl acetate in dichloromethane to give the title compound (70mg, 61%).

Part H. Preparation of *tert*-butyl 6-(3-*tert*-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxyphenyl)-3,4-dihydroisoquinolin-2(1*H*)-ylcarbamate.

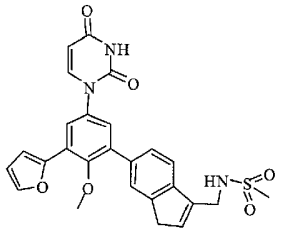
[0705] A mixture of the product from **Example C** (74.8mg, 0.187mmol), the product from Part G (70mg, 0.187mmol) in EtOH (1.0mL), toluene (1.0mL) 1M aq. Na_2CO_3 (281µl, 0.281mmol) was degassed by bubbling with N_2 gas for 10min. 1,1'-Bis(diphenylphosphino)ferrocene-palladium(II) dichloride dichloromethane complex (6.84mg, 9.35µmol) was added, and degassing with N_2 was continued for 5min. The reaction mixture was sealed and heated at 78°C for 16h. The reaction was cooled and diluted with 25% isopropanol in chloroform and washed with water. The organic was dried overmgSO4, filtered and concentrated. The crude product was purified by column chromatography on silica gel, eluting with a gradient starting with dichloromethane and ending with ethyl acetate to give the title compound (53mg, 54%).

Part I. Preparation of *N*-(6-(3-*tert*-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxyphenyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)methanesulfonamide.

[0706] To a solution of the product from **Part H** (25mg, 0.048mmol) in dichloromethane (0.5mL) at room temperature was added TFA (0.5mL) and the reaction was stirred for 30min, and then concentrated in vacuo. The residue was diluted with 25% isopropanol in chloroform and washed with sat $NaHCO_3$. The organic layer was dried over$mgSO_4$, filtered and concentrated to give a solid (17.8mg, 88%). To a solution of the solid in pyridine (0.5mL) at 0°C was added methanesulfonyl chloride (12.6µl, 0.162mmol) and the reaction was stirred at room temperature for 90min. Methanol was added and the reaction was stirred for 10min. The residue was diluted with 25% isopropanol in chloroform and washed with sat $NaHCO_3$. The organic layer was dried over$mgSO_4$, filtered and concentrated, and the product was purified by column chromatography on silica gel eluting with a gradient starting with dichloromethane and ending with ethyl acetate to give the title compound (11mg, 52%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.39 (s, 1 H) 8.53 (s, 1 H) 7.76 (d, *J*=7.72 Hz, 1 H) 7.11 - 7.42 (m, 5 H) 5.63 (d, *J*=7.72 Hz, 1 H) 4.04 (s, 2 H) 3.28 (s, 3 H) 3.10 (d, *J*=5.52 Hz, 2 H) 2.98 (s, 3 H) 2.90 - 3.05 (m, 2 H) 1.40 (s, 9 H).

Example 63. Preparation of *N*-((6-(5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-3-(furan-2-yl)-2-methoxyphenyl)-1*H*-inden-3-yl)methyl)methanesulfonamide (compound IB-L0-2.65).

[0707]



Part A. Preparation of *N*-((6-(3-bromo-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxyphenyl)-1*H*-inden-3-yl)methyl)methanesulfonamide.

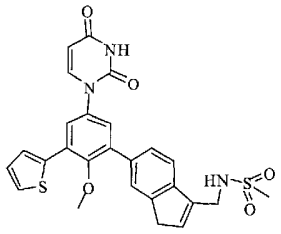
[0708] The product from **Example 18, Part C** (0.242gm, 0.573mmol) and the product from **Example 49, Part E** (0.200gm, 0.57mmol) was subjected to the conditions described for **Example 49, Part F** to give the title compound as an off-white solid (0.104gm, 35%).

Part B. Preparation of *N*-((6-(5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-3-(furan-2-yl)-2-methoxyphenyl)-1*H*-inden-3-yl)methyl)methanesulfonamide.

[0709] A solution of the product from **Part A** (25.2mg, 0.049mmol) in 3:1 v/v THF-water (1.3mL) was combined in a microwave tube at room temperature with furan-2-ylboronic acid (6.91mg, 0.062mmol) and potassium phosphate (16.84mg, 0.097mmol). To this was added 1,1'-bis(di-tert-butyl-phosphino)ferrocene palladium dichloride (1.65mg, 2.53umole). The tube was sealed and the resulting mixture was purged with nitrogen for 4min and then heated for 16.5h in an oil bath at 50°C. The reaction mixture was partitioned between dilute HCl and ethyl acetate, and the organic phase was dried (MgSO4) and concentrated in vacuo. The residue was purified by chromatography on silica gel (ethyl acetate-hexanes) to give the title compound as an off white solid (11.4mg, 46%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.45 (s, 1 H) 7.80 - 7.89 (m, 2 H) 7.73 - 7.79 (m, 2 H) 7.56 - 7.63 (m, 2 H) 7.50 (t, *J*=6.07 Hz, 1 H) 7.38 (d, *J*=2.94 Hz, 1 H) 7.09 (d, *J*=3.31 Hz, 1 H) 6.68 (dd, *J*=3.68, 1.84 Hz, 1 H) 6.58 (s, 1 H) 5.68 (d, *J*=7.72 Hz, 1 H) 4.19 (d, *J*=5.15 Hz, 2 H) 3.48 (s, 2 H) 3.34 (s, 3 H) 2.96 (s, 3 H).

Example 64. Preparation of *N*-((6-(5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxy-3-(thiophen-2-yl)phenyl)-1*H*-inden-3-yl)methyl)methanesulfonamide (compound IB-L0-2.63).

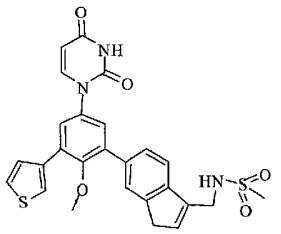
[0710]



[0711] The product from **Example 63, Part** A (26.5mg, 0.051mmol) was reacted with thiophen-2-yl boronic acid (8.3mg, 0.065mmol) as described in **Example 63, Part B** to give the title compound as an off-white solid (8.6mg, 32%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.47 (s, 1 H) 7.86 (d, *J*=7.72 Hz, 2 H) 7.55 - 7.78 (m, 5 H) 7.50 (t, *J*=6.25 Hz, 1 H) 7.38 (d, *J*=2.57 Hz, 1 H) 7.16 - 7.21 (m, 1 H) 6.58 (s, 1 H) 5.69 (d, *J*=7.72 Hz, 1 H) 4.19 (d, *J*=4.78 Hz, 2 H) 3.48 (s, 2 H) 3.30 (s, 3 H) 2.96 (s, 3 H).

Example 65. Preparation of *N*-((6-(5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxy-3-(thiophen-3-yl)phenyl)-1*H*-inden-3-yl)methyl)methanesulfonamide (compound IB-L0-2.62).

[0712]

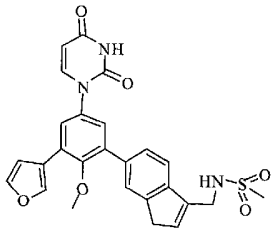


[0713] The product from **Example 63, Part A** (25.9mg, 0.050mmol) was reacted with thiophen-3-yl boronic acid (8.1mg, 0.063mmol) as described in **Example 63, Part B** to give the title compound as an off-solid (8.6mg, 33%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.45 (d, *J*=1.84 Hz, 1 H) 7.93 (d, *J*=2.94 Hz, 1 H) 7.87 (d, *J*=7.72 Hz, 1 H) 7.53 - 7.75 (m, 6 H) 7.49 (t, *J*=6.25 Hz, 1 H) 7.39 (d, *J*=2.57 Hz, 1 H) 6.57 (s, 1 H) 5.68 (dd, *J*=7.91, 2.02 Hz, 1 H) 4.19 (d, *J*=5.15 Hz, 2 H) 3.47 (s, 2 H) 3.21 (s, 3 H) 2.96 (s,

3 H).

Example 66. Preparation of *N*-((6-(5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-3-(furan-3-yl)-2-methoxyphenyl)-1*H*-inden-3-yl)methyl)methanesulfonamide (compound IB-L0-2.67).

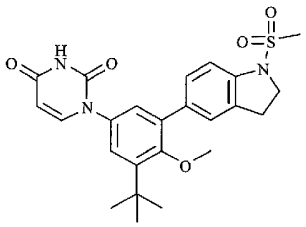
[0714]



[0715] The product from **Example 63, Part A** (25.9mg, 0.050mmol) was reacted with furan-3-yl boronic acid (7.2mg, 0.064mmol) as described in **Example 63, Part B** to give the title compound as an off-white solid (10.6mg, 45%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.46 (s, 1 H) 7.84 (d, *J*=8.09 Hz, 1 H) 7.80 (t, *J*=1.84 Hz, 1 H) 7.68 - 7.75 (m, 2 H) 7.54 - 7.64 (m, 2 H) 7.50 (t, *J*=6.07 Hz, 1 H) 7.35 (d, *J*=2.57 Hz, 1 H) 7.08 (d, *J*=1.47 Hz, 1 H) 6.57 (s, 1 H) 5.68 (d, *J*=8.09 Hz, 1 H) 3.47 (s, 2 H) 3.30 (s, 3 H) 2.96 (s, 3 H).

Example 67. Preparation of 1-(3-*tert*-butyl-4-methoxy-5-(1-(methylsulfonyl)indolin-5-yl) phenyl)pyrimidine-2,4(1*H*,3*H*)-dione (compound IB-L0-2.32).

[0716]



Part A. Preparation of 5-bromo-1-(methylsulfonyl)indoline.

[0717] To DMF (5.0ml) was added sodium hydride (53mg, 1.3mmol) and the solution stirred at room temperature for 30min. 5-Bromoindoline (240mg, 1.2mmol) was added and the solution was stirred at room temperature for 30min. Methanesulfonyl chloride (94ul, 1.2mmol) was added and the solution stirred at room temperature overnight, then concentrated in vacuo. The crude product was purified by column chromatography on silica gel eluting with 2% $CH_3OH/CHCl_3$ to give the title compound (202mg, 60%).

Part B. Preparation of 1-(methylsulfonyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) indoline.

[0718] The product from **Part A** (192mg, 0.70mmol) was subjected to the conditions described for **Example 42, Part B** to give the title compound (114mg, 51 %).

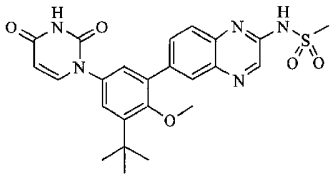
Part C. Preparation of 1-(3-*tert*-butyl-4-methoxy-5-(1-(methylsulfonyl)indolin-5-yl)phenyl) pyrimidine-2,4(1*H*,3*H*)-dione.

[0719] The product from **Example C** (58mg, 0.145mmol) and the product from **Part B** (56.2mg, 0.174mmol) were subjected to the conditions described for **Example 42, Part C to** give the title compound as a colorless solid (12mg, 18%). ^{1}H NMR (300 MHz,

DMSO-d_6): δ 11.40 (d, *J*=1.84 Hz, 1 H) 7.76 (d, *J*=7.72 Hz, 1 H) 7.53-7.67 (m, 1 H) 7.45 (s, 1 H) 7.32-7.41 (m, 2 H) 7.23 (dd, *J*=13.60, 2.57 Hz, 2 H) 5.63 (dd, *J*=8.09, 2.21 Hz, 1 H) 3.99 (t, *J*=8.46 Hz, 2 H) 3.29 (s, 3 H) 3.18 (t, *J*=8.46 Hz, 2 H) 3.04 (s, 3 H).

Example 68. Preparation of *N*-(6-(3-*tert*-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxyphenyl)quinoxalin-2-yl)methanesulfonamide (compound IB-L0-2.26).

[0720]



Part A. Preparation of *N*-(4-bromo-2-nitrophenyl)-3-oxobutanamide.

[0721] A solution of diketene (0.32ml, 4.15mmol) in toluene (2ml) was added to an 80°C solution of 4-bromo-2-nitroaniline (900mg, 4.15mmol) in toluene (7ml) and the solution was heated at reflux for 5h. Triethylamine (0.58ml, 4.15mmol) in toluene (2ml) was added and refluxing was continued for 30min. The cooled solution was concentrated in vacuo and the crude product purified by column chromatography on silica gel eluting with 2:1 hexane/EtOAc to give the title compound as a yellow solid (920mg, 74%).

Part B. Preparation of 6-bromoquinoxalin-2(1H)-one.

[0722] To a solution of sodium hydroxide (337mg, 8.4mmol) in H_2O (2.1ml) was added the product from **Part A** (423mg, 1.4mmol) and stirring was continued at 65°C for 1h. The cooled solution was diluted with H_2O (4ml) and sodium borohydride (31.9mg, 0.84mmol) was added and stirring was continued at room temperature for 1.5h. Ice was added to the solution followed by dropwise addition of 6N HCl until acidic. The resulting solid was collected by filtration, washed with H_2O, and dried in a vacuum oven to give the title compound (273mg, 86%).

Part C. Preparation of 6-bromo-2-chloroquinoxaline.

[0723] To a flask containing phosphorus oxychloride (3.4ml, 36.5mmol) was added the product from **Part B** (255mg, 1.1mmo and the solution was heated at 60°C overnight. The solution was cooled to room temperature, poured over ice and the resulting solid collected by filtration to give the title compound (239mg, 87%).

Part D. Preparation of 6-bromo-*N*-(4-methoxybenzyl)quinoxalin-2-amine.

[0724] To a solution of the product from **Part C** (2.8g, 11.5mmol) in ethanol (58ml) was added (4-methoxyphenyl)methanamine (7.5ml, 57.5mmol) and the solution was stirred at room temperature for 1h. Solvent was concentrated in vacuo and the crude product was purified by column chromatography on silica gel eluting with 20% EtOAc/hexane to give the title compound (1.97g, 50%).

Part E. Preparation of *N*-(4-methoxybenzyl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) quinoxalin-2-amine.

[0725] The product from **Part D** (500mg, 1.45mmol) was subjected to the conditions described for **Example 42, Part B** to give the title compound (378mg, 66%).

Part F. Preparation of 1-(3-*tert*-butyl-4-methoxy-5-(2-(4-methoxybenzylamino)quinoxalin-6-yl)phenyl)pyrimidine-

2,4(1*H*,3*H*)-dione.

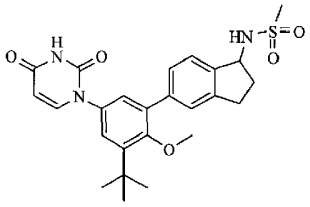
[0726] The product from **Part E** (133mg, 0.34mmol) was subjected to the conditions described for **Example 42, Part C** to give the title compound (125mg, 82%).

Part G. Preparation of *N*-(6-(3-*tert*-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*-yl)-2-methoxyphenyl)quinoxalin-2-yl)methanesulfonamide.

[0727] To a solution of the product from **Part F** (87mg, 0.16mmol) in CH_2Cl_2 (1.6ml) and H_2O (0.07ml) was added DDQ (40.4mg, 0.18mmol) and stirred vigorously at room temperature for 1h. The solution was filtered through Celite and the dark solid collected on the Celite was dissolved in 5ml CH_3OH. The methanol solution was filtered, solvent removed in vacuo and the crude intermediate was dissolved in pyridine (0.6ml). Methanesulfonyl chloride (11ul, 0.14mmol) was added and the solution was heated at 60°C overnight. The cooled solution was concentrated in vacuo and the crude product was purified by column chromatography on silica gel eluting with 2% $CH_3OH/CHCl_3$ to give the title compound (7.7mg, 12%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.42 (s, 1 H) 8.29 (s, 1 H) 8.13 (s, 1 H) 7.88 (d, 1 H) 7.54 (s, 1 H) 7.19-7.43 (m, 4 H) 5.83 (dd, *J*=7.91, 2.39 Hz, 1H) 3.32 (s, 3 H) 3.27 (s, 3 H) 1.46 (s, 9 H).

Example 69. Preparation of *N*-(5-(3-*tert*-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*-yl)-2-methoxyphenyl)-2,3-dihydro-1*H*-inden-1-yl)methanesulfonamide (compound IB-L0-2.44).

[0728]



Part A. Preparation of 5-bromo-2,3-dihydro-1*H*-inden-1-ol.

[0729] A suspension of 5-bromo-2,3-dihydro-1H-inden-1-one (2.07g, 9.81mmol) in ethanol (49mL) was treated with the sodium borohydride (186mg, 4.90mmol) all at once. After a few minutes, the solution warmed slightly and all solids dissolved. After stirring at room temperature for 1h, the mixture was concentrated in vacuo to remove ethanol. The gum obtained was partitioned between ethyl acetate and water. The organic layer was extracted with saturated sodium bicarbonate solution (2 x) and saturated sodium chloride solution. Drying (Na_2SO_4) and concentration in vacuo afforded the title compound (3.05g, 98%) as a colorless oil, which crystallized upon pumping under high vacuum overnight.

Part B. Preparation of 1-azido-5-bromo-2,3-dihydro-1*H*-indene.

[0730] A solution of the product from **Part A** (1.01g, 4.73mmol) in toluene (8.1mL) was treated with the diphenyl phosphoroyl azide (1.23mL, 1.56g, 5.67mmol) followed by cooling to 0°C. The solution was treated dropwise with DBU (855µL, 863mg, 5.67mmol) followed by stirring at 0°C for 2h, and then warming to room temperature for 48h. The mixture was diluted with ethyl acetate and extracted with water and 1 M citric acid solution, and then with saturated sodium chloride solution. Drying (Na_2SO_4) and concentration in vacuo afforded a brown oil, which was purified by flash chromatography, eluting with 5-50 % ethyl acetate in hexanes. These procedures afforded the title compound (889mg, 79%) as a light yellow oil.

Part C. Preparation of 5-bromo-2,3-dihydro-1*H*-inden-1-amine.

[0731] To a -15°C solution of 1M lithium aluminum hydride in THF (0.84ml, 0.84mmol) in THF (0.88ml) was added dropwise a solution of the product from **Part B** (200mg, 0.84mmol) and the solution was warmed to room temperature and stirred overnight. The solution was cooled to -10°C and 4:1 THF:H_2O (0.5ml) was added dropwise. The solution was stirred at room temperature for 4h, filtered through Celite and the filtrate concentrated in vacuo to give the title compound (151mg, 85%).

Part D. Preparation of *N*-(5-bromo-2,3-dihydro-1*H*-inden-1-yl)methanesulfonamide.

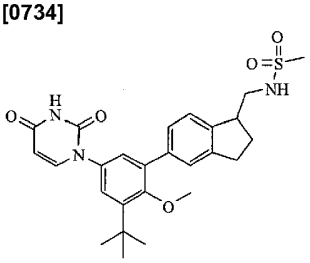
[0732] To a solution of the product from **Part C** (150mg, 0.71mmol) in pyridine (3.5ml) was added methanesulfonyl chloride (61ul, 0.78mmol) and the solution was stirred at room temperature overnight. The solution was concentrated in vacuo and the crude product was purified by column chromatography on silica gel eluting with 20% EtOAc/hexane to give the title compound (111mg, 54%).

Part E. Preparation of *N*-(5-(3-*tert*-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxyphenyl)-2,3-dihydro-1*H*-inden-1-yl)methanesulfonamide.

[0733] The product from **Part D** (109mg, 0.38mmol) was subjected to the conditions described for **Example 42, Part B** and **Part C** to give the title compound (39mg, 60%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.39 (d, *J*=1.84 Hz, 1 H) 7.77 (d, *J*=7.72 Hz, 1 H) 7.58 (d, *J*=8.82 Hz, 1 H) 7.39-7.48 (m, 3 H) 7.27 (d, *J*=2.57 Hz, 1 H) 7.19-7.23 (m, 1 H) 5.63 (dd, *J*=8.09, 2.21 Hz, 1 H) 4.86 (q, *J*=7.97 Hz, 1 H) 3.27 (s, 3 H) 3.04 (s, 3 H) 2.90-3.01 (m, 1 H) 2.71-2.90 (m, 1 H) 2.52-2.62 (m, 1 H) 1.85-1.98 (m, 1 H) 1.40 (s, 9 H).

Example 70. Preparation of *N*-((5-(3-*tert*-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*-yl)-2-methoxyphenyl)-2,3-dihydro-1*H*-inden-1-yl)methyl)methanesulfonamide (compound IB-L0-2.17).

[0734]



Part A. Preparation of (*E*)-5-bromo-1-(methoxymethylene)-2,3-dihydro-1*H*-indene.

[0735] To a suspension of (methoxymethyl)triphenylphosphonium chloride (39.7g, 116mmol) in THF (210ml) at -20°C was added dropwise 1M potassium t-butoxide (95ml, 95mmol) and the solution stirred at -20°C for 20min. To this solution was added dropwise a solution of 5-bromo-2,3-dihydro-1H-inden-1-one (10.0g, 47.4mmol) in THF (230ml) and stirring was continued at -20°C for 30min then warmed to room temperature and stirred for 2h. The solution was filtered through Celite and the filtrate was concentrated in vacuo to give crude product which was purified by chromatography on a silica gel cartridge eluting with CH_2Cl_2/hexane to give the title compound (10.56g, 93%).

Part B. Preparation of 5-bromo-2,3-dihydro-1*H*-indene-1-carbaldehyde.

[0736] To a solution of the product from **Part A** (1.44g, 6.0mmol) in CH_2Cl_2 (30ml) at -78°C was added dropwise 1M boron tribromide in CH_2Cl_2 (13.8ml, 13.8mmol) and stirring was continued at -78°C for 4h. The solution was poured into an ice-saturated. sodium bicarbonate mixture and stirred vigorously. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2x), the organic extracts were combined, dried (Na_2SO_4), and concentrated in vacuo to give crude product which

was purified by column chromatography on silica gel eluting with 10% EtOAc/hexane to give the title compound (604mg, 45%).

Part C. Preparation of 1-(5-bromo-2,3-dihydro-1*H*-inden-1-yl)-*N*-(4-methoxybenzyl)-methanamine.

[0737] To a solution of the product from **Part B** (300mg, 1.3mmol) in CH_3OH (18.5ml) was added 4-methoxybenzylamine (0.17ml, 1.3mmol) and decaborane (49mg, 0.4mmol) and stirring was continued at room temperature for 1h, solvent was concentrated in vacuo and the crude product was purified by column chromatography on silica gel eluting with 3% $CH_3OH/CHCl_3$ to give the title compound (264mg, 57%).

Part D. Preparation of *N*-((5-bromo-2,3-dihydro-1*H*-inden-1-yl)methyl)-*N*-(4-methoxybenzyl)methanesulfonamide.

[0738] To a solution of the product from **Part C** (88mg, 0.25mmol) in CH_2Cl_2 (1.0ml) was added triethylamine (39ul, 0.28mmol) and methanesulfonyl chloride (22ul, 0.28mmol) and stirring was continued at room temperature for 1h, solvent was concentrated in vacuo and the crude product was purified by column chromatography on silica gel eluting with EtOAc/hexane to give the title compound (55mg, 51%).

Part E. Preparation of N-(4-methoxybenzyl)-N-((5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3 -dihydro-1H-inden-1-yl)methyl)methanesulfonamide.

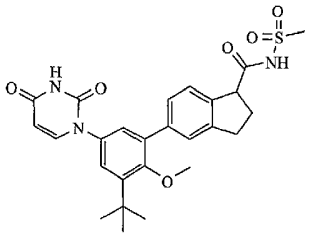
[0739] The product **from Part D** (1.15g, 2.71mmol) was subjected to the conditions described for **Example 42, Part B** to give the title compound (840mg, 66%).

Part F. Preparation of *N*-((5-(3-*tert*-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxyphenyl)-2,3-dihydro-1*H*-inden-1-yl)methyl)methanesulfonamide.

[0740] The product from **Part E** (840mg, 2.1mmol) was subjected to the conditions described for **Example 42, Part C** and the isolated material (1.28g, 2.07mmol) was dissolved in CH_2Cl_2 (10ml) and trifluoroacetic acid (10ml) was added slowly. After stirring at room temperature for 1h, solvent was concentrated in vacuo and the crude product was suspended in 10% $NaHCO_3$, extracted with CH_2Cl_2 (3x), the organic extracts combined, dried (Na_2SO_4), and solvent concentrated in vacuo to give crude product which was purified by column chromatography on silica gel eluting with 2% $CH_3OH/CHCl_3$ to give title compound (0.84g, 81%). ^1H NMR (300 MHz, DMSO-d_6) δ 11.39 (s, 1 H) 7.77 (d, *J*=8.09 Hz, 1 H) 7.29-7.59 (m, 3 H) 7.25 (d, *J*=2.94 Hz, 1 H) 7.10-7.22 (m, 2 H) 5.63 (dd, *J*=7.72, 1.84 Hz, 1 H) 3.93 (s, 3 H) 3.26 (s, 2 H) 3.23-3.40 (m, 1 H) 2.89 (s, 3 H) 2.71-3.09 (m, 2 H) 2.14-2.32 (m, 1 H) 1.75-1.95 (m, 1 H) 1.40 (s, 9 H).

Example 71. Preparation of 5-(3-*tert*-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxyphenyl)-*N*-(methylsulfonyl)-2,3-dihydro-1*H*-indene-1-carboxamide (compound IB-L0-2.34).

[0741]



Part A. Preparation of 5-bromo-2,3-dihydro-1*H*-indene-1-carboxylic acid.

[0742] To a solution of the product from **Example 70, Part B** (300mg, 1.3mmol) and 2-methyl-2-pentene (8ml) in tert-butanol (32ml) was added a solution of sodium chlorite (1.36g, 0.12mmol) in H_2O (12ml) containing sodium dihydrogen phosphate (1.07g, 8.9mmol) and the mixture was stirred vigorously for 20min at room temperature. Solvents were concentrated in vacuo and the residue was diluted with H_2O, extracted with EtOAc (3x), extracts combined, dried (Na_2SO_4), and concentrated in vacuo to give the title compound (180mg, 56%).

Part B. Preparation of 5-bromo-*N*-(methylsulfonyl)-2,3-dihydro-1*H*-indene-1-carboxamide.

[0743] To a solution of the product from **Part A** (100mg, 0.42mmol) in CH_2Cl_2 (1.7ml) was added carbonyldiimidazole (67.3mg, 0.42mmol) and the reaction was stirred for 2h at room temperature. Methanesulfonamide (39.5mg, 0.42mmol) and DBU (62.5mg, 0.42mmol) were added and stirring was continued at room temperature for 2h. Solution was diluted with CH_2Cl_2, washed 1N HCl, brine, dried (Na_2SO_4), concentrated in vacuo and the crude product was purified by column chromatography on silica gel eluting with 20% EtOAc/hexane to give the title compound (121mg, 92%).

Part C. Preparation of *N*-(methylsulfonyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1*H*-indene-1-carboxamide.

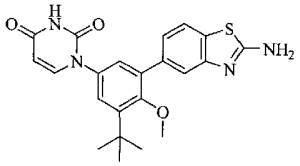
[0744] The product from **Part B** (159mg, 0.5mmol) was subjected to the conditions described for **Example 42, Part B** to give the title compound (144mg, 79%).

Part D. Preparation of 5-(3-*tert*-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxyphenyl)-*N*-(methylsulfonyl)-2,3-dihydro-1*H*-indene-1-carboxamide.

[0745] The product from **Part C** (134mg, 0.34mmol) was subjected to the conditions described for **Example 42, Part C** to give title compound (14mg, 8%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 (m, 1 H) 7.08-7.57 (m, 7 H) 5.80 (dd, *J*=7.91, 2.39 Hz, 1 H) 4.07 (dd, *J*=9.01, 6.07 Hz, 1 H) 3.33 (s, 3 H) 3.08 (s, 3 H) 2.91-3.22 (m, 1 H) 2.35-2.74 (m, 1 H) 1.44 (s, 9H) 1.17-1.34 (m, 1 H) 0.60-1.00 (m, 1 H).

Example 72. Preparation of 1-(3-(2-aminobenzo[*d*]thiazol-6-yl)-5-*tert*-butyl-4-methoxyphenyl)pyrimidine-2,4(1*H*,3*H*)-dione (compound IB-L0-2.39).

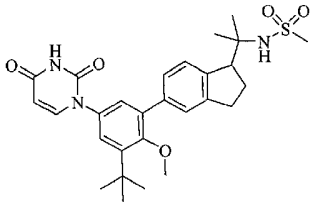
[0746]



[0747] The title compound was prepared using the procedures described for the preparation of **Example 53,** substituting 5-bromo[*d*]thiazol-2-amine for 6-bromobenzo[*d*]thiazol-2-amine. ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.40 (d, J=1.84 Hz, 1 H) 8.40 (s, 2 H) 7.84 (d, J=8.09 Hz, 1 H) 7.78 (d, J=7.72 Hz, 1 H) 7.54 (d, J=1.47 Hz, 1 H) 7.27 - 7.32 (m, 3 H) 5.64 (dd, J=8.09, 2.21 Hz, 1 H) 3.27 (s, 3 H) 1.41 (s, 9 H).

Example 73. Preparation of *N*-(2-(5-(3-*tert*-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxyphenyl)-2,3-dihydro-1*H*-inden-1-yl)propan-2-yl)methanesulfonamide (compound IB-L0-2.29).

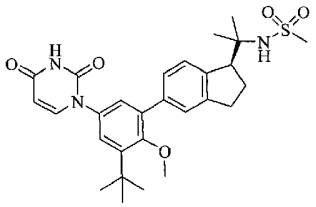
[0748]



[0749] To a solution of the product from **Example 45, Part D** (20mg, 0.038mmol) in 1:1 benzene: MeOH (0.6ml) was added platinum(IV) oxide (1mg). The resulting mixture was stirred under 1 atm H_2 at room temperature for 1h, and then filtered thru celite, and concentrated in vacuo. The crude product was purified by column chromatography on silica gel using 3% MeOH in $CHCl_3$ as the eluent to give the title compound as a solid (14mg, 70%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.39 (s, 1 H) 7.77 (d, *J*=7.72 Hz, 1 H) 7.58 (d, *J*=8.09 Hz, 1 H) 7.28 - 7.38 (m, 2 H) 7.21 - 7.26 (m, 2 H) 7.07 (s, 1 H) 5.63 (d, *J*=7.72 Hz, 1 H) 3.61 (dd, *J*=8.64, 5.33 Hz, 1 H) 3.25 (s, 3 H) 3.00 (s, 3 H) 2.75 - 2.98 (m, 2 H) 1.97 - 2.21 (m, 2 H) 1.40 (s, 9 H) 1.24 (d, *J*=8.46 Hz, 6 H).

Example 74. Preparation of (*S*)-*N*-(2-(5-(3-*tert*-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxyphenyl)-2,3-dihydro-1*H*-inden-1-yl)propan-2-yl)methanesulfonamide (compound IB-L0-2.22).

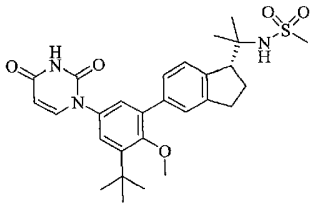
[0750]



[0751] The product from **Example 73** (10mg) was subjected to chiral chromatography (Chiralpak AD-H column; eluting with 1:3 2-PrOH:hexanes(0.1% TFA)). Isolation of the earlier eluting component gave the title compound (4.4mg). ^{1}H NMR identical to the product from **Example 103.**

Example 75. Preparation of (*R*)-*N*-(2-(5-(3-*tert*-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxyphenyl)-2,3-dihydro-1*H*-inden-1-yl)propan-2-yl)methanesulfonamide (compound IB-L0-2.37).

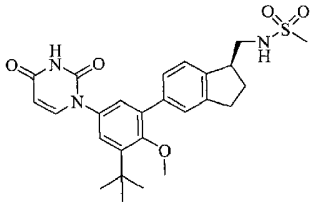
[0752]



[0753] The product from **Example 73** (10mg) was subjected to chiral chromatography (Chiralpak AD-H column; eluting with 1:3 2-PrOH:hexanes(0.1% TFA)). Isolation of the later eluting component gave the title compound (4.2mg). ^{1}H NMR identical to the product from **Example 73.**

Example 76. Preparation of (*S*)-*N*-((5-(3-*tert*-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxyphenyl)-2,3-dihydro-1*H*-inden-1-yl)methyl)methanesulfonamide (compound IB-L0-2.9).

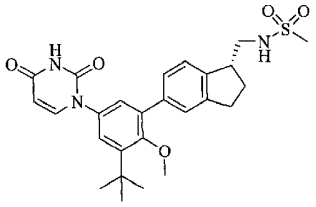
[0754]



[0755] The product from **Example 70, Part F** (20mg) was subjected to chiral chromatography (Chiralpak AD-H column; eluting with 1:4 2-PrOH:hexanes(0.1% TFA)). Isolation of the earlier eluting component gave the title compound (5.3mg). ^{1}H NMR identical to the product from **Example 70, Part F**.

Example 77. Preparation of (*R*)-*N*-((5-(3-*tert*-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxyphenyl)-2,3-dihydro-1*H*-inden-1-yl)methyl)methanesulfonamide (compound IB-L0-2.15).

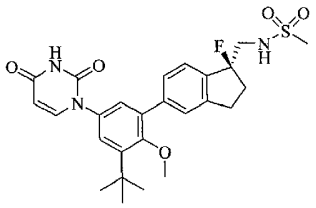
[0756]



[0757] The product from **Example 70, Part F** (20mg) was subjected to chiral chromatography (Chiralpak AD-H column; eluting with 1:4 2-PrOH:hexanes(0.1% TFA)). Isolation of the later eluting component gave the title compound (5.7mg). ^{1}H NMR identical to product from **Example 70, Part F.**

Example 78. Preparation of (*S*)-*N*-((5-(3-*tert*-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxyphenyl)-1-fluoro-2,3-dihydro-1*H*-inden-1-yl)methyl)methanesulfonamide (compound IB-L0-2.20).

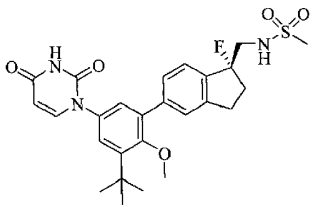
[0758]



[0759] The product from **Example 61, Part H** was subjected to the conditions described in **Example 74** to give the title compound. ^{1}H NMR identical to the product from **Example 61, Part H.**

Example 79. Preparation of (*R*)-*N*-((5-(3-*tert*-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxyphenyl)-1-fluoro-2,3-dihydro-1*H*-inden-1-yl)methyl)methanesulfonamide (compound IB-L0-2.10).

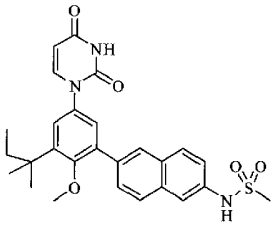
[0760]



[0761] The product from **Example 61, Part H** was subjected to the conditions described in **Example 104** to give the title compound. ^{1}H NMR identical to the product from **Example 61, Part H.**

Example 80. Preparation of *N*-(6-(5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxy-3-tert-pentylphenyl)naphthalen-2-yl)methanesulfonamide (compound IB-L0-2.52).

[0762]



Part A. Preparation of 1-(3-*tert*-butyl-5-iodo-4-methoxyphenyl)pyrimidine-2,4(1*H*,3*H*)-dione.

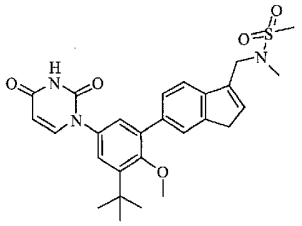
[0763] 2-*tert*-Amylphenol (5.0g, 30mmol) was reacted according to the procedure from **Example C, Part A, Part B,** and **Part C** to provide the title product as a colorless solid.(6.7g, 56% overall yield for 3 steps).

Part B. Preparation of *N*-(6-(5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxy-3-tert-pentylphenyl)naphthalen-2-yl)methanesulfonamide.

[0764] The product from **Part A** (100mg, 0.241mmol), the product from **Example 2A, Part B** (92mg, 0.266mmol), sodium carbonate (38.4mg, 0.362mmol) and 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (9.9mg, 0.012mmol) were dissolved in a toluene (4mL) and ethanol (4mL) solvent mixture which was sparged with nitrogen for 10min, then the mixture heated to 85°C for 18h. To the solution was then added CH_2Cl_2 (20mL) followed by 1N aqueous HCl (10mL), the organic layer separated 3-mercaptopropyl silica gel (100mg) and magnesium sulfate added. The solution was concentrated and purified by column chromatography on silica gel using 3% MeOH in CH_2Cl_2 as the eluent to provide the title compound as a colorless solid (71mg, 58%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.41(s, 1H), 10.04 (s, 1H), 8.03 (s, 1H), 7.95 (t, *J*=8.7Hz, 2H), 7.79 (d, *J*=7.7Hz, 1H), 7.73(d, *J*=1.8Hz, 1H), 7.69(dd, *J*=8.8,1.6Hz, 1H), 7.42 (dd, *J*=8.8,2.2Hz, 1H), 7.37 (d, *J*=2.6Hz, 1H), 7.25 (d, *J*=2.6Hz, 1H), 5.65 (dd, *J*=8.1,1.6Hz, 1H), 3.22 (s, 3H), 3.08 (s, 3H), 1.84 (m, 2H), 1.38 (s, 6H), 0.73 (t, *J*=7.5Hz, 3H).

Example 81. Preparation of *N*-((6-(3-*tert*-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxyphenyl)-1*H*-inden-3-yl)methyl)-*N*-methylmethanesulfonamide (compound IB-L0-2.16).

[0765]



Part A. Preparation of *N*-methyl-*N*-((6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-inden-3-yl)methyl)methanesulfonamide.

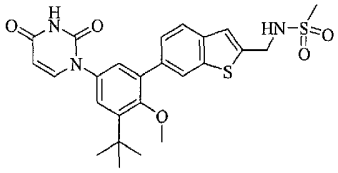
[0766] To a solution of the product from **Example 49, Part E** (210mg, 0.60mmol) in anhydrous THF (5m1) was added a 1.0M solution of lithium bis(trimethylsilyl)amide in toluene (0.60ml, 0.60mmol), and the resulting mixture was stirred at room temperature for 5min. Iodomethane (0.075ml, 1.20mmol) was added and the mixture was stirred at room temperature for 2h, and was partitioned between ethyl acetate and water. The organic layer was washed with brine, dried with sodium sulfate, filtered and concentrated in vacuo. The residue was purified by column chromatography on silica gel eluting with a gradient of ethyl acetate/ in hexane (10% to 25%) to give the title compound as a solid (125mg, 57%).

Part B. Preparation of N-((6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)-1H-inden-3-yl)methyl)-N-methylmethanesulfonamide.

[0767] A mixture of the product from **Example C** (60.0mg, 0.15mmol), the product of **Part A** (54.5mg, 0.15mmol), potassium phosphate (66.9mg, 0.315mmol), PA-Ph (CAS 97739-46-3, 1.32mg, 4.5µmol) and tris(dibenzylideneacetone)dipalladium(0) (1.37mg, 1.5µmol) in tetrahydrofuran (3.0ml) and water (1.0ml) was purged with N_2 for 30min. The mixture was stirred at 50°C for 2h, and then partitioned between ethyl acetate and 1M HCl. The organic layer was washed with saturated sodium bicarbonate, brine, dried with sodium sulfate, and filtered. The filtrate was treated with 3-mercaptopropyl functionalized silica gel, filtered through celite and concentrated in vacuo. The crude product was purified by column chromatography on C-18 reversed-phase silica gel using a solvent gradient of 10-100% acetonitrile in water(0.1% TFA) to give the title compound as a solid (19mg, 24%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.40 (d, J=1.84 Hz, 1 H) 7.78 (d, J=7.72 Hz, 1 H) 7.65 (m, 2 H) 7.49 (dd, J=7.72, 1.47 Hz, 1 H) 7.26 (m, 2.57 Hz, 2 H) 6.63 (s, 1 H) 5.64 (dd, J=7.72, 2.21 Hz, 1 H) 4.26 (s, 2 H) 3.51 (s, 2 H) 3.26 (s, 3 H) 3.01 (s, 3 H) 2.72 (s, 3 H) 1.41 (s, 9 H).

Example 82. Preparation of *N*-((6-(3-*tert*-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxyphenyl)benzo[b]thiophen-2-yl)methyl)methanesulfonamide (compound IB-L0-2.40).

[0768]



Part A. Preparation of ethyl 6-bromobenzo[*b*]thiophene-2-carboxylate.

[0769] To a solution of 4-bromo-2-fluorobenzaldehyde (1.02g, 4.83mmol) in DMSO (4mL), was added ethyl 2-mercaptoacetate (0.58mL, 5.31mmol), followed by Et_3N (1.35mL, 9.65mmol), and the mixture was heated at 80°C for 3h. The resulting dark mixture was poured into water (50mL) and extracted with EtOAc (2 x 50mL). The combined organic extracts were washed with 10% NaCl, dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo to give the title compound as a light yellow waxy solid (1.29g, 94%).

Part B. Preparation of (6-bromobenzo[b]thiophen-2-yl)methanol.

[0770] To a solution of the product from **Part A** (0.82g, 2.88mmol) in Et_2O (20mL) at 0°C was added a 1M solution of lithium aluminum hydride in Et_2O (3.16mL, 3.16mmol) dropwise, and the resulting slurry was stirred between 5-10°C for 1h. The slurry was treated with 0.3mL H_2O, 0.3mL 15 % aq NaOH, 0.7mL H_2O, stirred 30min, filtered and concentrated in vacuo to give the title compound as a colorless solid (0.58g, 83%).

Part C. Preparation of 6-bromo-2-(bromomethyl)benzo[*b*]thiophene.

[0771] A mixture of the product from Part B (85mg, 0.35mmol), *N*-bromosuccinimide (74mg, 0.413mmol) and triphenylphosphine (106mg, 0.403mmol) in CH_2Cl_2 (2mL) was stirred at room temperature for 2h. The reaction mixture was diluted with 50mL CH_2Cl_2, washed with water, 10% $NaHCO_3$ and 10% NaCl, dried over anhydrousmgSO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography on silica gel eluting with 9:1 hexane:EtOAc to yield the title compound as a white solid (96mg, 89%).

Part D. Preparation of *N*-(4-methoxybenzyl)methanesulfonamide.

[0772] To a solution of (4-methoxyphenyl)methanamine (1.317g, 9.60mmol) in CH_2Cl_2 (10mL) was added methanesulfonyl chloride (0.34mL, 4.36mmol) dropwise. The mixture was stirred at room temperature for 2h. The reaction mixture was diluted with 50mL CH_2Cl_2 washed with 1N H_3PO_4, 10% NaCl, dried over anhydrousmgSO_4, filtered and concentrated in vacuo to give the title compound as a white solid (0.84g, 89%).

Part E. Preparation of *N*-((6-bromobenzo[*b*]thiophen-2-yl)methyl)-*N*-(4-methoxybenzyl)-methanesulfonamide.

[0773] A solution of the product from **Part D** (0.223g, 1.037mmol) in EtOH (2mL) and 1.0M NaOH (1.1mL, 1.1mmol) was added to a slurry containing the product from **Part C** (0.317g, 1.037mmol) in EtOH (4mL). The resulting slurry was heated at reflux for 1h, and then concentrated in vacuo to give a pasty solid. The residue was partitioned between 40mL water and 40mL EtOAc. The organic layer was washed with 1N H_3PO_4, 10% $NaHCO_3$, 10% NaCl, dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo leaving a yellow oil. The crude product was purified by column chromatography on silica gel eluting with CH_2Cl_2 to give the title compound as a colorless solid (0.15g, 33%).

Part F. Preparation of *N*-(4-methoxybenzyl)-*N*-((6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[*b*]thiophen-2-yl)methyl)methanesulfonamide.

[0774] The product from **Part E** (0.15g, 0.34mmol) was subjected to the conditions described for the preparation of **Example 42, Part B** to give the title compound as a colorless solid (0.121g, 73%).

Part G. Preparation of *N*-((6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*-yl)-2-methoxyphenyl)benzo[*b*]thiophen-2-yl)methyl)-*N*-(4-methoxybenzyl)methanesulfonamide.

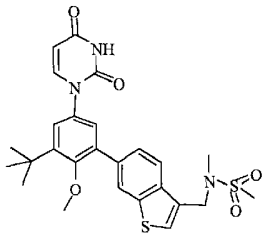
[0775] The product from **Part F** (24mg, 0.049mmol) was subjected to the conditions described for the preparation of **Example 42, Part C** to give the title compound as a colorless solid (20mg, 65%).

PartH. Preparation of *N*-((6-(3-*tert*-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxyphenyl)benzo[*b*]thiophen-2-yl)methyl)methanesulfonamide.

[0776] A solution of the product from **Part G** (14mg, 0.022mmol) in CH_2Cl_2 (0.3mL) and TFA (0.3mL) was stirred at room temperature for 4h and then concentrated in vacuo. The residue was partitioned between 10mL CH_2Cl_2 and 2mL 10% aq. $NaHCO_3$ and the organic layer was concentrated in vacuo. The crude product was purified by column chromatography on silica gel eluting with 99:1 CH_2Cl_2:MeOH to give the title compound as a colorless solid (5mg, 44%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.40 (s, 1 H) 8.09 (s, 1 H) 7.82 - 7.97 (m, 3 H) 7.79 (d, *J*=7.72 Hz, 1 H) 7.47 - 7.63 (m, 1 H) 7.40 (s, 1 H) 7.26 - 7.34 (m, 1 H) 5.64 (d, *J*=7.72 Hz, 1 H) 4.48 (d, *J*=5.88 Hz, 2 H) 3.23 (s, 3 H) 2.95 (s, 3 H) 1.41 (s, 9 H).

Example 83. Preparation of *N*-((6-(3-*tert*-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxyphenyl)benzo[*b*]thiophen-3-yl)methyl)-*N*-methylmethanesulfonamide (compound IB-L0-2.21).

[0777]



Part A. Preparation of *N*-((6-bromobenzo[*b*]thiophen-3-yl)methyl)-*N*-methylmethanesulfon-amide.

[0778] A mixture of the product from **Example 46, Part D** (0.100g, 0.382mmol), *N*-methylmethane-sulfonamide (45.9mg, 0.421mmol) and potassium carbonate (0.127g, 0.918mmol) in *N,N*-dimethylacetamide (5mL). The mixture was stirred at 80°C for 11 h, cooled to room temperature and partitioned between diethylether and water (3x), dried overmgSO_4, filtered and concentrated in vacuo to give the title compound as a colorless waxy solid (0.128g, quant.).

Part B. Preparation of *N*-methyl-N-((6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo [*b*]thiophen-3-yl)methyl)methanesulfonamide.

[0779] The product from **Part A** (0.128g, 0.3 82mmol) was subjected to the conditions described for the preparation of **Example 42, Part B** to give the title compound as a colorless, crystalline solid (0.120g, 82%).

Part C. Preparation of *N*-((6-(3-*tert*-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxyphenyl)benzo[*b*]thiophen-3-yl)methyl)-*N*-methylmethanesulfonamide.

[0780] The product from **Part B** (50.6mg, 0.133mmol) was subjected to the conditions described for the preparation of **Example 49, Part F** to give the title compound as a colorless solid (61.5mg, 88%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.41 (s, 1 H) 8.17 (d, *J*=1.47 Hz, 1 H) 8.09 (d, *J*=8.09 Hz, 1 H) 7.74 - 7.85 (m, 2 H) 7.63 (dd, *J*=8.46, 1.47 Hz, 1 H) 7.29 - 7.36 (m, 2 H) 5.65 (d, *J*=7.72 Hz, 1 H) 4.52 (s, 2 H) 3.24 (s, 3 H) 3.03 (s, 3 H) 2.70 (s, 3 H) 1.42 (s, 9 H).

[0781] The following compounds were prepared utilizing the above discussion:

N-(2-(3-tert-butyl-5-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-2-methoxyphenyl)-1H-benzo[d]imidazol-5-yl)-N-(methylsulfonyl)methanesulfonamide (compound **IA-L0-2.10**) ^{1}H NMR (300 MHz, DMSO-D6) δ ppm 1.45 (s, 9 H) 2.73 (t, J=6.62 Hz, 2 H) 3.48 (s, 3 H) 3.56 (s, 6 H) 3.83 (t, J=6.80 Hz, 2 H) 4.05 (s, 1 H) 7.38 (dd, J=8.46, 1.84 Hz, 1 H) 7.46 (d, J=2.57 Hz, 1 H) 7.71 (d, J=8.46 Hz, 1 H) 7.76 (d, J=2.57 Hz, 1 H) 7.82 (d, J=1.84 Hz, 1 H) 10.41 (s, 1 H)

N-((6-(3-tert-butyl-2-chloro-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)phenyl)benzo [b]thiophen-3-yl)methyl)methanesulfonamide (compound **IB-L0-2.35).** ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.52 (s, 9 H) 2.95 (s, 3 H) 4.44 (d, J=5.88 Hz, 2 H) 5.68 (d, J=8.09 Hz, 1 H) 7.40 (d, J=2.57 Hz, 1 H) 7.46 (dd, J=8.09, 1.47 Hz, 1 H) 7.56 (d, J=2.57 Hz, 1 H) 7.62 (t, J=6.07 Hz, 1 H) 7.72 (s, 1 H) 7.83

(d, J=8.09 Hz, 1 H) 8.01 (m, 2 H) 11.46 (s, 1 H).

1-(3-tert-butyl-5-(2-chlorobenzo[d]thiazol-6-yl)-4-methoxyphenyl)pyrimidine-2,4(1H,3H)-dione (compound **IB-L0-2.38).** ^{1}H NMR (300 MHz, DMSO-D6) δ ppm 1.41 (s, 9 H) 3.24 (s, 3 H) 5.65 (dd, J=8.09, 2.21 Hz, 1 H) 7.34 (s, 2 H) 7.73 (dd, J=8.64, 1.65 Hz, 1 H) 7.79 (d, J=8.09 Hz, 1 H) 8.07 (d, J=8.46 Hz, 1 H) 8.30 (d, J=1.84 Hz, 1 H) 11.42 (d, J=1.84 Hz, 1 H)

N-(2-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)quinolin-6-yl)methanesulfonamide (compound **IB-L0-2.48).**

1-(3-tert-butyl-4-methoxy-5-(1-oxo-2,3-dihydro-1H-inden-5-yl)phenyl)pyrimidine-2,4(1H,3H)-dione (compound **IB-L0-2.50**).

N,N'-(6,6'-(5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxy-1,3-phenylene) bis(naphthalene-6,2-diyl))dimethanesulfonamide (compound **IB-L0-2.76).** ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 3.08 (s, 6 H) 3.13 (s, 3 H) 5.72 (d, J=8.18 Hz, 1 H) 7.43 (dd, J=8.46, 1.84 Hz, 2 H) 7.59 (s, 2 H) 7.79 (m, 4 H) 7.96 (m, 5 H) 8.14 (s, 2 H) 10.05 (s, 2 H) 11.48 (s, 1 H).

HCV Polymerase Inhibition Assay

[0782] Either two-fold serial dilutions (fractional inhibition assay) or a narrower range of dilutions spanning the IC_{50} of the inhibitor (tight binding assay) of the inhibitors were incubated with 20mM Tris-Cl pH 7.4, 2mM $MnCl_2$, 1mM dithiothreitol, 1mM ethylene diamine tetraacetic acid (EDTA), 60 to 125μM GTP and 20 to 50nM Δ21 NS5B (HCV Strain 1B (BK, Genbank accession number M58335, or H77, Genbank accession number AF011751)) for 15min at room temperature. The reaction was initiated by the addition of 20μM CTP, 20μM ATP, 1μM ^{3}H-UTP (10mCi/umol), 5nM template RNA and 0.1 U/μl RNase inhibitor (RNasin, Promega), and allowed to proceed for 2 to 4h at room temperature. Reaction volume was 50μl. The reaction was terminated by the addition of 1 volume of 4mM spermine in 10mM Tris-Cl pH 8.0, 1mM EDTA. After incubation for at least 15 min at room temperature, the precipitated RNA was captured by filtering through a GF/B filter (Millipore) in a 96 well format. The filter plate was washed three times with 200μl each of 2mM spermine, 10mM Tris-Cl pH 8.0, 1mM EDTA, and 2 times with ethanol. After air-drying, 30μl of Microscint 20 scintillation cocktail (Packard) was added to each well, and the retained cpm were determined by scintillation counting. IC_{50} values were calculated by a two-variable nonlinear regression equation using an uninhibited control and a fully inhibited control sample to determine the minimum and maximum for the curve. Tight-binding assays were performed on those compounds exhibiting IC_{50} values less than 0.005μM in the fractional inhibition assay in order to more precisely measure the IC_{50} values. Retained cpm were plotted vs. inhibitor concentration and fit to equation 1 using non-linear regression (ref. 1) to obtain the IC_{50} values:

$$\text{Retained cpm}=A[\text{sqrt}\{(IC_{50}+I_t-E_t)\hat{}2+4*IC_{50}*E_t\}-(IC_{50}+I_t-E_t)] \quad \text{(eqn 1)}$$

where A=Vmax[S]/2(Km+[S]); It=total inhibitor concentration and Et=total active concentration of enzyme.

[0783] Ref. Morrison, J. F. and S. R. Stone. 1985. Approaches to the study and analysis of the inhibition of enzymes by slow- and tight-binding inhibitors. Comments Mol. Cell. Biophys. 2: 347-368.

[0784] The sequence of the template RNA used was: 5'-GGGCGAAUUG GGCCCUCUAG AUGCAUGCUC GAGCGGCCGC CAGUGUGAUG GAUAUCUGCA GAAUUCGCCC UUGGUGGCUC CAUCUUAGCC CUAGUCACGG CUAGCUGUGA AAGGUCCGUG AGCCGCUUGA CUGCAGAGAG UGCUGAUACU GGCCUCUCUG CAGAUCAAGUC-3'

[0785] When tested by the above method, the compounds of this invention inhibit HCV polymerase 1A and/or 1B. The legend in the table below is as follows: A -- $IC_{50} \leq 0.01$uM; B -- 0.1uM ≥ IC_{50} > 0.01uM; C -- 1uM ≥ IC_{50} > 0.1uM; and D -- IC_{50} > 1uM; ND - not determined.

Table IC_{50}

compound	1a	1b	compound	1a	1b
			IA-L0-2.1	C	C
IA-L0-2.2	B	B	**IA-L0-2.3**	C	C
IA-L0-2.4	B	B	**IA-L0-2.5**	C	C
IA-L0-2.6	C	C	**IA-L0-2.7**	C	C
IA-L0-2.8	B	B	**IA-L0-2.9**	A	A

compound	1a	1b	compound	1a	1b
IA-L0-2.10	D	D	**IB-L0-2.1**	C	C
IB-L0-2.2	C	C	**IB-L0-2.3**	A	A
IB-L0-2.4	A	A	**IB-L0-2.5**	B	B
IB-L0-2.6	B	B	**IB-L0-2.7**	B	B
IB-L0-2.8	B	B	**IB-L0-2.9**	A	A
IB-L0-2.10	A	B	**IB-L0-2.11**	A	A
IB-L0-2.12	A	B	**IB-L0-2.13**	A	B
IB-L0-2.14	A	A	**IB-L0-2.15**	A	B
IB-L0-2.16	A	B	**IB-L0-2.17**	A	B
IB-L0-2.18	A	B	**IB-L0-2.19**	A	B
IB-L0-2.20	A	B	**IB-L0-2.21**	B	B
IB-L0-2.22	B	B	**IB-L0-2.23**	B	A
IB-L0-2.24	B	B	**IB-L0-2.25**	B	B
IB-L0-2.26	B	B	**IB-L0-2.27**	B	B
IB-L0-2.28	B	B	**IB-L0-2.29**	B	B
IB-L0-2.30	B	B	**IB-L0-2.31**	B	B
IB-L0-2.32	B	B	**IB-L0-2.33**	B	B
IB-L0-2.34	B	B	**IB-L0-2.35**	B	B
IB-L0-2.36	B	C	**IB-L0-2.37**	C	C
IB-L0-2.38	C	B	**IB-L0-2.39**	C	C
IB-L0-2.40	C	C	**IB-L0-2.41**	C	C
IB-L0-2.42	C	C	**IB-L0-2.43**	C	c
IB-L0-2.44	C	C	**IB-L0-2.45**	C	C
IB-L0-2.46	C	C	**IB-L0-2.47**	D	D
IB-L0-2.48	D	D	**IB-L0-2.49**	D	D
IB-L0-2.50	B	B	**IB-L0-2.51**	A	B
IB-L0-2.52	A	B	**IB-L0-2.53**	A	B
IB-L0-2.54	A	B	**IB-L0-2.55**	A	B
IB-L0-2.56	A	B	**IB-L0-2.57**	A	B
IB-L0-2.58	A	B	**IB-L0-2.59**	A	B
IB-L0-2.60	A	B	**IB-L0-2.61**	A	B
IB-L0-2.62	B	B	**IB-L0-2.63**	B	B
IB-L0-2.64	B	B	**IB-L0-2.65**	B	A
IB-L0-2.66	B	B	**IB-L0-2.67**	B	B
IB-L0-2.68	B	B	**IB-L0-2.69**	B	B
IB-L0-2.70	B	C	**IB-L0-2.71**	C	C
IB-L0-2.72	C	C	**IB-L0-2.73**	C	C
IB-L0-2.74	C	C	**IB-L0-2.75**	C	D
IB-L0-2.76	C	D	**IB-L0-2.77**	D	D
IB-L0-2.78	D	D	**IB-L0-2.79**	B	B

HCV Polymerase Replicon Assay

[0786] Two stable subgenomic replicon cell lines were used for compound characterization in cell culture: one derived from genotype 1a-H77 and one derived from genotype 1b-Con1 (obtained from Apath, LLC, St. Louis, MO). All replicon constructs were bicistronic subgenomic replicons similar to those described by Bartenschlager and coworkers (Lohmann et al., Replication of Subgenomic Hepatitis C Virus RNAs in a Hepatoma Cell Line, SCIENCE 285:110-3(1999)). The genotype 1a replicon construct contains NS3-NS5B coding region derived from the H77 strain of HCV (1a-H77) (Blight et al., Efficient Replication of Hepatitis C Virus Genotype 1a RNAs in Cell Culture, J. VIROL. 77:3181-90 (2003)). The replicon also has a firefly luciferase reporter and a neomycin phosphotransferase (Neo) selectable marker. These two coding regions, separated by the FMDV 2a protease, comprise the first cistron of the bicistronic replicon construct, with the second cistron containing the NS3-NS5B coding region with addition of adaptive mutations E1202G, K1691R, K2040R and S2204I. The 1b-Con1 replicon construct is identical to the 1a-H77 replicon, except that the NS3-NS5B coding region was derived from the 1b-Con1 strain, and the adaptive mutations are E1202G, T1280I and S2204I. Replicon cell lines were maintained in Dulbecco's modified Eagles medium (DMEM) containing 10% (v/v) fetal bovine serum (FBS), 100 IU/ml penicillin, 100mg/ml streptomycin (Invitrogen), and 200mg/ml G418 (Invitrogen).

[0787] The inhibitory effects of compounds on HCV replication were determined by measuring activity of the luciferase reporter gene. Briefly, replicon-containing cells were seeded into 96 well plates at a density of 5000 cells per well in 100ul DMEM containing 5% FBS. 16-24h later, the compounds were diluted in dimethyl sulfoxide (DMSO) to generate a 200x stock in a series of eight half-log dilutions. The dilution series was then further diluted 100-fold in the medium containing 5% FBS. Medium with the inhibitor was added to the overnight cell culture plates already containing 100ul of DMEM with 5% FBS. In assays measuring inhibitory activity in the presence of human plasma, the medium from the overnight cell culture plates was replaced with DMEM containing 40% human plasma and 5% FBS. The cells were incubated for three days in the tissue culture incubators and were then lysed for RNA extraction. For the luciferase assay, 30ul of Passive Lysis buffer (Promega) was added to each well, and then the plates were incubated for 15min with rocking to lyse the cells. Luciferin solution (50 to 100ul, Promega) was added to each well, and luciferase activity was measured with a Victor II luminometer (Perkin-Elmer). The percent inhibition of HCV RNA replication was calculated for each compound concentration and the EC_{50} value was calculated using nonlinear regression curve fitting to the 4-parameter logistic equation and GraphPad Prism 4 software.

[0788] When tested by the above method, the compounds of this invention inhibit HCV polymerase 1A and/or 1B. The legend in the table below is as follows: A -- $EC_{50} \leq 0.01$uM; B -- 0.1uM $\geq EC_{50} >$ 0.01uM; C -- 1uM $\geq EC_{50} >$ 0.1uM; and D -- $EC_{50} >$ 1uM; ND - not determined.

Table EC_{50}

compound	1a	1b	compound	1a	1b
			IA-L0-2.1	D	D
IA-L0-2.2	C	B	**IA-L0-2.3**	C	C
IA-L0-2.4	D	C	**IA-L0-2.5**	D	D
IA-L0-2.6	D	D	**IA-L0-2.7**	D	C
IA-L0-2.8	C	B	**IA-L0-2.9**	A	A
IA-L0-2.10	ND	ND	**IB-L0-2.1**	D	C
IB-L0-2.2	D	D	**IB-L0-2.3**	A	A
IB-L0-2.4	ND	A	**IB-L0-2.5**	B	A
IB-L0-2.6	C	B	**IB-L0-2.7**	C	B
IB-L0-2.8	ND	B	**IB-L0-2.9**	A	A
IB-L0-2.10	A	A	**IB-L0-2.11**	B	A
IB-L0-2.12	B	A	**IB-L0-2.13**	B	A
IB-L0-2.14	C	B	**IB-L0-2.15**	C	B
IB-L0-2.16	C	A	**IB-L0-2.17**	B	A
IB-L0-2.18	C	B	**IB-L0-2.19**	B	B
IB-L0-2.20	C	B	**IB-L0-2.21**	C	B
IB-L0-2.22	C	B	**IB-L0-2.23**	C	B
IB-L0-2.24	B	B	**IB-L0-2.25**	C	B

compound	1a	1b	compound	1a	1b
IB-L0-2.26	D	C	**IB-L0-2.27**	C	B
IB-L0-2.28	D	C	**IB-L0-2.29**	C	B
IB-L0-2.30	C	B	**IB-L0-2.31**	C	B
IB-L0-2.32	C	B	**IB-L0-2.33**	C	C
IB-L0-2.34	D	C	**IB-L0-2.35**	D	C
IB-L0-2.36	C	B	**IB-L0-2.37**	D	C
IB-L0-2.38	D	D	**IB-L0-2.39**	D	C
IB-L0-2.40	D	C	**IB-L0-2.41**	C	C
IB-L0-2.42	C	C	**IB-L0-2.43**	D	C
IB-L0-2.44	D	D	**IB-L0-2.45**	D	C
IB-L0-2.46	ND	ND	**IB-L0-2.47**	ND	ND
IB-L0-2.48	ND	ND	**IB-L0-2.49**	ND	ND
IB-L0-2.50	C	C	**IB-L0-2.51**	B	A
IB-L0-2.52	B	A	**IB-L0-2.53**	B	B
IB-L0-2.54	B	B	**IB-L0-2.55**	B	A
IB-L0-2.56	C	A	**IB-L0-2.57**	C	B
IB-L0-2.58	B	A	**IB-L0-2.59**	C	B
IB-L0-2.60	C	B	**IB-L0-2.61**	C	B
IB-L0-2.62	C	B	**IB-L0-2.63**	C	B
IB-L0-2.64	C	A	**IB-L0-2.65**	C	B
IB-L0-2.66	C	B	**IB-L0-2.67**	C	B
IB-L0-2.68	D	C	**IB-L0-2.69**	C	B
IB-L0-2.70	D	C	**IB-L0-2.71**	C	B
IB-L0-2.72	D	C	**IB-L0-2.73**	C	C
IB-L0-2.74	D	C	**IB-L0-2.75**	D	D
IB-L0-2.76	ND	ND	**IB-L0-2.77**	ND	ND
IB-L0-2.78	ND	ND	**IB-L0-2.79**	C	C

REFERENCES CITED IN THE DESCRIPTION

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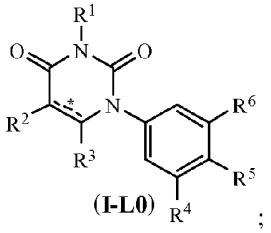
- **BLIGHT et al.**Efficient Replication of Hepatitis C Virus Genotype 1a RNAs in Cell CultureJ. VIROL, 2003, vol. 77, 3181-90 [0786]

Patentkrav

1. Enkeltformulering indeholdende én eller flere forbindelser med formlen **I-L0** eller salte deraf, og ét eller flere yderligere terapeutiske midler valgt fra gruppen bestående af interferonmidler, ribavirin, HCV-inhibitorer og anti-HIV-midler;

hvor formlen **I-L0** er:



(I-L0) ;

\-\-*\-\-

er valgt fra gruppen bestående af enkelt carbon-carbon-binding og dobbelt carbon-carbon-binding;

R^1 er valgt fra gruppen bestående af hydrogen og methyl;

R^2 er valgt fra gruppen bestående af hydrogen, halogen, hydroxy, methyl, cyclopropyl og cyclobutyl;

R^3 er valgt fra gruppen bestående af hydrogen, halogen, oxo og methyl;

R^4 er valgt fra gruppen bestående af halogen, alkyl, alkenyl, alkynyl, nitro, cyano, azido, alkyloxy, alkenyloxy, alkynyloxy, amino, aminocarbonyl, aminosulfonyl, alkylsulfonyl, carbocyclyl og heterocyclyl, hvor:

(a) amino, aminocarbonyl og aminosulfonyl eventuelt er substitueret med:

(1) én eller to substituenter uafhængigt valgt fra gruppen bestående af alkyl, alkenyl, alkynyl og alkylsulfonyl, eller

(2) to substituenter, der sammen med aminonitrogenet danner en enkelt heterocyklisk ring, og

(b) alkyl, alkenyl, alkynyl, alkyloxy, alkenyloxy, alkynyloxy og alkylsulfonyl eventuelt er substitueret med én eller flere substituenter uafhængigt valgt fra gruppen bestående af halogen, oxo, nitro, cyano, azido, hydroxy, amino, alkyloxy, trimethylsilyl, carbocyclyl og heterocyclyl, hvor:

amino eventuelt er substitueret med:

(1) én eller to substituenter uafhængigt valgt fra gruppen bestående af alkyl, alkenyl, alkynyl, alkylcarbonyl, alkylsulfonyl, alkyloxycarbonyl, carbocyclyl, heterocyclyl, carbocyclylalkyl og heterocyclylalkyl, eller

(2) to substituenter, der sammen med aminonitrogenet danner en heterocyclylgruppe med en enkelt ring, og

(c) carbocyclyl og heterocyclyl eventuelt er substitueret med op til tre substituenter uafhængigt valgt fra gruppen bestående af alkyl, alkenyl, alkynyl, halogen, oxo, nitro, cyano, azido, hydroxy, amino, alkyloxy, trimethylsilyl, carbocyclyl og heterocyclyl, hvor:

amino eventuelt er substitueret med:

(1) én eller to substituenter uafhængigt valgt fra gruppen bestående af alkyl, alkenyl, alkynyl, alkylcarbonyl, alkylsulfonyl, alkyloxycarbonyl, carbocyclyl, heterocyclyl, carbocyclylalkyl og heterocyclylalkyl, eller

(2) to substituenter, der sammen med aminonitrogenet danner en heterocyclylgruppe med en enkelt ring;

R^5 er valgt fra gruppen bestående af hydrogen, hydroxy, alkyl, alkenyl, alkynyl, alkyloxy, alkenyloxy, alkynyloxy, alkylsulfonyloxy, carbocyclylsulfonyloxy, halogenalkylsulfonyloxy og halogen;

R^6 er valgt fra gruppen bestående af kondenseret carbocyclyl med 2 ringe og kondenseret heterocyclyl med 2 ringe, hvor hver sådan substituent eventuelt er substitueret med én eller flere substituenter uafhængigt valgt fra gruppen bestående af R^E, R^F, R^G, R^H, R^I, R^J og R^K;

hvert R^E er uafhængigt valgt fra gruppen bestående af halogen, nitro, hydroxy, oxo, carboxy, cyano, amino, imino, azido og aldehydo, hvor:

amino eventuelt er substitueret med én eller to substituenter uafhængigt valgt fra gruppen bestående af alkyl, alkenyl og alkynyl;

hvert R^F er uafhængigt valgt fra gruppen bestående af alkyl, alkenyl og alkynyl, hvor:

hver sådan substituent eventuelt er substitueret med én eller flere substituenter uafhængigt valgt fra gruppen bestående af carboxy, hydroxy, halogen, amino, imino, nitro, azido, oxo, aminosulfonyl, alkylsulfonyl, alkyloxycarbonyl, alkenyloxycarbonyl, alkynyloxycarbonyl, alkylcarbonyloxy, alkenylcarbonyloxy,

alkynylcarbonyloxy, alkyloxy, alkenyloxy, alkynyloxy, carbocyclyl, heterocyclyl, cyano og aminocarbonyl, hvor:

amino, imino, aminosulfonyl, aminocarbonyl, carbocyclyl og heterocyclyl eventuelt er substitueret med én eller to substituenter uafhængigt valgt fra gruppen bestående af alkyl, alkenyl, alkynyl, alkylsulfonyl, alkenylsulfonyl, alkynylsulfonyl, alkylsulfonylamino, hydroxy og alkyloxy,

hvor:

aminodelen af alkylsulfonylaminogruppen eventuelt er substitueret med en substituent valgt fra gruppen bestående af alkyl, alkenyl og alkynyl;

hvert $\mathbf{R^G}$ er uafhængigt valgt fra gruppen bestående af carbocyclyl og heterocyclyl, hvor:

hver sådan substituent eventuelt er substitueret med én eller flere substituenter uafhængigt valgt fra gruppen bestående af alkyl, alkenyl, alkynyl, carboxy, hydroxy, halogen, amino, nitro, azido, oxo, aminosulfonyl, alkyloxycarbonyl, alkenyloxycarbonyl, alkynyloxycarbonyl, alkylcarbonyloxy, alkenylcarbonyloxy, alkynylcarbonyloxy, alkyloxy, alkenyloxy, alkynyloxy, carbocyclyl, heterocyclyl, cyano og aminocarbonyl, hvor:

amino, aminosulfonyl og aminocarbonyl eventuelt er substitueret med én eller to substituenter uafhængigt valgt fra gruppen bestående af alkyl, alkenyl, alkynyl, alkylsulfonyl, alkenylsulfonyl og alkynylsulfonyl;

hvert $\mathbf{R^H}$ er uafhængigt valgt fra gruppen bestående af alkyloxy, alkenyloxy, alkynyloxy, alkylsulfonyloxy, alkenylsulfonyloxy og alkynylsulfonyloxy, hvor:

hver sådan substituent eventuelt er substitueret med én eller flere substituenter uafhængigt valgt fra gruppen bestående af carboxy, hydroxy, halogen, amino, nitro, azido, oxo, aminosulfonyl, alkyloxycarbonyl, alkenyloxycarbonyl, alkynyloxycarbonyl, alkylcarbonyloxy, alkenylcarbonyloxy, alkynylcarbonyloxy, alkyloxy, alkenyloxy, alkynyloxy, carbocyclyl, heterocyclyl, cyano og aminocarbonyl, hvor:

amino, aminosulfonyl og aminocarbonyl eventuelt er substitueret med én eller to substituenter uafhængigt valgt fra gruppen bestående af alkyl, alkenyl, alkynyl, alkylsulfonyl, alkenylsulfonyl og alkynylsulfonyl;

hvert R^I er uafhængigt valgt fra gruppen bestående af alkylcarbonyl, alkenylcarbonyl, alkynylcarbonyl, aminocarbonyl, alkyloxycarbonyl, carbocyclylcarbonyl og heterocyclylcarbonyl, hvor:

(a) alkylcarbonyl, alkenylcarbonyl og alkynylcarbonyl eventuelt er substitueret med én eller flere substituenter uafhængigt valgt fra gruppen bestående af carboxy, hydroxy, halogen, amino, nitro, azido, oxo, aminosulfonyl, alkyloxycarbonyl, alkenyloxycarbonyl, alkynyloxycarbonyl, alkylcarbonyloxy, alkenylcarbonyloxy, alkynylcarbonyloxy, alkyloxy, alkenyloxy, alkynyloxy, carbocyclyl, heterocyclyl, cyano og aminocarbonyl, og

(b) aminocarbonyl eventuelt er substitueret med én eller to substituenter uafhængigt valgt fra gruppen bestående af alkyl, alkenyl, alkynyl, alkyloxyalkyl, carbocyclyl, heterocyclyl, alkylsulfonyl og alkylsulfonylamino, hvor:
carbocyclyl og heterocyclyl eventuelt er substitueret med én eller to substituenter uafhængigt valgt fra gruppen bestående af halogen, alkyl og oxo;

hvert R^J er uafhængigt valgt fra gruppen bestående af carbocyclylsulfonylamino, heterocyclylsulfonylamino, alkylcarbonylamino, alkenylcarbonylamino, alkynylcarbonylamino, alkyloxycarbonylamino, alkenyloxycarbonylamino, alkynyloxycarbonylamino, alkylsulfonylamino, alkenylsulfonylamino, alkynylsulfonylamino, aminocarbonylamino, alkyloxycarbonylaminoimino, alkylsulfonylaminoimino, alkenylsulfonylaminoimino og alkynylsulfonylaminoimino, hvor:

(a) aminodelen af sådanne substituenter eventuelt er substitueret med en substituent uafhængigt valgt fra gruppen bestående af carbocyclylalkyl, heterocyclylalkyl, alkylcarbonyloxy, aminocarbonylalkyl, alkyl, alkenyl, alkynyl, alkylcarbonyl, alkenylcarbonyl, alkynylcarbonyl, alkyloxycarbonyl, alkyloxyalkyloxycarbonyl, alkylcarbonyloxyalkyl og alkylsulfonyl, hvor:

(1) carbocyclyldelen af carbocyclylalkyl- og heterocyclyldelen af heterocyclylalkyl eventuelt er substitueret med én eller flere substituenter uafhængigt valgt fra gruppen bestående af alkyl, alkenyl, alkynyl, carboxy, hydroxy, alkyloxy, alkenyloxy, alkynyloxy, halogen, nitro, cyano, azido, oxo og amino, og

(2) aminodelen af aminocarbonylalkyl eventuelt er substitueret med én eller to substituenter uafhængigt valgt fra gruppen bestående af alkyl, alkenyl og alkynyl,

(b) alkyl-, alkenyl- og alkynyldelen af sådanne substituenter eventuelt er substitueret med én eller flere substituenter uafhængigt valgt fra gruppen bestående af carboxy, halogen, oxo, amino, alkyloxycarbonyl, alkylcarbonyloxy, hydroxy, alkyloxy, carbocyclyl, heterocyclyl og cyano, hvor:

amino eventuelt er substitueret med én eller to substituenter uafhængigt valgt fra gruppen bestående af alkyl, alkenyl, alkynyl, alkyloxy, alkenyloxy og alkynyloxy, hvor:

alkyl eventuelt er substitueret med én eller flere hydroxygrupper;

(c) carbocyclyl- og heterocyclyldelene af sådanne substituenter eventuelt er substitueret med én eller flere substituenter uafhængigt valgt fra gruppen bestående af alkyl, alkenyl, alkynyl, carboxy, hydroxy, alkyloxy, alkenyloxy, alkynyloxy, halogen, nitro, cyano, azido og amino, hvor:
amino eventuelt er substitueret med én eller to substituenter uafhængigt valgt fra gruppen bestående af alkyl, alkenyl og alkynyl; og

hvert $\mathbf{R^K}$ er uafhængigt valgt fra gruppen bestående af aminosulfonyl, alkylsulfonyl, alkenylsulfonyl og alkynylsulfonyl, hvor:

(a) alkylsulfonyl, alkenylsulfonyl og alkynylsulfonyl eventuelt er substitueret med én eller flere substituenter uafhængigt valgt fra gruppen bestående af carboxy, hydroxy, halogen, amino, nitro, azido, oxo, aminosulfonyl, alkyloxycarbonyl, alkenyloxycarbonyl, alkynyloxycarbonyl, alkylcarbonyloxy, alkenylcarbonyloxy, alkynylcarbonyloxy, alkyloxy, alkenyloxy, alkynyloxy, carbocyclyl, heterocyclyl, cyano og aminocarbonyl, hvor:

amino, aminosulfonyl og aminocarbonyl eventuelt er substitueret med én eller to substituenter uafhængigt valgt fra gruppen bestående af alkyl, alkenyl og alkynyl; og

(b) aminosulfonyl eventuelt er substitueret med én eller to substituenter uafhængigt valgt fra gruppen bestående af alkyl, alkenyl og alkynyl.

2. Formulering ifølge krav 1, i hvilken det eller de yderligere terapeutiske midler er valgt fra gruppen bestående af HCV-inhibitorer og anti-HIV-midler.

3. Formulering ifølge krav 1, i hvilken det eller de yderligere terapeutiske midler er valgt fra gruppen bestående af HCV-proteaseinhibitorer og anti-HIV-

midler.

4. Formulering ifølge krav 1, i hvilken det eller de yderligere terapeutiske midler er valgt fra gruppen bestående af HCV-inhibitorer.

5. Formulering ifølge krav 1, i hvilken det yderligere terapeutiske middel er ribavirin.

6. Produkt indeholdende én eller flere forbindelser med formlen **I-L0** som defineret i krav 1 eller salte deraf og ét eller flere yderligere terapeutiske midler valgt fra gruppen bestående af interferonmidler, ribavirin, HCV-inhibitorer og anti-HIV-midler som et kombinationspræparat til samtidig, sekventiel eller både samtidig og sekventiel anvendelse til inhibering af replikation af et ribonukleinsyre (RNA)-virus.

7. Produkt ifølge krav 6, hvori RNA-virusset er hepatitis C-virus (HCV).

8. Produkt indeholdende én eller flere forbindelser med formlen **I-L0** som defineret i krav 1 eller salte deraf og ét eller flere yderligere terapeutiske midler valgt fra gruppen bestående af interferonmidler, ribavirin, HCV-inhibitorer og anti-HIV-midler som et kombinationspræparat til samtidig, sekventiel eller både samtidig og sekventiel anvendelse til behandling af hepatitis C hos et pattedyr med behov for sådan behandling.

9. Produkt ifølge ethvert af kravene 6 til 8, i hvilket det eller de yderligere terapeutiske midler er valgt fra gruppen bestående af HCV-inhibitorer og anti-HIV-midler.

10. Produkt ifølge ethvert af kravene 6 til 8, i hvilket det eller de yderligere terapeutiske midler er valgt fra gruppen bestående af HCV-proteaseinhibitorer og anti-HIV-midler.

11. Produkt ifølge ethvert af kravene 6 til 8, i hvilket det eller de yderligere terapeutiske midler er valgt fra gruppen bestående af HCV-inhibitorer.

12. Produkt ifølge ethvert af kravene 6 til 8, i hvilket det yderligere terapeutiske middel er ribavirin.

13. Formulering ifølge krav 1 eller produkt ifølge krav 6 og 8, i hvilken forbindelsen med formlen **I-L0** er N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methansulfonamid eller et salt deraf.

14. Formulering eller produkt ifølge krav 13, hvor forbindelsen med formlen **I-L0** er N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methansulfonamid-mononatriumsalt.

DRAWINGS

Figure 1

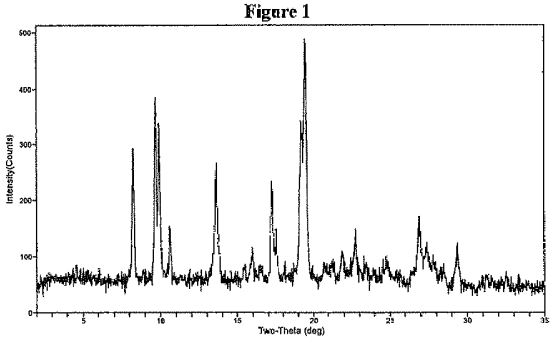
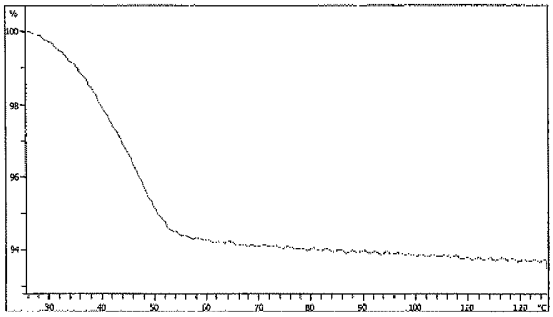


Figure 2



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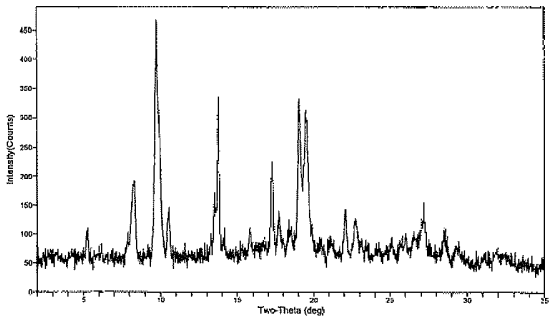

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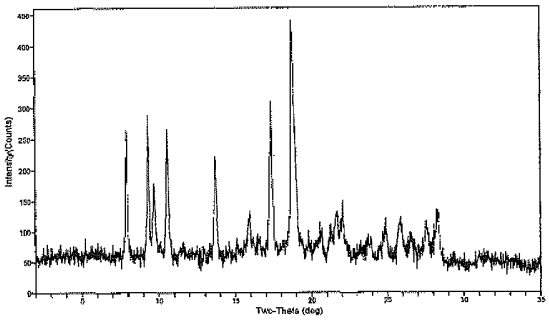
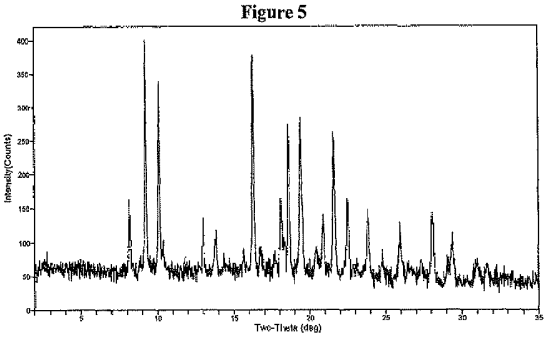


Figure 5



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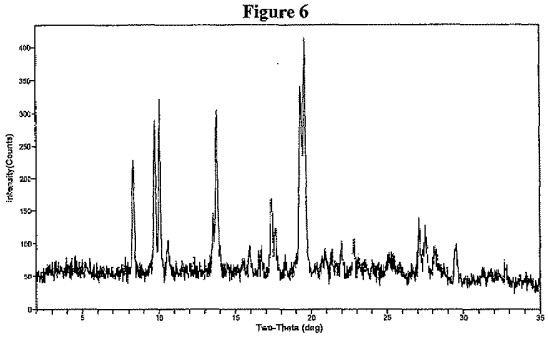

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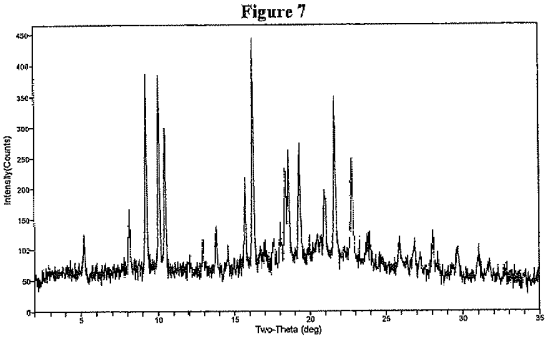


Figure 8

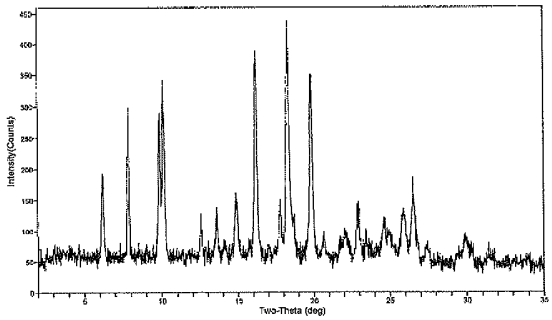
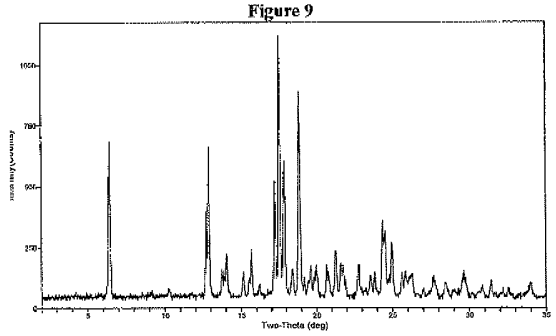


Figure 9



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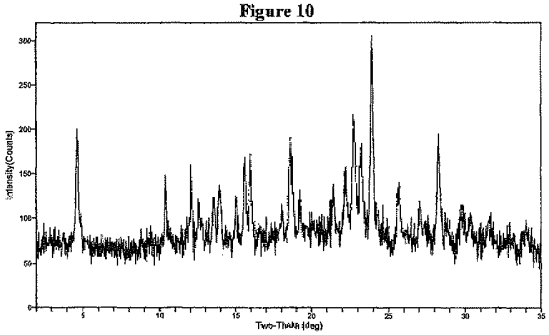

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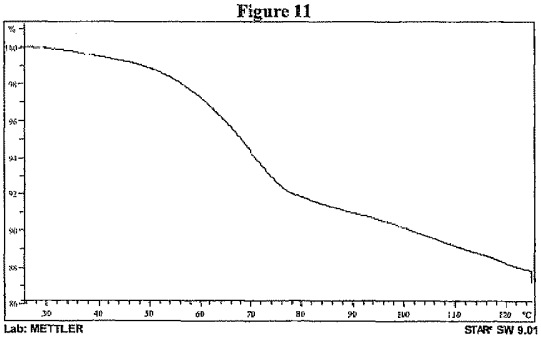


Figure 12

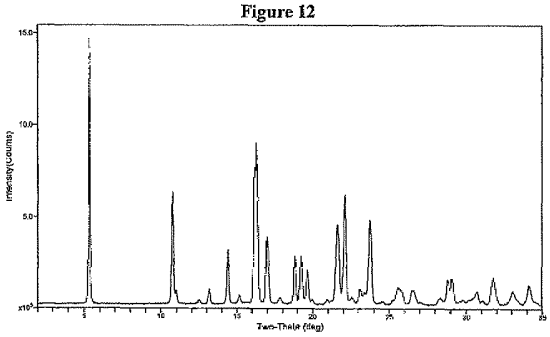


Figure 13

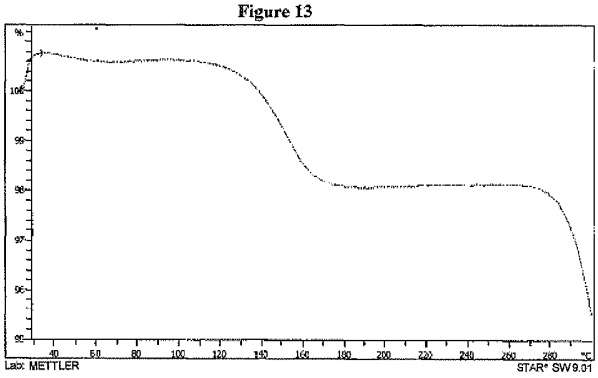
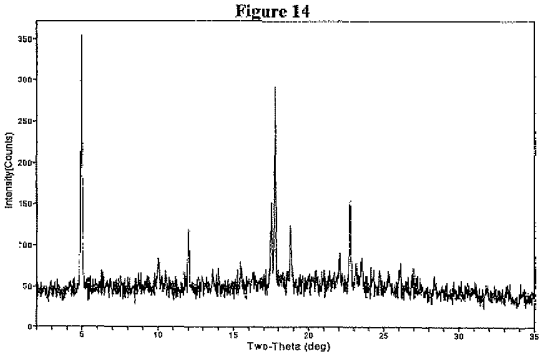


Figure 14



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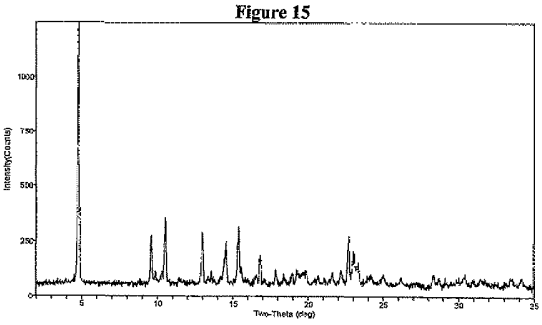

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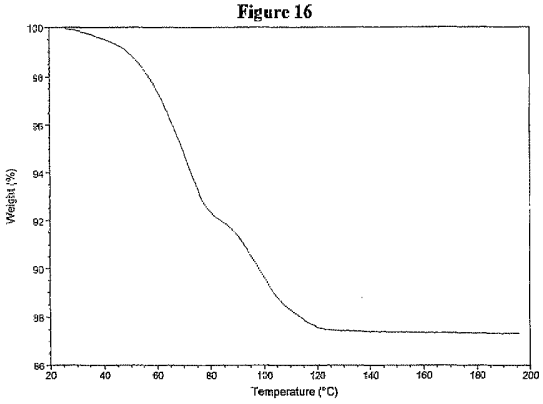

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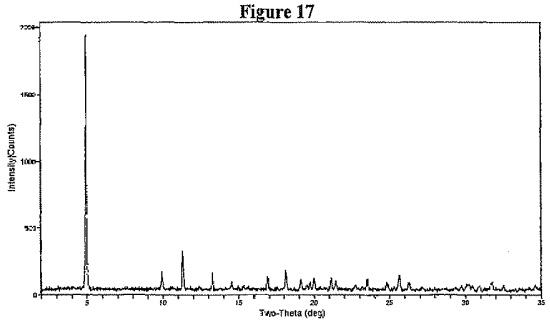

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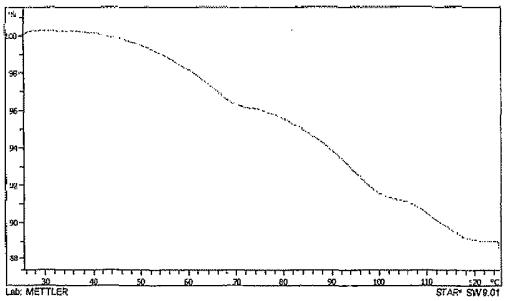

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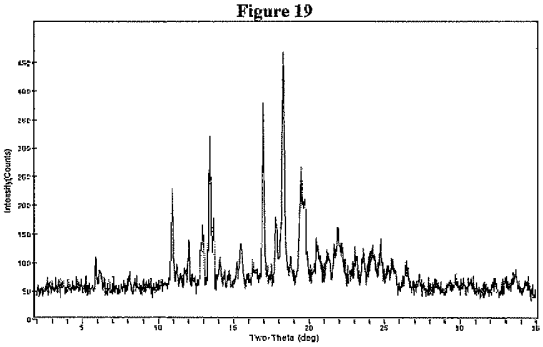


Figure 20

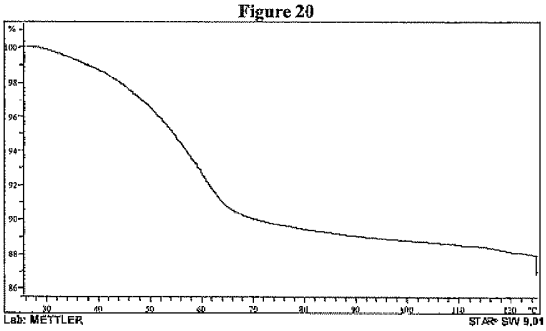
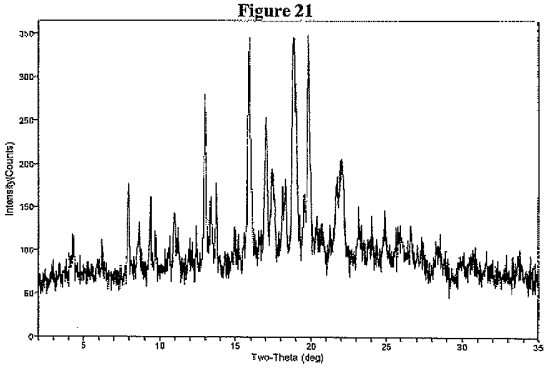


Figure 21



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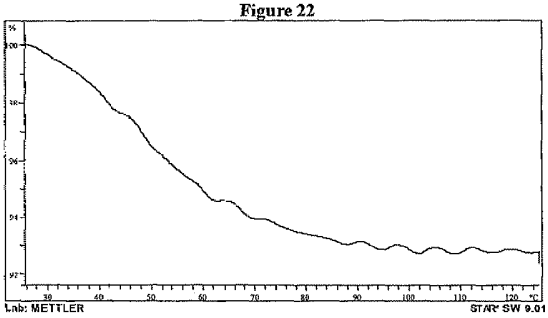

Figure 23